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CLINICAL VIGNETTES

LETTERS TO THE EDITOR

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Persistence of post-COVID lung parenchymal abnormalities during the three-month follow-up

Abstract

Introduction: COVID-19-associated pulmonary sequalae have been increasingly reported after recovery from acute infection. Therefore, we aim to explore the charactersitics of persistent lung parenchymal abnormalities in patients with COVID-19.

Material and methods: An observational study was conducted in patients with post-COVID lung parenchymal abnormalities from April till September 2020. Patients ≥18 years of age with COVID-19 who were diagnosed as post-COVID lung parenchymal abnormality based on respiratory symptoms and HRCT chest imaging after the recovery of acute infection. Data was recorded on a structured pro forma, and descriptive analysis was performed using Stata version 12.1.

Results: A total of 30 patients with post-COVID lung parenchymal abnormalities were identified. The mean age of patients was 59.1 (SD 12.6), and 27 (90.0%) were males. Four HRCT patterns of lung parenchymal abnormalities were seen; organizing pneumonia in 10 (33.3%), nonspecific interstitial pneumonitis in 17 (56.7%), usual interstitial pneumonitis in 12 (40.0%) and probable usual interstitial pneumonitis in 14 (46.7%). Diffuse involvement was found in 15 (50.0%) patients, while peripheral predominance in 15 (50.0%), and other significant findings were seen in 8 (26.7%) patients. All individuals were treated with corticosteroids. The case fatality rate was 16.7%. Amongst the survivors, 32.0% recovered completely, 36.0% improved, while 32.0% of the patients had static or progressive disease.

Conclusion: This is the first study from Southeast Asia that identified post-COVID lung parenchymal abnormalities in patients who had no pre-existing lung disease highlighting the importance of timely recognition and treatment of this entity that might lead to fatal outcome.

Key words: COVID-19, SARS-CoV-2, pulmonary sequelae, lung parenchymal abnormalities

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Introduction

The coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a global economic, psychosocial, political and medical challenge. As patients recover from COVID-19 disease, we are approaching an era where physicians would encounter COVID-19-associated pulmonary sequelae. These could be infectious, like COVID-19-associated pulmonary aspergillosis (CAPA) [1]; or noninfectious which could include COVID-19-associated interstitial lung disease (ILD). The previous epidemics of coronavirus due to severe acute respiratory distress syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) also led to the development of pulmonary fibrosis [2, 3].

ILD covers a wide spectrum of pulmonary parenchymal disorders of both known and unknown etiology. Different radiological and histopathologic patterns of ILD have been described, some of them include usual interstitial pneumonitis (UIP), nonspecific interstitial pneumonitis (NSIP), and organizing pneumonia (OP) [4]. Similar patterns

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can also occur as a result of pulmonary infections, like pneumocystis pneumonia or cytomegalovirus pneumonitis [5, 6].

The precise diagnosis of lung parenchymal abnormalities during COVID-19 pandemic remains challenging, mainly because invasive testing like bronchoscopies, open lung biopsies or autopsies are rarely performed in COVID-19 patients due to risk of disease transmission. Although there are multiple reports on the importance of CT in diagnosing COVID-19 infection, there is little or no data on the clinical presentation and management of patients with post-COVID lung parenchymal abnormalities. Myall *et al.* described the cohort of pateints with persistent inflammatory interstitial lung disease with remarkable improvement on early initiation of steroids [7]. The rationale of the study was that certain patients after recovery from COVID-19 infection might present with new, persistent or worsening respiratory symptoms due to long-term COVID-19-associated pulmonary sequelae which are usually underdiagnosed. Hence via this study, we aim to emphasize that diagnosing post-COVID lung parenchymal abnormalities with proper follow-up is of utmost importance so that early and proper management can be facilitated and fatal outcomes can be prevented.

Material and methods

Ethical approval

Approval of the Ethical Review Committee (ERC) of the Aga Khan University Hospital located in Karachi, Pakistan was obtained.

Study design and setting

This single-center observational study was performed between April 1, 2020 and September 15, 2020 at the Aga Khan University Hospital, the largest tertiary care center located in Karachi, Pakistan. We retrospectively collected the demographic, clinical, laboratory and radiological data of patients presenting with post-COVID lung parenchymal abnormalities from medical records. Disease severity of patients with COVID-19 infection was classified according to the WHO classification [8]. High- resolution computed tomography (HRCT) of the chest findings, treatment and outcomes were recorded.

Study subjects

Patients who were seen in the outpatient Pulmonology clinic or inpatient consultation service at the Aga Khan University Hospital owing to persistent respiratory symptoms after recovery from COVID-19 infection were included in the study. Follow-up imaging was performed 8 to 12 weeks after recovery from acute infection and was compared with previous imaging for disease progression, improvement or resolution.

Identification of post-COVID lung parenchymal abnormality

The identification of post-COVID lung parenchymal abnormality in our study was based on "new, persistent and/or worsening of respiratory symptoms and identification of lung parenchymal abnormality pattern on HRCT imaging of the chest after the initial recovery phase of acute COVID-19 infection defined as 8 to 12 weeks after the onset of infection with no previous history of lung disease. They were identified by specialists in ILD clinic or on inpatient consultation".

Inclusion and exclusion criteria

Adult patients (aged 18 and above) who were confirmed for SARS-CoV-2 by nasopharyngeal and/or oropharyngeal swabs for real-time RT-PCR at initial presentation and underwent chest imaging on subsequent follow-up visits were included in our study. The patients with pre-existing lung disease and those with incomplete medical records were excluded.

Operational definition of outcomes

We have defined outcomes as complete recovery, improvement and progression of the disease process. The patients were labelled as completely recovered if they returned to their baseline functional status and chest imaging showed complete clearance of lung infiltrates after the identification of post-COVID lung parenchymal abnormalities. Improvement was defined as subjective improvement in functional status but not to the baseline and at least 50% clearance of radiological infiltrates. The patients whose symptoms persisted with interval worsening of functional status and no significant improvement or worsening of lung infiltrates were defined as progression of the disease process.

HRCT chest analysis

The key HRCT chest findings of post-COVID lung parenchymal abnormalities were defined using standard taxonomy described in the literature with interstitial patterns including but not limited to diffuse ground-glass opacities with or without traction bronchiectasis (NSIP), basal and peripheral reticular opacities with honey combing (UIP) and peripheral and peribronchovascular consol-

idation with or without ground-glass opacities (OP) [9]. The main HRCT findings were described as ground-glass opacities (GGO), consolidation, honeycombing/fibrosis and interlobular septal thickening/reticulation. Other HRCT findings included crazy paving, reverse halo sign, traction bronchiectasis and emphysematous cysts. The distribution of pulmonary involvement was reported as either peripheral or diffuse.

Statistical analysis

Statistical analyses were performed using STATA version 12.1 (StataCorp LLC, College Station, Texas, USA). Quantitative data were presented as mean ± standard deviation (SD) or as median with inter-quartile range (IQR), while percentages of the total, unless stated otherwise, were used to represent qualitative (categorical) data.

Table 1. Clinical and demographic characteristics of patients with post-COVID lung parenchymal abnormalities (n = 30)

Variables	Findings
Age [years], mean ± SD	59.1 ± 12.6
Gender, n (%)	
Male	27 (90.0)
Female	3 (10.0)
Comorbidities, n (%)	
Diabetes mellitus	14 (46.7)
Hypertension	13 (43.3)
Chronic obstructive pulmonary disease	1 (3.3)
Chronic liver disease	1 (3.3)
Malignancy	1 (3.3)
Ischemic heart disease	1 (3.3)
Inflammatory bowel disease	1 (3.3)
Chronic kidney disease	1 (3.3)
Smoking, n (%)	
Current smokers	3 (10.0)
Ex-smokers	8 (26.7)
Non-smokers	19 (63.3)
Symptoms on presentation with COVID-19, n (%)	
Fever	30 (100)
Shortness of breath	23 (76.7)
Cough	19 (63.3)
Fatigue	9 (30.0)
Headache	2 (6.7)
Persistent respiratory symptoms, n (%)	
Persistent cough	13 (43.3)
Persistent shortness of breath	29 (96.7)
Severity of COVID-19 Disease on initial presentation, n (%)	
Non-severe	0 (0)
Severe	16 (53.7)
Critically ill	14 (46.7)
Treatment given for post-COVID lung parenchymal abnormalities, n (%)	
Home oxygen	28 (93.3)
Prednisolone	30 (100.0)
Pirfenidone	2 (6.7)

COVID-19 — coronavirus disease 2019; SD — standard deviation

Results

As shown in Table 1, our cohort included 30 patients, 27 were males (90.0%) with an average age of 59.14 ± 12.60. Common presenting symptoms of COVID-19 disease were fever (30, 100.0%), cough (19, 63.3%) and shortness of breath (23, 76.7%). During initial COVID-19 disease, 16 (53.3%) patients had severe disease and 14 (46.7%) had critically ill disease. All individuals required supplemental oxygen. Out of 14 critically ill patients, 12 (85.7%) were treated with non-invasive ventilation (NIV) and 2 (14.3%) patients were treated with invasive mechanical ventilation.

All patients in our cohort were found to have bilateral lung disease. Four HRCT patterns of lung parenchymal abnormalities were seen (Table 2). Diffuse involvement was found in 15 (50.0%) patients, while peripheral predominance in 15 (50.0%) and other significant findings were seen in 8 (26.7%) study subjects.

All patients were treated with corticosteroids (0.5–1 mg/kg/day) for average duration of 8 to 12 weeks. Two individuals were treated with pirfenidone for fibrotic lung disease. Home oxygen was needed in 28 (93.3%) patients.

Table 2. Radiological patterns of post-COVID lung parenchymal abnormalities (n = 30)

Variables	Findings
Main findings, n (%)	
Patchy consolidation with ground glass opacity (OP pattern)	10 (33.3)
Diffuse ground glass opacities (NSIP pattern)	17 (56.7)
Honeycombing/Fibrosis (UIP pattern)	12 (40.0)
Interlobular Septal Thickening/Reticulation (probable UIP)	14 (46.7)
Distribution, n (%)	
Peripheral	15 (50.0)
Diffuse	15 (50.0)
Other findings, n (%)	
Crazy paving	2 (6.7)
Reverse halo sign	1 (3.3)
Traction bronchiectasis	4 (13.3)
Emphysematous cysts	1 (3.3)

COVID-19 — coronavirus disease 2019; OP — organizing pneumonia; NSIP — nonspecific interstitial pneumonia; UIP — usual interstitial pneumonia

A total of eight subjects had pulmonary functions test (PFT). Median and IQR of forced vital capacity (FVC) was 92.5% (43.2%–102.7%). Four patients had normal pulmonary functions. However, three persons had reduced FVC. Diffusion capacity of the lungs for carbon monoxide (DL_{CO}) was done in three cases, out of which two patients had moderately reduced and one individual had normal DL_{CO}.

Five patients died during the disease course; 4 (80.0%) patients died due to hypoxic respiratory failure, while 1 (20.0%) succumbed to superimposed aspergillus infection. Majority of the study subjects who died; 3 (60.0%), had progressive disease with UIP pattern. The CT images of 3 patients with different patterns of lung parenchymal abnormalities are shown in Figure 1–3. Out of the 25 alive patients, 8 (32.0%) recovered completely, 9 (36.0%) improved, while 8 (32.0%) patients had static or progressive disease.

Discussion

Our study found four distinct lung parenchymal abnormalities associated with COVID-19 disease. Development of lung parenchymal abnormalities amongst survivors of COVID-19 disease has been reported during the ongoing pandemic, however, data is limited to case reports [10–12]. Literature from the previous outbreaks of viral infections such as SARS and MERS, in 2002 and 2012 respectively, reported that clinico-radiological changes persisted in approximately one-third of patients even after 12 weeks of discharge [2, 3].

The majority of our patients who developed lung parenchymal abnormalities were males, which is reported in literature with certain ILDs-like idiopathic pulmonary fibrosis [13, 14]. COVID-19-associated fibrosis is one of the lung insults already described with previous coronavirus infections [2, 3], and there are emerging studies now reporting COVID-19- associated early pulmonary fibrosis. In the initial papers, Pan *et al*. and Zhou *et al*. reported fibrotic changes in the imaging features of patients with COVID-19 pneumonia [15, 16]. Since then, fibrotic lung parenchymal remodelling [17, 18], fibrosing diffuse alveolar damage (DAD) [19] and honeycombing [20] have also been confirmed after invasive testing such as cryobiopsies and autopsies in smaller cohorts. Li Yan *et al.* described DAD on autopsy of 30 patients with COVID-19, showing 43% developing fibrosing patterns while 25% showing organizing pattern [19].

Post-infectious secondary OP is also a known entity, well described with certain viruses like Cytomegalovirus and Influenza-A (H1N1) [6, 21]. Pathology in patients who recovered from SARS-CoV has shown fibrogranulation tissue proliferation and organizing pneumonia-like patterns [22] while MERS-associated organizing pneumonia has also been documented [23, 24]. Studies of COVID-19 CT imaging, coupled with postmortem lung biopsies and autopsies during the ongoing pandemic, suggest the development of a secondary OP, which at present remains an underrecognized complication [25].

A distinct feature of organizing pneumonia and NSIP is the resolution with corticosteroid treatment. Although the use of corticosteroids has been recommended in the treatment of COVID-19 disease [26[, there is limited data on response of prolonged or higher dose corticoste-

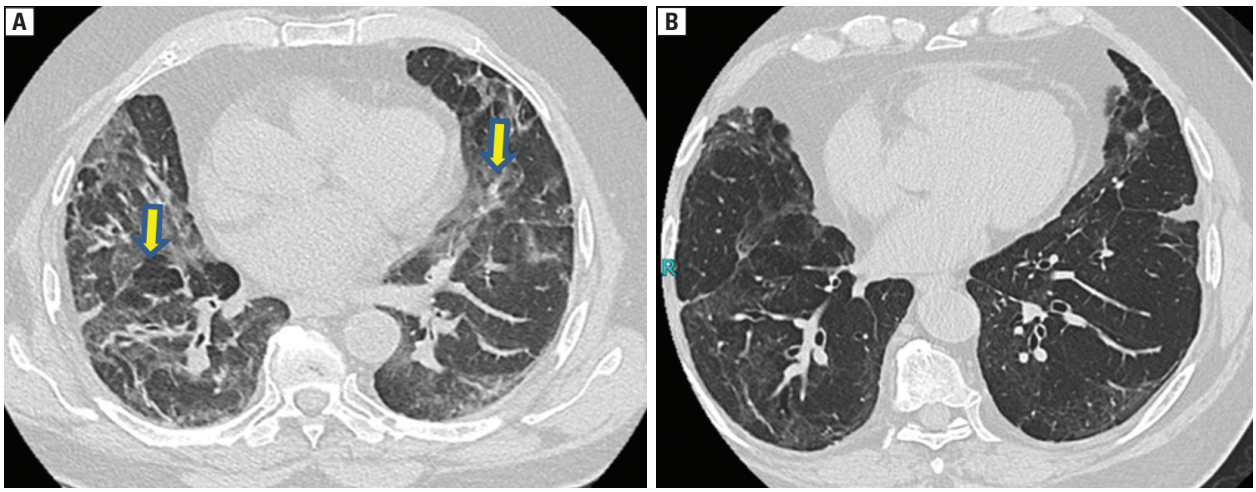

Figure 1. HRCT of the chest showing **A.** ground glass opacities (GGOs) and interlobular septal thickening (yellow arrow showing GGOs and septal thickening); and **B.** interval reduction in GGOs and septal thickeneing after initiation of corticosteroids

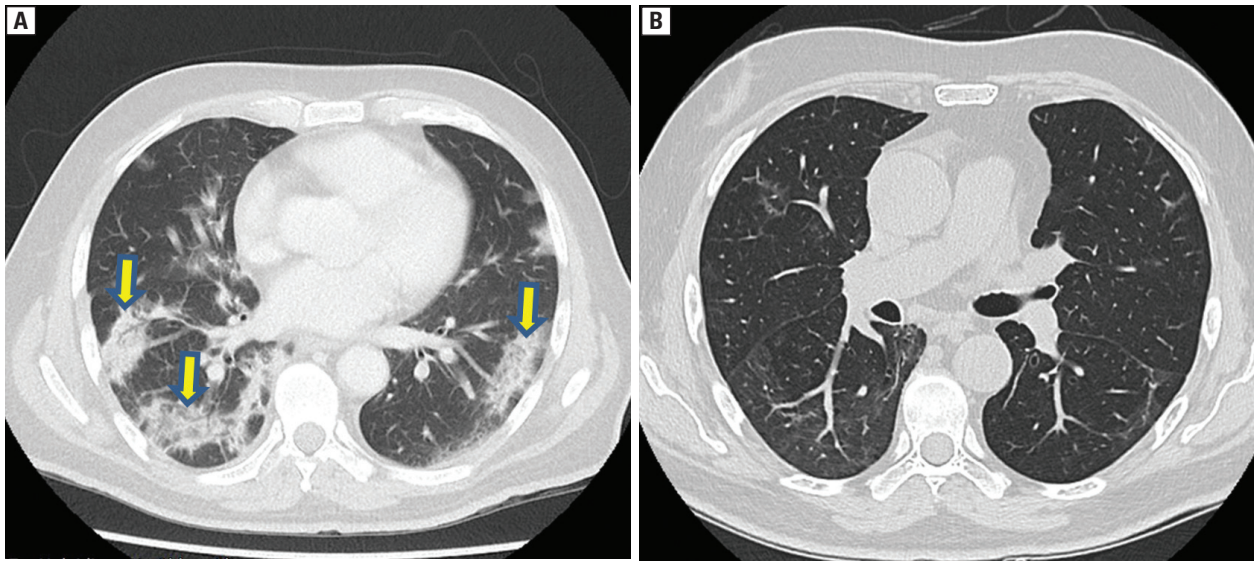

Figure 2. HRCT of the chest of showing **A.** peripheral patchy areas ground glass opacities (GGOs) with consolidation consistent with an OP (organizing pneumonia) pattern (yellow arrow pointing towards peripheral patchy GGOs); and **B.** near complete resolution of peripheral patchy consolidation after initiation of corticosteroids

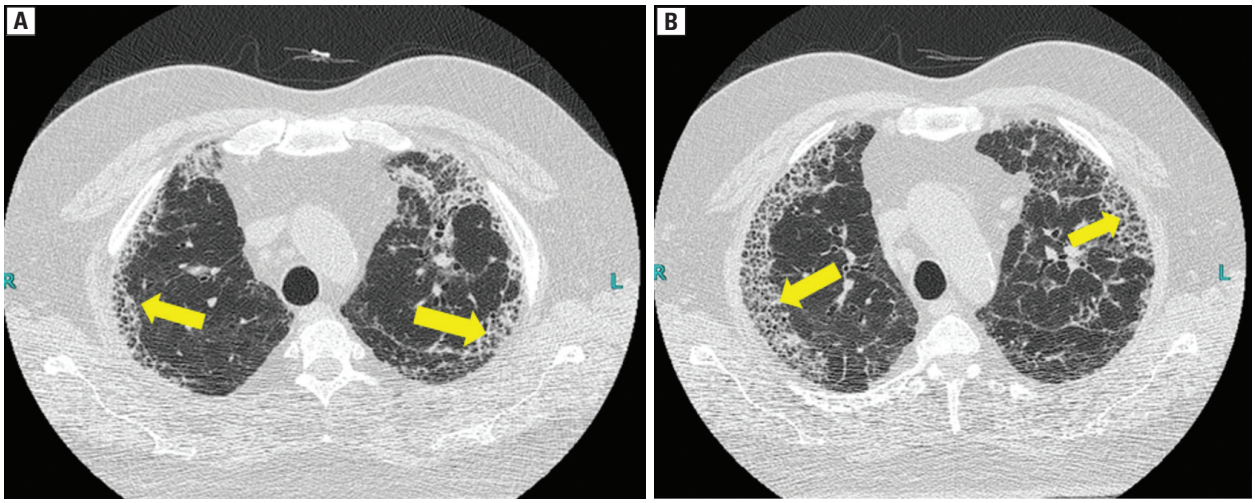

Figure 3. HRCT of the chest showing **A.** honeycombing and reticulation (yellow arrow showing honeycombing); and **B.** persistent and worsening of honeycomb fibrosis (yellow arrow showing honeycombing)

roids in post-COVID lung parenchymal abnormalities. Myall *et al.* described the cohort of pateints in which thirty individuals with post-COVID organising pneumonia pattern were treated with corticosteroids with significant improvement [7].

In our cohort, most patients developed a predominant OP or NSIP pattern with severe to critically ill disease. Most persons with an OP and NSIP pattern improved significantly with steroids, showing both clinical and radiological improvement. The patients showing UIP pattern, however, largerly remained static or progressed. Majority of the deaths in our cohort were in the patients showing UIP pattern.

Disease severity did not seem to have a significant impact on development of any particular pattern of lung parenchymal abnormality. This proves that these reported lung microstructure changes are not only a result of post-ARDS fibrosis or ventilator-induced lung damage, but also a consequence of the direct virus-induced injury and aberrant local immune response leading to lung parenchymal abnormalities. Combet *et al.* recently described a case of a spontaneously breathing patient who developed rapid honeycombing following COVID-19 disease which responded to high-dose steroids and nintedanib [27]. Tale *et al.* also reported a similar case of a patient with

persistent hypoxemia after recovery from moderate COVID-19 disease with 3-week follow-up HRCT showing artitechtural distortion, interlobar septal thickening and traction bronchiectasis [28]. These case reports reiterate our stance that predisposed patients who are moderately ill, and do not require mechanical ventilation can also develop early fibrotic changes. However, study conducted by Han *et al.* had findings contrary to that of ours. They extrapolated that in patients with age greater than 50, increased heart rate on admission, increased duration of hospital stay, non-invasive mechanical ventilation and extensive CT involvement at initial CT were risk factors for fibrotic changes at 6-month follow-up [29]. Post-viral pulmonary fibrosis associated with previous coronaviruses has been seen in patients with critical disease leading to ARDS with longer duration of illness requiring ICU stay and invasive mechanical ventilation [2]. However, SARS-CoV-2 has shown to induce fibrosis in patients who did not require invasive mechanical ventilation or ICU stay in our study.

To the best of our knowledge, this is a first case series emphasizing and presenting data of 30 patients with different patterns of post-COVID lung parenchymal abnormalities along with their follow-up from a low to middle income country.

Our study has several limitations which include, among others, the absence of histopathologic confirmation of lung parenchymal abnormalities. Transbronchial and open lung biopsies were not performed due to the cost, invasive nature of procedure and risk of transmission of COVID-19; therefore, our patients were diagnosed solely on clinical and radiological grounds. A limited number of PFTs and DL_{CO} were performed to assess the physiologic function.

Conclusion

Post-COVID lung parenchymal abnormalities are an increasingly recognized clinical entity. A close follow-up is essential in these patients, as they may require prolonged treatment with corticosteroids in relatively higher doses. The long-term effects of post-COVID lung sequelae are yet to be determined, and a longitudinal follow-up will help us further explore the nature of the disease.

Ethics approval and consent to participate

Approval of the Ethical Review Committee (ERC) of the Aga Khan University Hospital located in Karachi, Pakistan was obtained (ERC Reference # 2020-5269-11494) and informed consent requirement was waived because of retrospective nature of the study.

Conflict of interest

The authors declare that they have no competing interests.

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On-admission versus in-hospital thromboembolism due to COVID-19 infection. What is the particular characteristic of those with early thrombotic events?

Abstract

Introduction: Increasing evidence has declared a hypercoagulable state in the coronavirus 2019 infection (COVID-19), while the etiology has remained a question. For the first time, the current study has aimed to compare the contributors of thromboembolism among those whose primary manifestations of COVID-19 were thrombosis vs the patients with a thrombotic event during the period of hospitalization.

Material and methods: This case-control study has been conducted on 267 COVID-19 patients, including 59, 48, and 160 ones with an on-admission, in-hospital, and without a thrombotic event, respectively. The events were defined as deep vein thrombosis (DVT), ischemic cerebrovascular accidents (CVA), pulmonary thromboembolism (PTE), or acute myocardial infarction (AMI). The demographic, physical examination, clinical and laboratory assessments of the groups were compared.

Results: The DVT (OR: 5.18; 95% CI: 1.01–26.7), AMI (OR: 11.1; 95% CI: 2.36–52.3), and arterial thrombosis (OR: 5.93; 95% CI: 0.63–55.8) were significantly associated with an on-admission thrombosis compared to those who presented in-hospital events. Lower levels of oxygen saturation were the only significant predictor index inversely associated with on-admission thrombosis compared to those with an event during the hospital admission period.

Conclusion: PTE development was the most common in-hospital thrombotic event, whereas other thromboembolism types were remarkably more often among cases with on-admission events. Oxygen saturation was the only predictor of premature thrombosis that was inversely associated with outpatient events.

Key words: COVID-19, thrombophilia, thromboembolism, SARS-CoV-2, case-control studies

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Introduction

The pandemic of the novel coronavirus infection (COVID-19) is still progressing worldwide and is the underlying etiology of numerous daily deaths since December 2019 [1]. COVID-19 presentation varies from asymptomatic courses in 30–40% of the cases. Of those symptomatic ones, 81% experience a mild disease, 14% are moderate cases, and the remained 5% develop intense endothelial activation with exuberant inflammatory response, a remarkable cytokine release associated with Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure (MOF). The overall fatality of COVID-19 accounts for 2.3% [2, 3].

An increasing body of evidence declares that patients with COVID-19 are predisposed to venous and arterial thrombosis [4]. The mecha-

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nism by which the patients are at a hypercoagulable state is not well-recognized; nevertheless, it may link to overactivation of neutrophil traps and platelets, proinflammatory cytokine release, endothelial dysfunction, and complement activation [5–7].

Due to an increasing trend in the number of confirmed cases with severe COVID-19, numerous reports have been emerged suggesting that the patients with severe courses of COVID-19, requiring hospitalization, intensive care unit (ICU) admission, and in general, critically ill patients are at significantly increased risk of thrombotic events development [8, 9]. Nevertheless, a paucity of knowledge is available regarding thrombosis incidence among mild-to-moderate cases who have developed on-admission thrombosis [10].

Thromboprophylaxis is a debating issue among COVID-19 patients; however, inadequate evidence for anticoagulant agents' routine use is available [11–13]. The current study aims to compare the characteristics of the COVID-19 patients with thrombosis on admission, during the period of hospital admission and with no thrombotic event, to make a thorough vision of thromboprophylaxis necessity in target populations.

Material and methods

Study population

The current case-control study has been conducted on 267 patients in three groups, including 59 ones with an on-admission thrombotic event, 48 ones with thrombosis during hospitalization, and 160 ones without any thromboembolism. This multicentric study has been performed among the patients admitted at Amin and Alzahra Hospitals (affiliated at Isfahan University of Medical Sciences) due to SARS-CoV-2 from May to June 2020.

This study met the Helsinki ethics declaration criteria and was derived from the approved proposal by Isfahan University of Medical Sciences Ethics Committed by code IR.MUI.MED.REC.1399.692. Written consent was obtained from the patients if possible; or by their legal guardians.

The case groups were selected from the patients with any thrombotic event, including deep vein thrombosis (DVT), ischemic cerebrovascular accidents (CVA), pulmonary thromboembolism (PTE), or myocardial infarction (MI) whose COVID-19 infection was approved by a positive polymerase chain reaction (PCR) test. The participants who met the inclusion criteria entered into the study using convenience sampling. The cases were divided into two groups, including on-admission thromboembolism, defined as admission due to any of the above events or thrombosis incidence by the first two days of hospitalization; otherwise, assigned as those with thromboembolism during the period of hospital admission.

Similar criteria were adopted for the control group.

Pregnancy, immune deficiency, history of coagulopathies, and a thromboembolic event within a month before the hospitalization regardless of its type (DVT, PTE, CVA, or MI) were determined as the exclusion criteria.

Diagnosis of thrombotic events

Presentations compatible with Well's criteria with a confirmatory Doppler ultrasonography were administered to make a DVT diagnosis [14]. Suspicion of PTE due to clinical manifestation was confirmed using computed tomographic pulmonary angiography (CTPA) [15]. Acute MI was defined as ST-segment elevation myocardial infarction (STEMI) or non-STEMI according to a typical chest pain plus a significant increase in highly-sensitive troponin as a sensitive and specific cardiac biomarker. ST-segment elevation in two or more electrocardiogram leads indicating the involvement of a particular epicardial territory or new-onset left bundle branch block (LBBB) was defined as STEMI; otherwise, non-STEMI. Hemiplegia, facial hemiparesis, or dysarthria with a CT scan compatible with an ischemic CVA were the CVA determinants.

The included patients received anti-COVID-19 infection and anticoagulation therapies according to Iran's national guidelines.

Data collection

The demographic characteristics, including age, gender, smoking, comorbidities (diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), any malignancy, cerebrovascular accidents (CVA), ischemic heart disease (IHD), and history of PTE), smoking and medical history, were entered into the study checklist.

On admission, hemodynamic information (oxygen saturation, pulse rate, systolic and diastolic blood pressure, respiratory rate, and mobility) and laboratory assessments (complete blood count, albumin, ferritin, C-reactive protein (CRP), d-dimer, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen, troponin, and lactate dehydrogenase (LDH)) were recorded in the study

checklist as well. A reference laboratory did all the assessments to minimize the potential bias.

The course of disease severity was defined according to an on-admission level of oxygen saturation; therefore, oxygen saturation > 93%, 90–93%, and < 90% were determined as mild, moderate, and severe diseases.

Anticoagulation in the studied group was classified as no anticoagulant therapy, prophylactic, intermediate dose, and therapeutic dose. The remedies were initiated before thrombosis incidence. Prophylactic doses included 5000 IU subcutaneous unfractionated heparin (UFH) (3 times a day) [for BMI > 40 kg/m^2:7500 IU subcutaneous UFH (three times a day)] or 40 mg subcutaneous enoxaparin (once daily) (for BMI > 40 kg/m^2:40 mg subcutaneous enoxaparin (twice daily)) was administered. Intermediate doses included 7500 IU subcutaneous UFH (three times a day) or 60 mg subcutaneous enoxaparin (daily). The therapeutic doses were determined as 80 IU/kg UFH bolus infusion followed by 18 IU/kg/h UFH infusion or 1 mg/kg subcutaneous enoxaparin (twice daily). The doses were defined according to national protocols. The anticoagulant-related adverse effects, including gastrointestinal (GI) bleeding, hemoptysis, hematuria, were recorded. The other probable side effects such as easy bruising, petechiae, or purpura were categorized as other.

The latter outcomes were ICU admission requirement, discharge/death, and non-invasive ventilation (NIV)/ intubation.

Data analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 22.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, median, range for the continuous variable, and frequency and percentages for categorical variables. Regarding the three separate primary case-control studies, we aimed to compare the groups in pairs (without thrombotic event group with thrombose on admission group; without thrombotic event group with thrombosis during hospital group, thrombosis during hospital with thrombose on admission group). As the sample size in the two groups was less than 100, the normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the distribution of some variables was not normal, nonparametric tests were used. The chi-square test or Fisher's exact test was utilized to compare the categorical variables between the groups. The continuous variables were compared using the Mann-Whitney U test. Binary logistic regression analysis was applied to estimate the odds ratio and determine the association between the assessed factors and thrombotic events in the crude and adjusted model. Logistic regression was separately constructed for each of the factors in the crude model, while all variables were entered together in the adjusted model. In addition, logistic regression models were verified in terms of goodness of fit by –2 log-likelihood. A p-value of less than 0.05 was considered as a significant level.

Results

The current study has been conducted on 267 COVID-19 patients. In-hospital thromboembolism was significantly more frequent in males than in controls ($p = 0.006$). Among the hemodynamic parameters, oxygen saturation ($p = 0.020$) and respiratory rate ($p = 0.021$) were statistically different between those with thrombosis during the hospitalization period and the controls, but not the other groups. Mobility status was another significant difference among the studied groups. The laboratory parameters assessments revealed a remarkable difference in neutrophil, lymphocyte, and platelet counts, albumin, ferritin, d-dimer, INR, fibrinogen, troponin, and LDH levels. PTE incidence ($p < 0.0001$) was the primary type of event in those who experienced thromboembolism during hospitalization, whereas AMI was statistically more frequent among those with on-admission thrombosis ($p = 0.003$). The severity of COVID-19, anticoagulation and respiratory aid type were remarkably associated with thrombosis incidence ($p < 0.05$) (Table 1).

The time assessments revealed significant correlations between symptom initiation to admission and thrombosis incidence, the period between hospitalization to ICU admission, and the period between hospitalization to discharge or death ($p < 0.05$) (Table 2).

DVT, MI, and arterial thrombosis were significantly associated with on-admission thrombosis compared to those who presented any thrombotic event during hospitalization. Lower levels of oxygen saturation were the only significant predictor index inversely associated with on-admission thrombosis compared to those with an event during the hospital admission period.

Discussion

Patients with COVID-19 infection are typically admitted to the hospital because of respi-

Table 1. Demographic and clinical characteristic of the studied population

	Group 1. COVID-19 with thrombotic events on admission (n = 59)	Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)	Group 3. COVID-19 without thrombotic events (n = 160)	P-value		
				1.2	1.3	2.3
Demographic						
Age-year mean (SD)	61.8 (17.8)	63.2 (18.8)	58.8 (17.8)	0.690	0.261	0.134
Gender-male, n (%)	37 (62.2)	36 (75.0)	84 (52.5)	0.175	0.178	0.006*
Comorbidities, n (%)						
Diabetes	15 (25.4)	8 (18.2)	37 (23.1)	0.383	0.723	0.484
COPD	1 (1.7)	0 (0)	6 (3.8)	0.381	0.453	0.192
ESRD	2 (3.4)	1 (2.3)	13 (8.1)	0.739	0.218	0.174
Malignancy	1 (1.7)	1 (2.3)	10 (6.3)	0.833	0.171	0.301
CVA	4 (6.8)	3 (6.8)	8 (5.0)	0.994	0.608	0.636
IHD	15 (25.4)	13 (29.6)	25 (15.6)	0.642	0.096	0.036*
PTE history	1 (1.7)	0 (0)	1 (0.63)	0.386	0.460	0.599
Smoking, n (%)	8 (13.6)	3 (6.8)	1 (10.6)	0.273	0.545	0.452
Pre-hospitalization medication — n (%)						
None	35 (59.3)	31 (64.6)	118 (73.8)	0.578	0.039*	0.217
Aspirin	19 (32.2)	10 (20.8)	28 (17.5)	0.188	0.019*	0.600
Clopidogrel	4 (6.8)	1 (2.1)	0 (0)	0.252	0.001*	0.067
Prophylaxis anticoagulant	2 (3.4)	3 (6.3)	3 (1.9)	0.486	0.506	0.112
Anticoagulant therapy	1 (1.7)	0 (0)	3 (1.9)	0.365	0.930	0.339
On-admission clinical presentations						
O2 saturation, mean (SD)	84.2 (10.8)	80.9 (10.8)	86.3 (8.1)	0.620	0.800	0.020*
Pulse rate, mean (SD)	95.3 (21.2)	90.1 (15.2)	92.6 (19.8)	0.376	0.147	0.950
Pulse rate > 100, n (%)	19 (32.2)	12 (25.0)	35 (21.9)	0.414	0.116	0.650
Systolic blood pressure mean (SD)	121.4 (18.1)	125 (19.2)	124 (20.6)	0.851	0.570	0.622
Systolic blood pressure < 90 mm Hg, n (%)	2 (3.4)	0 (0)	4 (2.5)	0.198	0.720	0.269
Diastolic blood pressure, mean (SD)	76.4 (12.7)	78.3 (14.3)	75.6 (14.4)	0.985	0.464	0.249
Diastolic blood pressure < 60 mm Hg, n (%)	4(6.8)	0 (0)	5 (3.1)	0.066	0.227	0.215
Respiratory rate, n (%)	23.3 (7.3)	25.7 (5.4)	23.7 (6.2)	0.078	0.856	0.021*
RBR	17 (28.8)	23 (47.9)	83 (51.9)	0.042*	0.002*	0.630
CBR	48 (81.4)	37 (77.1)	101 (63.1)	0.587	0.010*	0.073
On admission, laboratory characteristics						
Neutrophil count, median (IQR)	8160 (5753–12288)	5760 (5005–9120)	5430 (3289–8562)	0.006*	< 0.0001*	0.656
Lymphocyte count, median (IQR)	1117 (787–1428)	700 (607– 832)	963 (700–1385)	< 0.0001*	0.03 *	< 0.0001*
LNR, median (IQR)	7.3 (4.2–13.3)	8.5 (6.2–13.9)	5.3 (3.17–8.9)	0.434	0.062	0.001*
Hemoglobin (g/dL), median (IQR)	12.4 (10–13.6)	13.1 (11.2–14.8)	13.1 (11.6-14.3)	0.232	0.174	0.984
Platelet× 10 ^ -3, median (IQR)	211 (147–272)	174 (135–240)	171 (137–227)	0.096	0.030*	0.929
Albumin [g/dL], median (IQR)	3.4 (3.0–3.5)	3.1 (2.9–3.6)	3.5 (3.1–3.9)	0.151	0.002*	0.008*

→

Table 1. cont. Demographic and clinical characteristic of the studied population

	Group 1. COVID-19 with thrombotic events on admission (n = 59)	Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)	Group 3. COVID-19 without thrombotic events (n = 160)	P-value		
				1.2	1.3	2.3
On admission, laboratory characteristics						
CRP, n (%)	82 (47–111)	96 (40–127)	63 (21–104)	0.768	0.112	0.198
D-dimer [ng/mL], median (IQR)	3307 (2238– 6766)	3500 (1076–6824)	1491 (859–3175)	0.849	< 0.0001*	0.010*
INR, median (IQR)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	0.95 (1.1–1.3)	0.655	< 0.0001*	0.012*
PT [s], median (IQR)	13.5 (11.8–15.3)	13.1 (11.6–15.6)	12.7 (11.4–14.1)	0.928	0.437	0.128
PTT [s], median (IQR)	29 (28–33)	30 (28–35)	31 (28–34)	0.407	0.032*	0.442
FDP [μg/mL], median (IQR)	25 (25–28)	25 (22–27)	25 (18–36)	0.677	0.588	0.549
Fibrinogen [mg/dL], median (IQR)	339 (224–421)	249 (210–285)	339 (243–415)	0.117	0.923	0.003*
Troponin [ng/mL], median (IQR)	36 (7–942)	9 (1–108)	8 (2–20)	0.147	0.007*	1.000
LDH [IU/L], median (IQR)	897 (622–1331)	951 (668–1208)	725 (576–1024)	0.476	0.105	0.009*
Thrombosis type, n (%)						
PTE	29 (49.2)	43 (89.6)	–	< 0.0001*	–	–
DVT	7 (11.8)	2 (4.2)	–	0.182	–	–
MI	15 (25.4)	2 (4.2)	–	0.003*	–	–
CVA	4 (6.8)	0 (0)	–	0.126	–	–
Arterial	4 (6.8)	1 (2.1)	–	0.377	–	–
Disease severity, n (%)						
Severe	37 (62.7)	41 (85.4)	99 (61.9)	0.022*	0.810	0.009*
Moderate	14 (23.7)	3 (6.3)	34 (21.3)			
Mild	7 (13.6)	4 (8.3)	27 (16.9)			
Anticoagulation before thrombosis incidence, n (%)						
None	53 (89.8)	9 (18.8)	30 (18.8)	< 0.0001*	< 0.0001*	0.427
Prophylactic doses	4 (6.8)	24 (50.0)	97 (60.6)			
Intermediate doses	0 (0)	4 (8.3)	11 (6.9)			
Therapeutic doses	2 (3.4)	11 (22.9)	22 (13.8)			
Side effects of Anticoagulants, n (%)						
GI-bleeding	2 (3.4)	6 (12.5)	8 (5.0)	0.075	0.613	0.069
Hemoptysis	2 (3.4)	4 (8.3)	6 (3.4)	0.269	0.900	0.193
Hematuria	0 (0)	3 (6.3)	3 (1.9)	0.051	0.290	0.112
Others	2 (3.4)	4 (8.3)	2 (1.3)	0.269	0.294	0.010*
Hospitalization outcome, n (%)						
ICU admission	28 (47.5)	30 (62.5)	84 (52.5)	0.120	0.508	0.222
NIV	7 (11.9)	17 (35.4)	19 (11.9)	0.004*	0.998	<0.0001*
Intubation	13 (22.0)	12 (25.0)	38 (23.8)	0.718	0.790	0.859
Discharge	43 (72.9)	36 (75.0)	129 (80.6)	0.804	0.216	0.399
Death	16 (27.1)	12 (25.0)	31 (19.4)			

Chi^2/exact test for categorical variable and Mann-Whitney U for a continuous variable were significant if $p < 0.05$

Table 2. Time intervals [day]

	Day median (IQR)			P-value		
	Group 1. COVID-19 with thrombotic events on admission (n = 59)	**Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)**	**Group 3. COVID-19 without thrombotic events (n = 160)**	**1.2**	**2.3**	**1.3**
Symptom initiation to admission	7 (2–14)	7.5 (7–14)	7 (3–10)	0.312	0.012*	0.527
Symptom initiation to thrombosis incidence	7 (2–14)	18.5 (12–24.5)	—	< 0.0001*	—	—
Admission to thrombosis incidence	0	7 (4–11.5)	—	< 0.0001*	—	—
Hospital-to-ICU admission	1 (0–2.5)	2.5 (1–6)	2 (1–5)	0.007*	0.051	0.179
Admission to discharge	8 (5–10)	17 (12.5–21)	10 (6–17)	< 0.0001*	0.0001*	0.027*
Admission to death	6.5 (2–14)	13 (8.5–20.5)	16 (9–21)	0.022*	0.115	0.011*

Chi^2/exact test for categorical variable and Mann-Whitney U for a continuous variable were significant if $p < 0.05$

ratory distress, coughing, shortness of breath, and fever. Nevertheless, an increased risk of thrombosis in numerous cases has been noted [16], particularly among critically ill patients [17]. Although numerous studies have notified the significance of anticoagulant prophylaxis or therapy for ill ICU-admitted and even, to lower extents, for hospital admitted patients with COVID-19 pneumonia, risk of thrombosis development due to COVID-19 infection among unadmitted, hospitalized due to thrombosis and the SARS-CoV-2-infected patients without pneumonia had been underestimated.

To the best of our knowledge, no effort has been made to compare the patients with an event before hospital admission versus those who developed it in the hospital. Our study's main scope was to make a thorough vision of thromboprophylaxis necessity in outpatients with mild-to-moderate COVID-19 infections.

In the current 3-armed parallel case-control study, we observed that the patients with on-admission thrombosis were similar to the second group who developed thrombosis in the course of hospitalization, and to the control group who did not experience any event, in terms of demographic, past medical history, smoking and pre-admission medications. These findings were consistent with most of the previous studies in the literature [18–20].

An ineffective role of antiplatelet therapy to prevent thrombosis, either by aspirin or clopidogrel, was a noteworthy finding of our study. Accordingly, we do not recommend antiplatelet treatment initiation for outpatients to minimize the risk of thrombotic events; however, by risk assessment, those on the treatment with these agents should continue [21]. Nevertheless, the insights about the routine administration of antiplatelet agents to prevent COVID-19-related complications are different. On the one hand, some of the researchers favored antiplatelet agents, aspirin in particular, as they present early antiplatelet therapy may be beneficial due to their inhibitory effects on platelet activation and neutrophil-to-platelet aggregation generation; the critical mechanisms for thrombosis formation [22, 23]. It should be noted that most of the studies recommending aspirin administration have targeted patients with cardiovascular disorders, not all types of thrombotic events. On the other hand, growing evidence suggests antiplatelet therapy's inefficacy for the primary prevention of thrombosis. According to the guideline, these agents are recommended regardless of being infected with SARS-CoV-2 to secondarily prevent the events such as AMI, stroke, and peripheral artery disease in intervened cases [21].

Among the on-admission hemodynamic parameters, oxygen saturation and mobility status were the only significant differences among the three studied groups. Oxygen saturation is a determinant of disease severity. Thus those with a more severe course of COVID-19 had worse

Table 3. Factors associated with premature thrombosis

	Odds ratio for premature thrombosis (95% CI)	
	Thrombotic events during hospitalization	
	Crude	Adjusted
Age	0.99 (0.97–1.02)	1.01 (0.97–1.04)
Comorbidity		
0	1	1
1	1.10 (0.46–2.61)	0.46 (0.12–1.47)
2	2.03 (0.36–11.3)	1.79 (0.18–17.80)
3	0.81 (0.10–6.16)	0.37 (0.019–5.35)
4	No data	No data
Thrombosis type		
PTE	1	1
DVT	5.18 (1.01–26.7)*	3.59 (0.21–59.73)
MI	11.1 (2.36–52.3)*	7.04 (0.95–52.04)
CVA	No data	No data
Arterial	5.93 (0.63–55.8)*	1.42 (0.88–23.2)
On admission clinical or laboratory presentations		
O_2 sat < 90	0.28 (0.10–0.74)*	0.13 (0.017–1.04)
Respiratory rate	0.94 (0.88–1.01)	0.94 (0.83–1.04)
Lymphocyte count	1.00 (0.99–1.00)	0.99 (0.99–1.01)
D-dimer [ng/mL]	1.00 (0.99–1.00)	1.00 (1.00–1.00)*
CRP [mg/L]	0.99 (0.98–1.01)	1.00 (0.98–1.01)
LDH [IU/L]	1.00 (0.99–1.00)	1.00 (0.99–1.01)

Comorbidity: 0 = none, 1, 2, 3 = have at least one, two, or three of underlying disease (DM, COPD, CVA, IHD). Logistic regression was used to estimate the Crude and Adjusted (all variables entered in the model) odds ratio. In the crude model, the goodness fit was good so that the -2 log Likelihood was above 62 for each variable separately. However, in the adjusted model, it was about 44.57; *$p < 0.05$

oxygenation status that leads to immobility, non-invasive or mechanical ventilation requirement, ICU admission, and therefore, were prone to venous thromboembolic events [24, 25].

Higher levels of absolute neutrophil count among those with on-admission thrombosis in comparison to the two other groups not only reinforced the theory about the rule of neutrophil hyperactivity and neutrophil traps in COVID-19-related hypercoagulability pathogenesis [26] but also ignites a hypothesis in terms of neutrophil count administration to make a decision for thromboprophylaxis administration in outpatient cases [27]. Because of the significance of neutrophil count, Petito *et al*. have even marked it as a more vital predictor of thrombosis than platelet in COVID-19 [28]. Albumin, d-dimer, platelet, and FDP were the other on-admission laboratory parameters that differed between the patients with on-admission events and the controls but not with the second group. However, we have no appropriate scale to decide for thromboprophylaxis in COVID-19. The similarity of these on-admission parameters regardless of the time of event among the cases with thrombosis versus the control group can help provide a comprehensive view in this term.

On the other hand, a hypothesis is ignited that an appropriate cumulative cut-off value for these parameters may appropriately stratify thrombosis risk. It is worth noting that d-dimer and FDP are well-known representatives of coagulopathy and thrombosis [29], and albumin is an acute phase reactant relating to the severity of an inflammatory process [30]. PTE was the most common type of in-hospital thrombotic event, while the other types were more prominent in the latter group. Forty-three cases developed PTE, while only 24 and 11 were under prophylactic and therapeutic doses of anticoagulants, respectively. In addition, most of the cases with in-hospital events had severe courses of the disease. Throm-

boembolism in critically ill patients has been reported in numerous studies [31–33], while Mestre-Gómez *et al*. represented a considerable rate of venous thromboembolic events among non-critical cases [19]. Moreover, the incidence of thromboembolism under anticoagulation has been notified as well; findings that promote the theory about the routine therapeutic anticoagulant therapy among hospital admitted patients in general and severe COVID-19 cases in particular [19, 34].

The evaluation of predictors for premature thromboembolism incidence versus in-hospital events revealed that DVT, AMI, and arterial thrombosis incidence were considerably more probable to occur than PTE. None of the demographic, laboratory and hemodynamic parameters other than oxygen saturation was associated with on-admission events. Decreased oxygen saturation was a predicting factor for in-hospital thromboembolism, which is discussed above as a factor associated with disease severity, mobility, and ICU admission; accounted as risks of thrombosis, particularly PTE.

We observed a significant interval between the day of symptom initiation and thrombosis incidence among those with on-admission versus in-hospital events, reinforcing the logic for routine use of anticoagulant agents in outpatients to prevent further events. Most of the studies regarding anticoagulation in outpatient cases have been conducted on hospital discharged subjects who continued their treatment rather than outpatients [35, 36]. However, promising outcomes have been achieved for those outpatients treated with anticoagulant agents; the etiology has not been well investigated yet. According to IMPROVEDD [37] or other validated scoring systems, some of the researchers believe that thromboembolism risk assessment is required, and only moderate-to-high risk cases should be administered the agents [13]. In contrast, the others claimed that anticoagulation is required for inpatients only [38]. However, according to growing data about the increased risk of thrombotic events, the incidence thereof in mild-to-moderate COVID-19 patients have weighed the theory over the routine use of anticoagulants for outpatients [39].

Conclusion

Based on this study, significant differences were observed in clinical and laboratory parameters between the cases with and without thrombotic events, while the patients with on-admission or in-hospital events were not notably different. PTE development was the most common in hospital, whereas other thromboembolism types were remarkably more frequent among cases with on-admission events. Oxygen saturation was the only predictor of premature thrombosis that was inversely associated with outpatient events. To make a decision for routine anticoagulation for patients with mild-to-moderate COVID-19 infection, further studies are required.

Conflict of interests

None declared.

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Influence of obstructive sleep apnea on right heart structure and function

Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder associated with increased cardiovascular morbidity and mortality. This study aimed to investigate heart structure and function and their correlation with the degree of OSAS and sleep indexes in patients diagnosed with OSAS.

Materials and methods: A cohort of 77patients (48 males, aged 58.1 ± 11.0 years, body mass index [BMI] = 32.4 ± 6.2) admitted to the hospital due to suspected OSAS was examined using echocardiography and polysomnography.

Results: Patients with moderate-to-severe OSAS compared to patients without diagnosed OSAS or with mild OSAS had greater right ventricular outflow tract (RVOT) dimensions (32.6 ± 3.6 vs 30.9 ± 2.4 mm; $p < 0.05$), larger right atrial area (RAA; 21.1 ± 4.8 vs 17.2 ± 3.2 mm; $p = 0.002$), greater right ventricular mid-cavity diameter (RVD; 35.5 ± 7.0 vs 32.2 ± 4.7 mm; $p = 0.02$), and diminished tricuspid annular plane systolic excursion (TAPSE, 21.9 ± 4.5 vs 25.8 ± 4.4 mm; $p = 0.04$), while there were no significant differences in tissue doppler imaging (TDI) parameters (S' and E') and in valvular regurgitation gradient for both groups. Moreover, significantly greater RVOT dimensions (31.6 ± 2.6 vs 30.9 ± 3.0 mm, $p = 0.04$), RVD (39.3 ± 7.0 vs 32.7 ± 5.2 mm, $p = 0.003$), and RAA (21.4 ± 4.4 vs 18.1 ± 4.2 mm, $p = 0.02$) as well as reduction in TAPSE (20.9 ± 5.3 vs 25.0 ± 4.3 mm, $p = 0.01$) were observed in patients having ≥ 10 episodes of obstructive apnea (OA) per hour.

Conclusions: In moderate-to-severe OSAS patients, right ventricular (RV) enlargement was observed together with RV dysfunction as measured by TAPSE. Examination using TDI is not superior to standard echocardiography for the detection of heart pathology in OSAS patients. Right heart pathology is present predominantly in patients with obstructive apnea.

Key words: sleep apnea, CPAP, polysomnography, echocardiography, right ventricle

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Introduction

Obstructive sleep apnea syndrome (OSAS) is the most common type of sleep-related breathing disorder caused by repetitive airway collapse during sleep, affecting approximately 2–10% of the middle-aged global population [1, 2]. It is characterized by daytime sleepiness; however, serious complications such as hypertension, ischemic heart disease, diabetes, and stroke have also been linked to OSAS [3–6]. Moreover, breathing disturbances may alter pulmonary circulation, resulting in the deterioration of right heart function and structure. As current studies emphasize the influence of RV function on outcomes, accurate RV assessment is essential in OSAS patients [7].

Obstructive sleep apnea syndrome has been linked to alterations in cardiac structure, but the pathophysiologic mechanisms between these cardiac abnormalities and OSAS are not completely understood [8]. It is now considered that recurrent hypoxia in OSAS leads to oxidative stress and increased sympathetic tone, consequently raising the levels of circulating inflammatory markers leading to endothelial dysfunction and elevated blood pressure, which eventually promotes blood-clotting disturbances [9]. As chest pressure becomes highly negative during respi-

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ration in OSAS patients, the decreased pressures according to the respiratory cycle have a negative effect on pulmonary and systemic hemodynamics, mainly by increasing afterload [10]. The relationship between OSAS and RV wall thickness as well as right heart dimensions was previously reported; however, analysis of the data has been inconclusive [11].

The aims of this study were (I) to evaluate heart structure and function in patients diagnosed with OSAS; (II) to assess the influence of the degree of OSAS on changes in the structure and function of the right heart, and finally; (III) to assess the correlation between sleep indexes and right heart structure and function.

Materials and methods

Patients

A cohort of 77 consecutive patients admitted to the Department of Diagnostic Medicine due to suspected OSAS was examined using echocardiography and polysomnography. Patients were eligible if they were over 18 years of age and were able to give informed consent. The exclusion criteria were as follows: inability to perform the testing procedures or to self-operate a continuous positive airway pressure (CPAP) device, severe or moderate valvular disease, heart failure of any etiology, diminished ejection fraction (< 50%), congenital heart disease, pulmonary hypertension, history of pulmonary embolism, uncontrolled arterial hypertension, uncontrolled or severe asthma, chronic obstructive pulmonary disease (COPD) or any other pulmonary disease, other untreated or uncontrolled diseases (diabetes mellitus, hypo/hyperthyroidism, renal failure, hepatic failure), patients treated previously with CPAP or any other effective treatment for OSAS. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. All subjects gave their written informed consent to participate in the study (Jagiellonian University Ethics Committee approval number 112.6120.2.2016) (Table 1).

Table 1. Baseline demographic characteristics of the study cohort

	Patients without OSAS and with mild OSAS (n =27)	Patients with moderate and severe OSAS (n = 50)
Age	53.9 ± 11.0	60.3 ± 10.3
Sex		
Male	16 (20%)	32 (42%)
Female	14 (18%)	15 (20%)
BMI [kg/m^2]	29.1 ± 5.3	34.1±6.0
NT-proBNP [pg/ml]	75.1 ± 70.9	98.8±120.3
Hypertension	16 (59%)	41 (82%)
Diabetes mellitus	2 (7%)	15 (30%)
Prediabetes	7 (26%)	12 (24%)
Dyslipidemia	19 (70%)	42 (84%)
Active smoker	3 (11%)	9 (18%)
Prior smoker	12 (44%)	15 (30%)
Hypothyroidism	5 (19%)	12 (24%)
Medication		
ACEi/ARB	9 (33%)	30 (60%)
ß-blockers	7 (26%)	31 (62%)
CCB	5 (19%)	18 (36%)
Insulin	0 (0%)	5 (10%)
Diuretics	8 (29%)	18 (36%)
Statin	10 (37%)	24 (48%)

ACEi — angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; BMI — body-mass index; CCB — calcium channel blockers; NT-proBNP — N-terminal part of the propeptide of BNP; OSAS — obstructive sleep apnea syndrome.
The values for moderate and severe OSAS group do not differ significantly as compared to no and mild OSAS group

Sleep study

The occurrence and severity of daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS). All patients enrolled in this study underwent an overnight sleep study. A standardized recording sleep-monitoring system (Embletta MPR, type III according to American Academy of Sleep Medicine, AASM) was used to perform a nocturnal sleep study in all patients and control subjects. Standard recommendations of sleep scoring criteria were used [12]. Electrocardiography, airflow analysis, and pulse oximetry were performed. Ventilatory flows, at both the nose and mouth, were measured with airflow cannulas. Respiratory movements of the chest and abdomen were monitored using inductive plethysmography belts. Body position was determined using a built-in gyro and position sensor, providing the following position outputs: supine, right, left, prone, or upright. Arterial oxygen saturation (SpO_2) was measured transcutaneously with a finger pulse oximeter.

Respiratory events were scored using the 2012 AASM criteria [13]. Obstructive apnea (OA) was defined as a ≥ 90% reduction in the respi-

ratory airflow amplitude lasting at least 10 seconds. Hypopnea (H) was defined as a 30–89% reduction in the respiratory airflow amplitude lasting at least 10 seconds and accompanied by a decrease of at least 3% in oxygen saturation. Apnea was described as central (CA) in the absence of thoracoabdominal motion. Mixed apnea (MIX) was defined as an event which met apnea criteria and was associated with absent respiratory effort in the initial part of the event, followed by resumption of respiratory effort in the second part of the event. The average number of episodes of apnea and hypopnea per hour was defined as the apnea-hypopnea index (AHI). Obstructive sleep apnea syndrome was defined as an AHI of > 5 per hour, when clinical symptoms were present. Desaturation was defined as a decrease in the SpO_2 of 3% or more from baseline, and oxygen desaturation index (ODI) was calculated as the total number of desaturation episodes per hour. Subjects were classified into 4 groups according to AHI: patients without OSAS (AHI < 5/h), patients with mild OSAS (AHI 5–14/h), patients with moderate OSAS (AHI 15–29/h), and patients with severe OSAS (AHI ≥ 30/h).

Echocardiography

All patients underwent transthoracic echocardiography using a Philips IE33 device (transducer X5-1; 1.3 to 4.2 MHz). Two-dimensional (2-D) echocardiographic imaging in standard views was conducted, including conventional 2-D, Doppler, Color-Doppler and Tissue Doppler imaging (TDI). Examinations were performed in the left lateral decubitus and supine positions. Echocardiograms were recorded from standard parasternal, suprasternal, subcostal, and apical images. The RV and right atrial (RA) parameters were measured from the right ventricular-focused 4-chamber view. Tissue Doppler imaging was performed from the apical 4-chamber view with the pulse wave directed towards the lateral tricuspid annulus, aligned parallel to the motion of the free lateral wall towards the apex. Assessment of TDI parameters included peak systolic (S') tricuspid annular velocity and peak early (E') diastolic tricuspid annular velocity. The same position was used to assess tricuspid annular plane systolic excursion (TAPSE). Tricuspid valve flow pattern was obtained, determining the regurgitant flow velocity [14]. All echocardiographic measurements were obtained by an observer blinded to sleep test data and other patient characteristics (Figure 1).

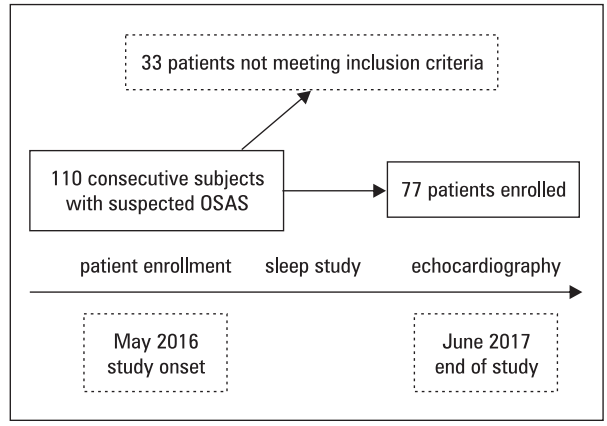

Figure 1. Flow-chart of the study design.

Statistical analysis

The Shapiro-Wilk test was used to determine if variables were normally distributed. Continuous variables are presented as means and standard deviations. The Student's t-test for continuous variables was performed to assess for differences between the groups. Chi-square test was used to examine differences in proportion. The accepted statistical significance threshold was established as a p-value of < 0.05.

Results

Patient characteristics

The group consisted of more males (48 patients, 62%) than females and the mean age was 58.1 ± 11.0 years. The average body-mass index (BMI) was 32.4 ± 6.2. Among the patients, 57 (74%) had hypertension, 17 (22%) had diabetes mellitus type 2, 19 (25%) had prediabetes, 61 (79%) had hypercholesterolemia, 5 (6%) had a history of deep vein thrombosis, and 7 (9%) had superficial venous thrombosis in the past. Asthma was present in 5 (6%) patients, while 12 (16%) patients were active smokers and 27 (35%) were ex-smokers. The following were the most frequently used drugs in the study group: beta-blockers in 38 (49%) patients, statins in 34 (44%) patients, ACE-inhibitors in 23 (30%) patients, ARBs in 16 (21%) patients, and diuretics in 26 (34%) patients. Baseline demographic data for moderate and severe OSAS group did not differ significantly as compared to no and mild OSAS group.

Sleep study

After an overnight complete sleep study, comprising at least 4 hours of sleep, 50 patients were classified as having moderate-to-se-

Table 2. Sleep study results

	Patients without OSAS and with mild OSAS (n = 27)	Patients with moderate and severe OSAS (n = 50)	P-value
ESS	7.5 ± 4.2	9.3 ± 6	ns
AHI (h^{-1})	9 ± 3.5	37.4 ± 19.2	< 0.0001
OA (h^{-1})	2 ± 1.9	17.1 ± 17.7	< 0.0001
CA (h^{-1})	0.5 ± 0.7	1.3 ± 2.6	0.03
MIX (h^{-1})	0.1 ± 0.2	3.4 ± 6.3	0.03
H (h^{-1})	6.5 ± 2.9	15.8 ± 8.5	< 0.0001
SpO_2 (%)	93.5 ± 18	90.7 ± 3.7	0.0004
ODI (h^{-1})	9 ± 4	38.8 ± 3.3	< 0.0001
Advised CPAP treatment	0	38	

ESS — Epworth Sleepiness Scale score; AHI — apnea-hypopnea index; OA — obstructive apnea; CA — central apnea; MIX — mixed apnea; H — hypopnea; mean SpO_2 — mean blood oxygen saturation; ODI — oxygen desaturation index; CPAP — continuous positive airway pressure; OSAS — obstructive sleep apnea syndrome

vere OSAS (AHI ≥ 15/h), while the other 27 patients were classified as having mild or no OSAS (AHI < 15/h) and served as control subjects. Sleep study variables acquired from both groups are shown in Table 2.

Association between OSAS and echocardiographic evaluation

The general quality of echocardiographic images was high (Table 3). All individuals had normal left ventricular (LV) systolic function. Furthermore, the patients did not have significant valvular heart disease, according to the exclusion criteria. Mild mitral regurgitation was present in 63 (81%) patients, mild tricuspid regurgitation was present in 59 (77%) patients, 3 (4%) patients had moderate tricuspid regurgitation, 2 (3%) patients had moderate mitral regurgitation, while mild aortic regurgitation was present in 1 (1%) patient. Additionally, transvalvular gradients measured across the aortic, mitral, tricuspid, and pulmonary valves were within the normal range (Table 4).

Patients with a diagnosis of moderate-to-severe OSAS had greater RVOT dimensions when compared to patients without diagnosed OSAS or patients with mild OSAS. A similar relationship between the examined groups was demonstrated regarding the RAA and RVD dimensions. The analysis of RV systolic function revealed a significant difference in the mean TAPSE, with moderate-to-severe OSAS patients having a decreased TAPSE There were no significant differences in TDI parameters (S' and E') when comparing moderate-to-severe OSAS patients to mild OSAS patients or those without OSAS. Similarly, between the two groups there was no significant difference in valvular regurgitation gradient (Table 5).

Table 3. Echocardiographic image quality in obstructive sleep apnea syndrome (OSAS) patients

	Patients with optimal image quality, n (%)
RVOT	75 (97%)
RVD	70 (91%)
RAA	72 (94%)
S'	73 (95%)
E'	73 (95%)
TAPSE	76 (99%)
TRPG	64 (83%)

E' — peak early diastolic tricuspid annular velocity; RAA — right atrial area; RVD — right ventricular diameter; RVOT — right ventricular outflow tract; S' — peak early systolic tricuspid annular velocity; TAPSE — tricuspid annular plane systolic excursion; TRPG — tricuspid regurgitant peak gradient

In order to examine the impact of OSAS on cardiac function, the association between sleep study variables and several echocardiographic parameters as measured by 2-D, M-mode, and TDI were analyzed. A statistically significant difference in RVOT dimension was demonstrated for patients with severe OSAS (AHI ≥ 30/h), indicating RV enlargement. Significantly greater RVOT dimensions, RVD, and RAA were observed in patients with ≥ 10 OA episodes per hour, while no significant differences in these parameters were observed depending on the degree of CA and H. Interestingly, the occurrence of at least 1 MIX episode during sleep was associated with a lower

Table 4. Echocardiographic parameters

	No OSAS or mild OSAS (n = 27)	Moderate-to-severe OSAS (n = 50)	P-value
LVEF [%]	63.7 ± 3.0	63.2 ± 3.8	ns
RVOT [mm]	30.9 ± 2.4	32.6 ± 3.6	0.05
RVD [mm]	32.2 ± 4.7	36.5 ± 7.0	0.02
RAA [cm^2]	17.2 ± 3.2	21.1 ± 4.8	0.002
S'[cm/s]	13.9 ± 2.7	15.0 ± 3.7	ns
E' [cm/s]	10.6 ± 2.5	11.0 ± 3.1	ns
TAPSE [mm]	25.8 ± 4.4	21.9 ± 4.5	0.004
TRPG [mm Hg]	21.2 ± 6.9	23.5 ± 5.7	ns

LVEF — left ventricular ejection fraction; RVOT — right ventricular outflow tract; RVD — right ventricular diameter; RAA — right atrial area; S' — peak early systolic tricuspid annular velocity; E' — peak early diastolic tricuspid annular velocity; OSAS — obstructive sleep apnea syndrome; TAPSE — tricuspid annular plane systolic excursion; TRPG — tricuspid regurgitant peak gradient

Table 5. OSAS severity and echocardiographic results

	RVOT	RVD	RAA	TAPSE
AHI < 30 (h^{-1})	31.2 ± 3.2	33.2 ± 5.8	18.5 ± 4.5	24.7 ± 4.4
AHI ≥ 30 (h^{-1})	33.5 ± 1.8	38.1 ± 6.8	20.6 ± 3.9	20.7 ± 5.7
P-value	0.05	ns	ns	0.02
OA < 10 (h^{-1})	30.9 ± 3.0	32.7 ± 5.2	18.1 ± 4.2	25.0 ± 4.3
OA ≥ 10 (h^{-1})	31.6 ± 2.6	39.3 ± 7.0	21.4 ± 4.4	20.9 ± 5.3
P-value	0.04	0.003	0.02	0.01
CA < 1 (h^{-1})	31.3 ± 2.8	34.2 ± 5.4	18.6 ± 3.8	24.2 ± 4.9
CA ≥ 1 (h^{-1})	32.4 ± 4.0	33.9 ± 8.4	19.8 ± 6.0	24.2 ± 4.9
P-value e	ns	ns	ns	ns
MIX < 1 (h^{-1})	31.2 ± 3.2	33.6 ± 5.9	18.4 ± 4.5	24.7 ± 4.4
MIX ≥ 1 (h^{-1})	33.1 ± 2.3	36.5 ± 7.0	21.0 ± 4.0	21.1 ± 5.7
P-value	ns	ns	ns	0.03
H < 15 (h^{-1})	31.2 ± 3.0	33.8 ± 6.5	18.7 ± 4.7	23.9 ± 5.1
H ≥ 15 (h^{-1})	33.5 ± 3.1	35.7 ± 4.5	20.1 ± 2.9	24.2 ± 4.0
P-value	ns	ns	ns	ns
SpO_2 < 95%	32.0 ± 3.0	34.8 ± 6.0	19.5 ± 4.7	23.7 ± 5.2
SpO_2 ≥ 95%	29.9 ± 3.3	31.8 ± 6.7	16.2 ± 1.7	25.1 ± 3.4
P-value	ns	ns	0.05	ns

AHI — apnea-hypopnea index; OA — obstructive apnea; CA — central apnea; MIX — mixed apnea; H — hypopnea; OSAS — obstructive sleep apnea syndrome; SpO_2 — mean blood oxygen saturation; RVOT — right ventricular outflow tract; RVD — right ventricular diameter; RAA — right atrial area; TAPSE — tricuspid annular plane systolic excursion

TAPSE. Moreover, patients with mean saturation levels < 95% during the overnight sleep study had a significantly larger RAA.

Discussion

The main finding of our study was the presence of RV enlargement and dysfunction in OSAS patients, which was diagnosed by standard 2-D echocardiography with M-mode function. We evaluated patients with various stages of OSAS who had symptoms of daytime sleepiness, but not having other significant cardiac or pulmonary diseases, or other comorbidities affecting the pulmonary circulation.

Analysis of individual parameters from the sleep study revealed a significant relationship between OA and right heart structure remodeling, and a reduction in longitudinal RV systolic function presented as TAPSE. This suggests the potential influence of OA episodes on the morphology and function of right heart structure. In

contrast, no difference between the frequency of H and CA in both groups suggests that these types of disorders have no significant correlation with the severity of OSAS and its effects on heart structure. This has been confirmed by several studies, which showed that OA may lead to more severe SpO_2 desaturation when compared to hypopneic episodes [15, 16]. It has been argued that because apneic episodes arise as the result of complete upper airway collapse, they may have a more serious pathophysiologic impact than hypopneas, which are a consequence of partial upper airway collapse. Indeed, apneas should be regarded as more significant than hypopneas when assessing the severity of OSAS and its related impact on long-term cardiac risk.

Numerous studies evaluating right heart structure and function, based on echocardiographic measurements, showed significant changes in both RV morphology and efficiency in OSAS patients [17]. It has recently been demonstrated, that 3-dimensional (3D) echocardiography and speckle tracking echocardiography revealed lower 3D RV ejection fraction and global RV strain in patients with moderate and severe OSAS compared with controls [18]. This is in complete agreement with Shivalkar *et al.* [19], who found that among 43 patients with severe OSAS there was RV dilatation. Contrary to results reported in our study, they also showed reduced TDI systolic and diastolic velocities in the left and right ventricles. However, several researchers did not demonstrate any differences in RV structure and function, while conventional echocardiography remained the main method of evaluation [20, 21].

Karamanzanis *et al.* [1] described the correlation between OSAS severity and the degree of RV systolic dysfunction, which was reflected in TAPSE values. Similar conclusions can be drawn from a study by Tugcu *et al.* [22], which evaluated newly diagnosed OSAS patients. The most commonly used parameter in the quantification of RV function is TAPSE, owing to its ease of interpretation and the fact that the tracing can be acquired quickly [23]. Assessment of TAPSE is based on a one-dimensional measurement, and therefore, represents only a part of global RV function. However, this may represent the majority of total RV function, because longitudinal contraction accounts for up to 80% of shortening of the chamber. Anatomically, this can be explained by the arrangement of muscle fibers, which run mostly longitudinally and obliquely. A potential disadvantage of TAPSE is the fact that it is angle- and load- dependent. In addition, there remains controversy regarding cut-off values and prognostic value in the prediction of cardiovascular events [24].

On the other hand, TAPSE is a reliable echocardiographic tool as it correlates well with RV ejection fraction as determined by radionuclide angiography or cardiac magnetic resonance (CMR) [25]. The other advantage of TAPSE, which is confirmed by our study, is the possibly of being derived in the vast majority of patients, regardless of difficulties in acquiring high-quality images of the entire RV free wall. Furthermore, TAPSE is considered to have strong predictive power in various diseases. For example, it is associated with a lower cardiac index and worse survival in patients with several diseases. However, there is a lack of long-term studies examining the impact of this parameter in OSAS patients [26, 27]. Despite its simplicity and some limitations mentioned above, our study shows that TAPSE links sleep study variables to RV systolic function disturbances and appears to confirm the effect of OSAS on RV function.

In contrast, Gulay *et al.* [28] did not detect a significant correlation between TAPSE and polysomnographic variables when studying a group of 60 OSAS patients, although the mean AHI (24.5/h; 6–98) in this study was lower than our observed values. Similarly, Hammerstingl *et al.* [29] observed in a group of 82 patients that RV functional parameters such as TAPSE and RV-MPI were not significantly decreased in patients with increased AHI at baseline and after 6 months of CPAP treatment.

Other echocardiographic techniques frequently used for assessing RV function include the measurement of myocardial strain by two-dimensional speckle tracking echocardiography (STE) and fractional area change (FAC). Strain evaluation requires specialized software. In addition, RV STE assessment should take into account the differences resulting from the various myocardial tracking algorithms used by software producers [30]. On the other hand, conventional measures of RV longitudinal contractility, such as TAPSE or TDI derived S', reflect RV basal function, whereas RV strain and FAC account for a greater area of RV free wall deformation and are not prone to the errors that can occur due to translational motion. However, both of these techniques require good visibility of endocardial borders and may constitute a challenge in the assessment of RV function in patients with OSAS, especially in those who are obese.

Surprisingly, our study showed no significant difference in the assessment of TDI parameters. Similarly, the components of TDI evaluation are susceptible to comparable limitations as those of TAPSE. By analogy, S' measures only a small region of the RV and it cannot be used in patients with regional wall-motion abnormalities. Moreover, it is not dependent on the presence of optimal image quality. S' belongs to the most common parameters describing RV functionality, although there exists much controversy in the literature related to its utility in OSAS patients. Altekin *et al.* [31] assessed the relationship between AHI and RV function, expressed as S'. In their study, which included a similar group of 79 patients with various stages of OSAS, no correlation was found between those parameters. Similarly, in a study conducted by Zhou *et al.* [32], assessment of S' revealed no significant difference between healthy subjects and patients with OSAS. On the other hand, they observed regional RV systolic dysfunction and a diminished inflow EF and global EF as measured by real-time 3-D **echocardiography** in moderate and severe OSAS patients. Additionally, Kepez *et al.* [33] did not show a difference in S' values, but they noted that the regional pattern of RV dysfunction correlated with the severity of OSAS, when assessed with strain analysis.

Our study has some limitations. No other measurement of right heart structures was attempted. It should be remembered that CMR imaging is a reference standard for the assessment of cardiac function and structure. However, echocardiographic techniques do have some advantages over CMR, including wider availability, lower cost, less patient distress related to claustrophobia, and the ability to examine patients with contraindications to CMR, such as those with implanted pacemakers or defibrillators. Moreover, our study population was relatively small but proportional to comparable studies performed in OSAS patients.

Conclusions

In summary, RV enlargement along with RV dysfunction, as measured by TAPSE, was observed in moderate-to-severe OSAS patients. Examination with TDI is not superior to standard echocardiography in the detection of heart pathology in OSAS patients. Right heart pathology is present predominantly in patients with obstructive apnea. Further prospective studies using echocardiography are needed to demonstrate the impact of observed changes on the long-term prognosis of OSAS patients.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

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Prediction of three-month readmission based on haematological parameters in patients with severe COPD exacerbation

Abstract

Introduction: Approximately one-third of patients hospitalised for an exacerbation of chronic obstructive pulmonary disease (COPD) are readmitted to the hospital within 90 days. It is of interest to identify biomarkers that predict relapse in order to prevent readmission in these patients. In our prospective study of patients admitted for COPD exacerbation, we aimed to analyse whether routine haematological parameters can help predict the three-month readmission risk.

Material and methods: 106 patients were included, of whom 23 were female (22%). The age (mean ± SD) was 73 ± 10 years, and the forced expiratory volume in 1 second (FEV_1) was 44 ± 15%. The haematological parameters were obtained from the first blood test result during admission. The variables were as follows: red cell distribution width, mean platelet volume (MPV), platelet (PLT) count, neutrophil to lymphocyte ratio, PLT to lymphocyte ratio, MPV to PLT ratio, and eosinophil count. Patients were differentiated into two groups for each haematological parameter according to median value, and the percentage of readmissions in each of the groups was recorded.

Results: Twenty-five patients (24%) were readmitted to hospital within three months of discharge. Only the difference in low-MPV and high-MPV patients was significant (37% *vs* 10%, $p = 0.001$). The predictive capacity for three-month readmission measured by the area under the curve (AUC) did not show clinically applicable values; the best result was for MPV (AUC 0.64). In the remaining values, the AUC was between 0.52 and 0.55.

Conclusion: Routine haematological parameters proposed as prognostic biomarkers in COPD obtained at the moment of hospital admission were not useful for predicting three-month readmission.

Key words: biomarkers, COPD, prognosis, readmission

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Introduction

Severe exacerbations of chronic obstructive pulmonary disease (COPD), defined as those leading to hospitalization, are associated with high mortality, a negative impact on the quality of life, and a significant burden on the healthcare system [1]. Importantly, between 12–45% of patients hospitalised for exacerbations of COPD are readmitted to the hospital within 90 days [2, 3]. If patients at an increased risk can be detected, a personally tailored post-discharge plan may potentially reduce readmissions [4]. Consequently, it is of interest to identify biomarkers in order to prevent readmission of these patients [2]. However, although COPD exacerbation prediction tools have been proposed [5], no clear consensus exists on markers that can predict readmission [3].

A small number of studies, mainly retrospective, have evaluated the role of routine haematological parameters in different circumstances as prognostic biomarkers in COPD patients (including the prediction of the risk of readmission) with sometimes contradictory results. These easily accessible and inexpensive tests include: red blood cell distribution width (RDW), mean platelet volume (MPV), platelet (PLT) count, neutrophil to lymphocyte ratio, the PLT to lymphocyte ratio, the MPV to PLT ratio, and the number of eosinophils [6–11].

In a prospective study of patients admitted for COPD exacerbations, we aimed to analyse

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Table 1. Percentage of three-month readmission with haematological parameters

Parameter	Median value	Low	High	P-value
Red cell distribution width [%]	15.5	18%	31%	0.103
Mean platelet volume [fL]	9.0	37%	10%	0.001
Platelets [$\times 10^9$/L]	226	25%	23%	0.95
Neutrophil to lymphocyte ratio	8.56	28%	21%	0.87
Platelet to lymphocyte ratio	0.21	26%	22%	0.97
MPV to platelet ratio	38.4	24%	25%	0.99
Eosinophils [cells/μL]	120	25%	23%	0.95

Low: Below or equal to median value. High: Above the median value

whether routine haematological parameters obtained at the time of admission can help to predict three-month readmission.

Material and methods

The study was approved by the local ethics committee and the patients signed an informed consent form (reference PI 31/2019). Our study initially included 115 consecutive patients admitted because of exacerbation of COPD in a respiratory ward of a university hospital over a 14-month period. Only the first episode was taken into consideration if more than one occurred for the same patient. Nine patients were excluded; six because of death, two because no follow-up was available, and one due to leukaemia. 106 patients completed the three-month follow-up since discharge and were included in the study. Of these participants, 23 were female (22%) and 83 were male (78%). The average age (mean ± SD) was 73 ± 10 years, and the forced expiratory volume in 1 second (FEV_1) was 44 ± 15% of predicted value. Of those patients, 63 (59%) had at least one admission in the previous year. The haematological parameters were obtained from the first blood test during admission, as per clinical practice. Blood analysis was performed in the centralized laboratory with the analyser model Vitros 5600 (Ortho Clinical Diagnostics, Raritan, NJ, USA). The variables included for evaluation were as follows: RDW, MPV, platelet (PLT) count, neutrophil to lymphocyte ratio, PLT to lymphocyte ratio, MPV to PLT ratio, and eosinophil count. Patients were differentiated into two groups for each haematological parameter: those with low values (below or equal to the median) and those with high values (above the median of the parameter). The percentage of three-month readmissions in each of the groups was recorded.

A chi-squared test was performed to compare categorical variables, and a Mann–Whitney U test was used to compare quantitative variables. The discriminating performance of the parameters was evaluated using receiver operating characteristic (ROC) curves with corresponding areas under the curve (AUC). Statistical analysis was performed using the programs SPSS version 22 (IBM Corp., Armonk, NY, EEUU) and the R statistics package (*www.r-project.org*). A p-value below 0.05 was considered statistically significant.

Results

Twenty-five of the 106 patients (24%) were readmitted to hospital within three months of discharge for a new COPD exacerbation. Readmissions occurred in a median of 41 days (interquartile range [IR], 20–68 days). Of these 25 patients, 22 (88%) had at least one admission in the previous year. Of the remaining (non-readmitted) 81 patients, 41 (51%) had been admitted in the previous year ($p < 0.001$). Compared with those not requiring readmission, patients with readmission had a higher number of admissions in the previous year (median, IR: 3.0 [1.0–4.3] *vs* 0.0 [0.0–2.0, $p < 0.001$) and lower FEV_1 in terms of percentage of predicted value (36% [29–48] *vs* 45% [34–55], $p = 0.048$). There were no significant differences in age, gender, or duration of admission.

The percentage of patients who were readmitted in the first three months after discharge was calculated for each haematological parameter. As shown in Table 1, only the difference in low-MPV and high-MPV patients was significant. The predictive capacity for three-month readmission of each parameter measured by the AUC did not show clinically applicable values; the best result was for MPV (AUC 0.64, Figure 1).

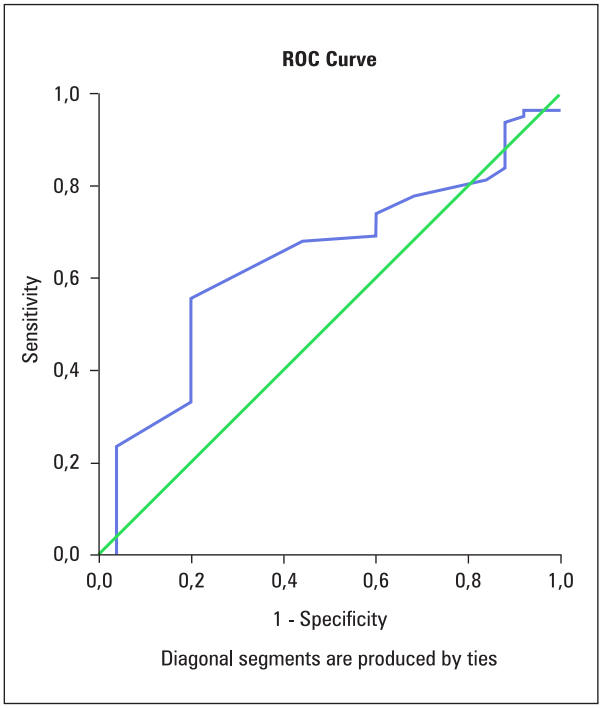

Figure 1. Area under the curve for predicting three-month readmission with mean platelet volume

In the remaining values, the AUC was between 0.52 and 0.55.

Discussion

Numerous parameters of routine blood tests are considered to be underlying biomarkers of inflammation and potentially useful in establishing a prognosis in patients with COPD [12]. These tests have the advantage of being inexpensive and immediately available for clinicians. Therefore, the potential contribution of their possible clinical application is of great interest. In retrospective studies, RDW was an independent risk factor for readmission [6]. MPV, although less frequently evaluated, has shown inconclusive results [7]. The neutrophil to lymphocyte ratio and the PLT to lymphocyte ratio are both elevated in stable COPD patients, and their values further increased during exacerbations [9, 10]. These ratios have been identified as being able to predict COPD progression and outcomes such as hospital mortality [9, 10]. Eosinophil counts have been proposed as being predictors of the one-year risk of hospitalisation [11]. Consequently, we considered it necessary to study the possibility that these parameters would offer prognostic information in patients admitted for acute COPD. Theoretically, the values of these indices obtained in a blood test at the time of admission could indicate the risk of readmission in the three months after discharge and thus, enable specific therapeutic plans.

Unfortunately, in our prospective study of consecutive COPD patients, we have not been able to confirm any of the promising results of these parameters obtained at the moment of hospital admission. Only MPV showed significant differences between patients with and without readmission. However, in view of the AUC results, its values do not allow for its application in individual cases. MPV is a component of routine blood analysis that correlates highly with platelet activation and is linked to the pathophysiology of the inflammatory process during COPD exacerbations [7]. In fact, previous studies have shown that MPV may represent an inflammatory marker for multiple conditions such as vascular diseases, rheumatoid diseases, and diabetes mellitus [7]. Platelet distribution width (PDW) is an additional parameter with prognostic value, but was not available in our study [13]. In our series, as described in other studies [2], hospitalisation in the year prior to index admission was the key predictor of COPD-related readmission. Although conducted prospectively and applied in a real clinical setting, our work has the limitation of having been conducted in a single centre, so the results should be confirmed in other series. An additional limitation of this study is the absence of a definition of the probable causes of exacerbation (infectious *vs* non-infectious). This data could have allowed an analysis according to the cause of admission and would perhaps have detected subgroups in which biomarker analysis could be more useful. New research continues to be undertaken on biomarkers and factors that can help clinicians predict subsequent exacerbations of COPD.

Conclusions

The routine haematological parameters proposed as prognostic biomarkers in COPD, when obtained at the moment of hospital admission, were not useful for predicting three-month readmission.

Conflict of interest

Authors have no conflict of interest to declare.

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Progressive fibrosis in interstitial lung diseases — proposed definition and management

Abstract

Interstitial lung diseases may have an unpredictably progressive course, which is manifested as progression of pulmonary fibrosis, causing an increasing impairment of lung function affecting a poor prognosis. The possibility of an effective antifibrotic treatment is a chance for patients to slow down the progression of the disease, perhaps even extend their life. For this reason, standardization of the definition as well as identification criteria for progressive fibrosis interstitial lung disease is a method for optimizing the management in this group of patients.

Key words: interstitial lung disease, progressive fibrosis, antifibrotic treatment

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Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases differing in aetiopathogenesis, clinical course and prognosis [1]. The common characteristic of some of them is the possible progressive nature of lesions that leads to advanced fibrosis that is not amenable (at a certain stage) to anti-inflammatory or immunomodulating causative treatment [2]. A classic example of progressive fibrosing interstitial lung disease (PF-ILD) is idiopathic pulmonary fibrosis (IPF). IPF is a disease of unknown aetiology (despite identification of potential risk factors) with lesions that have a morphology of usual interstitial pneumonia (UIP), which is diagnosed by ruling out other causes of the observed lesions [3, 4].

IPF has an unpredictably progressive course, which is manifested as progression of pulmonary fibrosis, causing an increasing impairment of lung function and inevitably leading to death [3–6]. The natural course of the disease is associated with a median survival (3–5 years) shorter than in the course of many types of cancer [7, 8]. Progressive pulmonary fibrosis is a characteristic encountered also in the course of other ILDs. It affects patients with hypersensitivity pneumonitis (HP), interstitial lung lesions associated with connective tissue diseases (CTD; in particular diffuse systemic sclerosis, rheumatoid arthritis, systemic myositis and other), idiopathic non-specific interstitial pneumonia (NSIP), sarcoidosis or unclassifiable idiopathic interstitial pneumonia (uILD). As demonstrated by studies in the recent years, identification of the PF-ILD phenotype and adequate therapeutic management may improve the prognosis in this patient group [9, 10].

Definition of PF-ILD

An initial attempt at defining PF-ILD with specification of its diagnostic criteria was made at the stage of clinical trials to select patients for conducting an assessment of the effect of antifibrotic treatment [9–11]. On the basis of those experiences, an international expert panel published proposed recommendations for both identification and management of patients with this phenotype of interstitial pulmonary fibrosis [2].

Until 2019, the usefulness of the antifibrotic effect in non-IPF interstitial disorders leading

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to pulmonary fibrosis was only a hypothesis (presumption) [12, 13]. Numerous trials are now ongoing, but in some of the completed ones evidence was obtained that nintedanib can effectively slow down the progression of interstitial lesions in patients with systemic sclerosis (the SENSCIS trial) as well as with other ILDs where disease progression was observed despite the existing treatment (the INBUILD trial) [9, 10]. Different eligibility criteria for patients with progressive interstitial pulmonary fibrosis were adopted in clinical trials investigating the efficacy of antifibrotic treatment. At the current stage, on the basis of the evidence that already exists, it is considered that progressive fibrosis associated with an interstitial lung disease is a situation (phenotype) in which pulmonary lesions still progress despite conventional treatment. The definition of PF-ILD should take into account the combination of aggravating lesions in the radiological image (CT), decline of lung function and clinical symptoms experienced by the patient. The role of a multidisciplinary team is emphasised – both at the stage of diagnostic work-up, determining the proper, precise diagnosis of ILD and assessment of disease progression or the lack of efficacy of the first-line treatment used, dedicated to the given diagnosis. In the case of non-IPF PF-ILD, the antifibrotic therapy should be a type of second-line treatment when progression of fibrosis is evidenced despite the use of conventional treatment [2].

The diagnosis of PF-ILD requires confirmation of disease progression during the previous 24 months of follow-up, occurring despite the use of adequate therapy. However, it worth to point out that the observation period for the PF-ILD diagnosis is not established and in clinical trials the adopted observation time was different (6–24 months).

Disease progression was defined as meeting one of the following criteria:

1. ↓ forced vital capacity (FVC) by ≥ 10% of the predicted value or
2. ↓ FVC by ≥ 5% of the predicted value with ↓lung transfer factor for carbon monoxide (TLCO) by ≥15% of the predicted value, or
3. ↓ FVC by ≥ 5% of the predicted value with ↑ respiratory symptoms, or
4. ↓ FVC by ≥ 5% of the predicted value with ↑ extent of fibrosis in high resolution computed tomography (HRCT), or
5. Severe respiratory symptoms and ↑ extent of fibrosis in HRCT [2].

Scale of the problem

The question of how many patients in clinical practice have the progressive fibrosing phenotype preoccupies the researchers concerned with this issue.

The incidence of PF-ILD is an estimate based on retrospective analyses of groups of patients with interstitial pulmonary lesions with such a course of the disease. The disease outcomes vary, which is not surprising in view of different criteria of group selection and different criteria of assessment of fibrosis progression [14–17].

In an extensive international questionnaire survey with participation of 486 specialists (243 pulmonologists, 203 rheumatologists and 40 internists), the estimated prevalence of PF-ILD was 18–32% of patients diagnosed with ILD [18]. On the basis of the obtained data, 25–50% of patients with evidence of PF-ILD do not receive pharmacological treatment and the time from symptoms onset to death was assessed as 61–80 months [18]. Failure to initiate a therapeutic intervention was explained by different issues arising from disease advancement (both mild and too severe course), intolerance of medicines and also the lack of an effective treatment [18].

In a recently published review of literature concerning this issue, the prevalence of PF-ILD was estimated as 2.2–20.0 per 100,000 in Europe and 28.0 per 100,000 in the USA, with an estimated percentage of 13–40% of ILDs cases [19].

The clinical course — the rate of decline in pulmonary function — in non-IPF PF-ILDs is similar to that of IPF, which indicates an adverse prognosis in this patient group [20]. In the INBUILD study in patients with PF-ILD with pulmonary lesions of the UIP pattern, the rate of deaths in the placebo arm was identical to that found in patients with IPF in the placebo arm in the INPULSIS studies (7.8% in a one-year follow-up) [20].

The key issue, noted on many occasions, is the lack of the generally adopted (diagnostic and therapeutic) management standard in PF-ILD patients.

Efficacy of treatment of non-IPF PF-ILD with antifibrotic agents

In randomised placebo-controlled clinical trials, nintedanib (TOMMOROW, INPULSIS-1, INPULSIS-2) and pirfenidone (CAPACITY-004, CAPACITY-006, ASCEND) were found to effectively and significantly reduce the decline in

FVC, which translates into slowing down the IPF progression [21–24]. Both medicines have been approved for the treatment of IPF, and the positive effects obtained in clinical practice, along with the trends towards prolonged survival in the treated patients with an acceptable treatment tolerability, prompted further studies in indications extended to other interstitial diseases associated with fibrosis [25–29].

So far, on the basis of the existing results of clinical trials, only nintedanib obtained an extension of its approved indications by the treatment of patients with systemic sclerosis-associated ILD (the SENSCIS study) and patients with other non-IPF interstitial lung diseases with progressive pulmonary fibrosis in their course (the INBUILD study) [9, 10].

Nintedanib is an oral tyrosine kinase inhibitor with a multitarget mechanism of action that involves inhibition of vascular endothelial growth factor receptors (VEGFR 1–3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptor (FGFR 1–3), which participate in the pathogenic process of fibrosis [21].

As demonstrated by post-hoc analyses of databases of marketing authorisation and post-marketing studies investigating nintedanib in IPF patients, the beneficial treatment effect is maintained in the long term, occurs regardless of disease advancement, and contributes to a reduction of the risk of sudden exacerbations and probably to extended survival of patients [25, 26, 30–35]. By analogy, similar effects against other PF-ILDs were expected.

Another antifibrotic agent — pirfenidon is also investigated in non-IPF ILDs, but so far is not registered for treatment in this indication [11].

Efficacy of nintedanib treatment of ILD associated with systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a rare multiorgan autoimmune disease. It is characterised by blood vessels injury, the presence of autoantibodies and progressive fibrosis of the skin and internal organs. The clinical course may vary. It depends on the rate of development of organ complications in the individual patients [36]. Lung involvement, which unfortunately occurs in most patients, has a significant impact on the prognosis. Pulmonary fibrosis and pulmonary hypertension are the main causes of deaths related to disease progression [37]. Unfortunately, the existing anti-inflammatory and immunomodulating treatment is sometimes toxic and is not sufficiently effective — it does not stop over a long term the progression of interstitial lesions in the lungs [38–40].

In the randomised double-blind placebo-controlled SENSCIS study including a group of 576 SSc patients, nintedanib treatment (during a 52-week follow-up) was found to significantly reduce the rate of decline in pulmonary function [10]. Unfortunately, it was not found to have a beneficial effect on the skin lesions whose improvement was assessed as a secondary objective. Although in INPULSIS studies the decline in pulmonary function in the group that received placebo was more than a half lower than in the group of IPF patients treated with nintedanib (–93.3 mL *vs* –223 mL), the relative effect on the reduction of FVC decline was similar (–44% *vs* 49%, respectively). The absolute (numerical) difference in FVC decline may seem small (41 mL in favour of the nintedanib group) but it should also be considered that immunosuppressive treatment was allowed in the study group and almost a half of the patients received mycophenolate mofetil (MMF). An annual difference in FVC decline was visible in the placebo group that received MMF or not (–66.5 mL *vs* –119.3 mL) [10].

Antifibrotic treatment gave hope to SSc patients for slowing down the progression of ILD [41].

Efficacy of nintedanib treatment of ILD associated with non-IPF PF-ILD

Another double-blind placebo-controlled phase 3 study abbreviated as INBUILD included 663 patients at 15 sites around the world, with different non-IPF ILDs (including also SSc) who have developed progressive pulmonary fibrosis [9].

The inclusion criteria for the study became the basis for establishing the proposed PF-ILD definition [2]. The predominant basic diagnosis was HP, followed by autoimmune diseases, idiopathic NSIP, uIIP, and other ILDs (e.g. sarcoidosis). Also in this case a significant benefit for patients treated with nintedanib was demonstrated, in the form of a reduced FVC decline in a 52-week follow-up (–80.8 mL *vs* –187.8 mL in the placebo group). The inter-group difference was 107 mL/year (95% confidence interval [CI], 65.4–148.5; $p < 0.001$). For patients with the HRCT pattern of pulmonary lesions consistent with UIP, the difference was even larger than in the overall population and was 128.2 ml (95% CI, 70.8–185.6; $p < 0.001$) [9]. As demonstrated in a further analysis, regardless of the diagnosis, i.e. regardless of whether a patient with CTD-as-

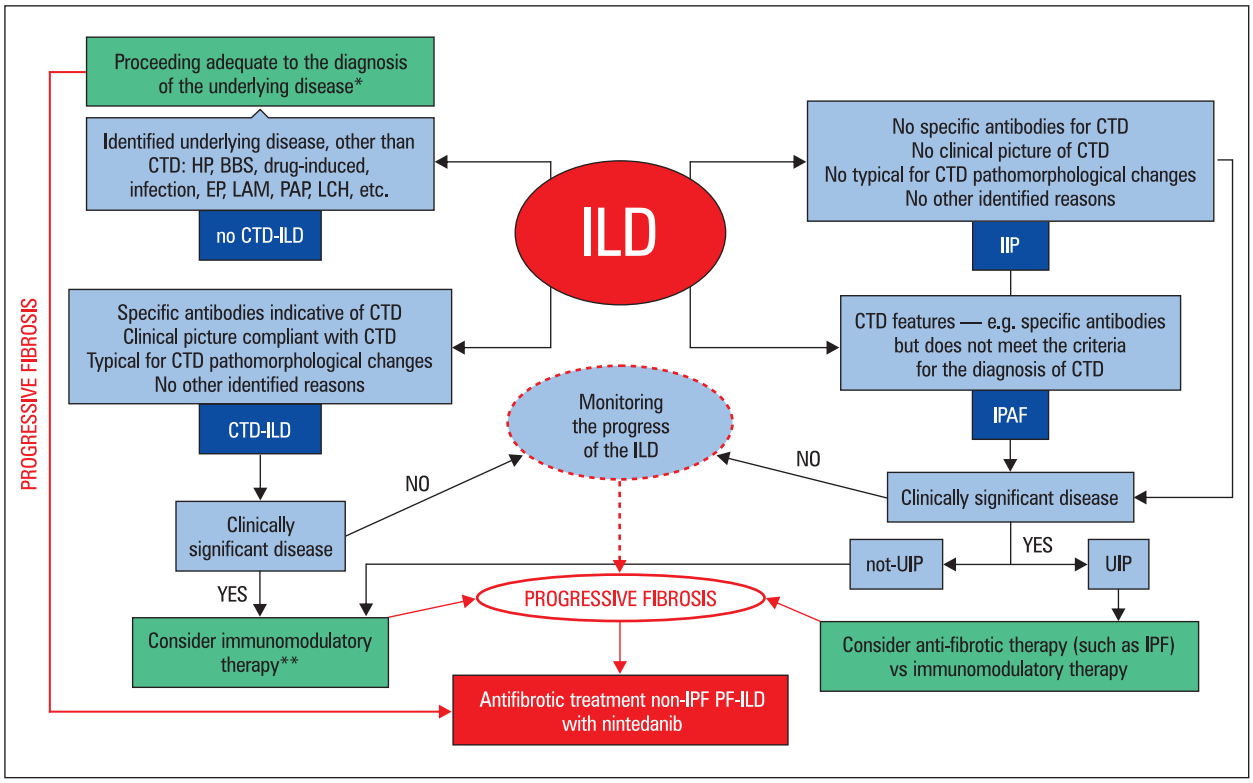

Figure 1. Proposed algorithm of diagnostic and therapeutic management of patients with ILDs (developed by the authors).

ILD — interstitial lung disease, CTD — connective tissue disease, CTD-ILD — CTD-associated interstitial lung disease, HP — hypersensitivity pneumonia, BBS – Besnier-Boeck-Schaumann's disease, sarcoidosis, EP — eosinophilic pneumonia, LAM — lymphangioleiomyomatosis, PAP — pulmonary alveolar proteinosis, LCH – Langerhans cell histiocytosis, IIP — idiopathic interstitial pneumonia, IPAF — interstitial pneumonia with autoimmune features, IPF — idiopathic pulmonary fibrosis, non-IPF — non-IPF diseases, PF-ILD — interstitial lung disease with a progressive fibrosing phenotype

*The procedure should follow the current recommendations regarding the treatment of a specific disease entity (in some situations it may be avoiding the causative factor, monitoring the progress of ILD, in others undertaking pharmacological treatment)

**The rheumatological consultation is necessary for each CTD-ILD, including an assessment of indications for treatment due to systemic disease. In the case of CTD-ILD with UIP pattern, with no indications for systemic treatment due to CTD, antifibrotic treatment can be considered as the first-line therapy.

sociated ILD, HP or with another form of PF-ILD was treated, all those patients had similar benefits from the treatment with nintedanib [42].

It seems justified to consider the antifibrotic treatment with nintedanib in all patients with PF-ILD in whom conventional treatment consistent with the standard of care dedicated to the underlying disease has failed or is contraindicated.

The proposed algorithm of diagnostic and therapeutic management is presented in Figure 1.

Safety of PF-ILD treatment with nintedanib

The antifibrotic treatment with nintedanib is associated with a risk of adverse drug reactions that nevertheless do not preclude the therapy in most cases, which has been known after the previous studies in groups of IPF patients [22, 26, 43–45].

The profile of adverse drug reactions in studies on non-IPF PF-ILDs was consistent with the previous observations. The most common adverse drug reaction was diarrhoea, observed in 66.9–75.7% of the patients [9, 10]. Elevated transaminases were found in 4.9% of the patients diagnosed with SSc in the SENSCS study and 13% of the patients in the INBILD study treated with nintedanib, and this reaction was mostly transient and reversible [9, 10]. No differences in the severity of adverse drug reactions were observed between patients with the UIP-like pattern of pulmonary lesions and patients with a different pattern [9].

The generally adopted rules that have been determined in studies and observations in patients with IPF should be used for patient selection and treatment monitoring. The possible treatment contraindications, comorbidities and potential interactions with other medicines should be taken into account. The standard therapeutic doses and methods of managing adverse drug reactions are similar as in the treatment of IPF (300 mg per day in two divided doses, and if adverse drug reactions occur, it is recommended

to use symptomatic treatment and, if necessary, to reduce the medicine dose to 200 mg per day or to temporarily interrupt the treatment).

Conclusions

The existing observations indicate that PF-ILD may affect a significant percentage of patients with ILDs. The need for defining this patient group arises mainly from the practical aspect of the demonstrated efficacy of antifibrotic treatment (currently proven for nintedanib) in patients with non-IPF ILDs associated with progressive pulmonary fibrosis.

The standardisation of the diagnostic criteria of PF-ILD would enable easier identification and selection of an adequate patient group for antifibrotic treatment.

Conflict of interest

MMM-B and WJP reports fees for lectures, consultancy and travel to medical meetings from Boehringer Ingelheim and Roche outside the submitted work.

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Pulmonary blastoma: a comprehensive overview of a rare entity

Abstract

Introduction: Pulmonary blastoma is a rare malignancy, accounting for less than 0.5% of primary lung tumors. It belongs to the group of pulmonary sarcomatoid carcinomas, and it is typically characterized by a biphasic pattern of an epithelial and a mesenchymal component. Only a few hundred cases have been reported worldwide. The aim of this study is to review and critically assess the literature regarding pulmonary blastoma.

Material and methods: A narrative literature review of PubMed database from the inception of the database up to January 2021, limited to the English language, was conducted, using combinations of the following keywords: "pulmonary blastoma", "biphasic pulmonary blastoma", "sarcomatoid carcinoma".

Results: Pulmonary blastoma is composed of an epithelial and a mesenchymal malignant component. Regarding pathogenesis, the origin of the biphasic cell population remains elusive. Characteristic immunohistochemical stains are supportive of diagnosis. Clinically, the symptomatology is non-specific, while 40% of the cases are asymptomatic. It is diagnosed at a younger age compared to other types of lung cancer, and it is often non-metastatic at diagnosis allowing for surgical treatment. Data on management and survival are scarce and mainly come from isolated cases. Advances on targeted therapy may provide novel treatment options. Given the rarity of the cases, multicenter collaboration is needed in order to establish therapeutic guidelines.

Key words: pulmonary blastoma, sarcomatoid lung carcinoma, biphasic pulmonary blastoma

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Introduction

Pulmonary blastoma (PB) is a rare malignancy that is estimated to account for 0.25 to 0.5% of all pulmonary neoplasms. It was seminally described in 1945 by Barrett and Barnard and was referred to as "embryoma"; however, in 1961, Spencer termed the tumor "blastoma" due to its histologic resemblance to the fetal lung at the 10–16-week stage of development (paraadenomal stage of lung development) [1]. Koss *et al.* (1991) classified pulmonary blastoma into 3 different subtypes: a) classic biphasic pulmonary blastoma (CBPB), b) pleuropulmonary blastoma (PPB) and c) well-differentiated fetal adenocarcinoma (WDFA) [2]. Pleuropulmonary blastoma predominantly presents in children and represents the most common primary pediatric pulmonary malignancy [3]. Classic biphasic pulmonary blastoma is typically characterized by a biphasic pattern consisting of a primitive mesenchymal stroma along with an epithelial component of fetal adenocarcinoma, while well-differentiated fetal adenocarcinoma is a monophasic tumor, presenting with immature adenocarcinoma as histologic characteristics [2]. Of note, since the WHO classification of lung tumors in 1999, pleuropulmonary blastoma is grouped with mesenchymal tumors, while fetal adenocarcinoma is classified as a subtype of lung adenocarcinoma [4]. Pulmonary blastoma is separately categorized as a type of sarcomatoid carcinoma of the lung

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[4, 5]. No significant changes have been made in the following versions, and therefore, the same terminology and categorization are adopted in the current WHO classification of lung tumors [6].

Only a few hundred cases of PB have been reported in the literature worldwide [7, 8]. Data on pathogenesis, epidemiology, management, and survival of pulmonary blastoma is scarce, and most evidence comes from case reports and case series. Additionally, the changes in the nomenclature of the tumor have led to confusion regarding the interpretation of earlier studies. Recently, the interest in rare pulmonary tumors has increased regarding both the pathogenetic and the clinical perspectives. To this end, the aim of this narrative review is to summarize updated data on pathogenesis, epidemiology, management, and outcome of pulmonary blastoma.

Pathogenesis

As far as the etiology is concerned, a correlation with smoking has been proposed with some cases demonstrating p53 mutation [9, 10]. Mutations in the gene of β-catenin have also been detected, similarly to other blastomas occurring in extrapulmonary sites, and those mutations are associated with the formation of morules in the tissue [11, 12]. Beta-catenin presents with a characteristic pattern of nuclear accumulation, which is unveiled with immunohistochemistry [11]. Of note, the mutations in β-catenin indicate a possible implication of the Wnt signaling pathway in the pathogenesis of PB [11]. In addition, a pathologic and molecular analysis of sixteen cases of PB demonstrated mutations in nine cancer-associated genes, namely *BRCA2*, *ERBB4*, *ALK*, *MET*, *BRAF*, *RAF1*, *PTEN*, *EGFR*, and *PIK3CA* [7].

PB belongs to the group of pulmonary sarcomatoid carcinomas, which are poorly differentiated non-small cell lung cancers (NSCLC), including a part of sarcoma-like elements or true sarcomatous areas [5, 6]. An interesting question regarding the pathogenesis of sarcomatoid carcinomas is whether the biphasic population of cells derives from a single ancestor cell or not. Two hypotheses have been proposed; the convergent hypothesis, suggesting that the different cancer cell types arise from different stem cells of epithelial and mesenchymal origin, and the divergent hypothesis proposing a single totipotential stem cell origin [13]. Moreover, the pathogenesis of sarcomatoid carcinomas has gained interest due to the potential involvement of the epithelial-mesenchymal transition (EMT) resulting in the formation of a mesenchymal component in an otherwise epithelial tumor [5]. Regarding pulmonary blastoma, evidence supportive of a single cell origin has been derived from genetic studies [11, 14]. Additionally, a study exploring whole-genome allelic imbalance in a case of pulmonary blastoma demonstrated common alterations in both epithelial and mesenchymal components of the tumor [15].

Histology

Histologically, the tumor is composed of an epithelial and a mesenchymal component (Figure 1A, B). The epithelial element is morphologically characterized by irregularly branching glandular structures, lined by pseudostratified columnar cells with clear cytoplasm and little nuclear atypia. The appearance is similar to the gestational lung in the pseudoglandular phase [2]. An embryonic stroma with oval cells with a high nuclear-to-cytoplasmic ratio is present, but up to one-quarter of the cases contain foci of osteosarcoma, chondrosarcoma, and rhabdomyosarcoma [5]. Areas of necrosis and hemorrhage are commonly observed within the tumor [2]. Tissue sampling from multiple areas is essential to confirm the presence of both epithelial and mesenchymal malignant components and establish the diagnosis [16]. Formally, a definite diagnosis is not possible based on small biopsy or cytology specimens because it requires a sarcomatoid/sarcomatous component in at least 10% of the neoplasm. However, a diagnosis of "NSCLC with sarcomatoid/sarcomatous component, possible sarcomatoid carcinoma" is reasonable [6].

Due to diagnostic dilemmas, immunohistochemistry is largely used, and it is supportive in reaching the diagnosis of PB. On the one hand, epithelial components stain positive for Cytokeratin, CEA, epithelial membrane antigen (EMA), thyroid transcription factor-1 (TTF-1), and surface protein alpha [17]. On the other hand, the stromal components stain positive for vimentin, desmin, muscle-specific actin, myoglobin, and S-100 [14, 18–20]. It has been proposed that b-catenin accumulation in the nucleus could be used as an additional criterion for the diagnosis of pulmonary blastoma [21] (Figure 1C, D).

Clinical and radiographic characteristics

PB has both a local growth pattern invading adjacent structures and a hematogenous metastatic spread. The most common symptoms

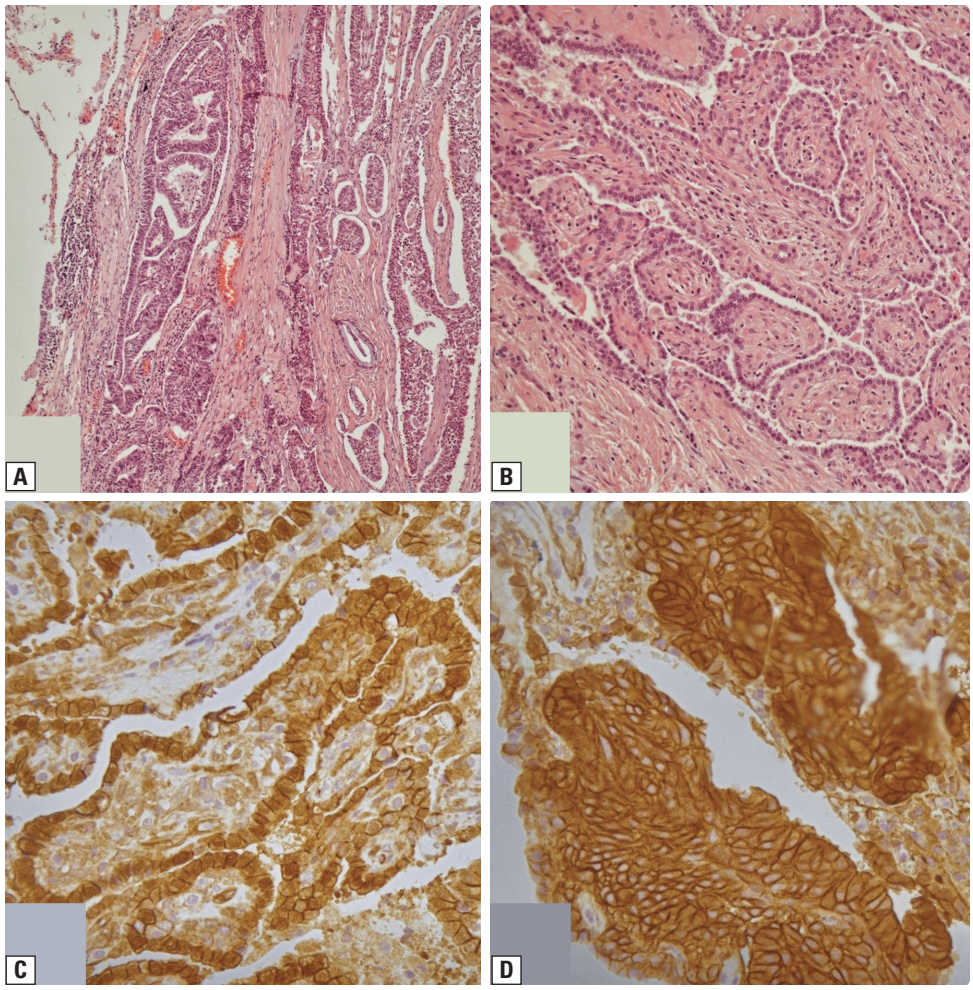

Figure 1. Biphasic tumor consisting of areas of fetal adenocarcinoma (**A**) and a mesenchymal fibroblastic-like cells (**B**). Both epithelial and mesenchymal blastematous cells show accumulation of β-catenin (**C, D**)

that occur are cough, hemoptysis, shortness of breath, recurrent pneumonia, fever, and weight loss, but asymptomatic tumors, accounting for 40% of cases, may also be detected incidentally [22–25]. There is a similarity in the anatomical presentation of these tumors. Involvement of the upper lobes, restriction to only one lung, and mean tumor size of 7–10cm are some of them [8, 26–28]. Hematogeneous metastases in the brain, bones, and liver, similar to NSCLC, but also in the breast, ovaries, peritoneum have been reported [8, 29]. There is no established biomarker indicating the diagnosis of PB, however, alpha-fetoprotein (AFP) increase has been identified in a few cases [30, 31].

In computed tomography of the chest, PB is characterized by well-circumferenced lesions, with dense and vesical elements with varying contrast uptake and central necrosis. Invasion of the pleura is possible and endobronchial growth is present in 25% of cases [16, 22]. The proximity to the pleura renders the bronchoscopy and biopsy difficult in the majority of the cases. A CT-guided transthoracic biopsy may be more convenient for diagnosis [32].

Table 1 summarizes typical histologic, immunohistochemical, clinical, and radiographic characteristics of pulmonary blastoma.

Epidemiology

Pulmonary blastoma is typically diagnosed at a younger age compared to NSCLC, as the majority of the patients are diagnosed before 50 years old [33–59]. A bimodal age distribution with peaks of incidence in the 4th and 7th decade of life has been reported [18], however, this has not been confirmed in a recent epidemiological study [60]. Regarding the gender predilection of the neoplasm, the results are ambiguous. Some studies report a male predominance [18, 40, 61], while others describe equal prevalence or even predominance of female gender [32, 60]. It should

Table 1. Histologic, immunohistochemical, clinical, and radiographic characteristics of pulmonary blastoma

Pulmonary blastoma	Characteristics
Pathology	**Epithelial component**: irregularly branching glandular structures, lined by pseudostratified columnar cells with clear cytoplasm and little nuclear atypia (fetal adenocarcinoma). **Mesenchymal component:** oval cells with a high nuclear-to- cytoplasmic ratio is present by definition, but up to one-quarter of the cases contain foci osteosarcoma, chondrosarcoma, and rhabdomyosarcoma
Immunohistochemistry	**Epithelial component**: Cytokeratin, CEA, epithelial membrane antigen (EMA), thyroid transcription factor-1 (TTF-1), and surface protein alpha **Mesenchymal component**: stromal components stain positive for vimentin, desmin, muscle-specific actin, myoglobin, and S-100
Clinical presentation	Cough, hemoptysis, shortness of breath, recurrent pneumonia, fever, and weight loss Asymptomatic tumors (40% of cases)
Radiographic presentation	Well-circumferenced lesions, with dense and vesical elements with varying contrast uptake and central necrosis

be noted that earlier studies may have included fetal adenocarcinomas within the term of pulmonary blastoma, which may differ concerning the epidemiological features and thus, it needs to be considered when interpreting the data [55].

Prognosis of pulmonary blastoma has been considered poor, based on the reported survival of isolated case reports and case series [2, 39, 29]. Nevertheless, in the most recent epidemiological study, with data deriving from the Surveillance, Epidemiology and End Results (SEER) database of the US population, it has been demonstrated that nearly half of the PB patients achieved long-term survival [60]. In fact, the 5- and 10-year survival rates in all PB patients were 58.2 and 48.5% [60].

Management and outcome

The majority of the patients with pulmonary blastoma are diagnosed at earlier stages, which allows for surgical treatment [29]. Similar to NSCLC, lobectomy is the most frequent procedure performed [8, 27, 47]. A study of 5 patients with PB by Liman *et al*. between 1987 and 2000 reported long-term survival after radical surgery, in patients with small size tumors (< 5 cm) without nodal involvement [47]. Specifically, in this study, one patient presented with stage T1N0M0, one individual with T2N0M0, and three patients with T2N1M0. As it was anticipated, the subjects without nodal involvement had the most favorable outcome [47].

The efficacy of adjuvant therapy has not been established with clinical trials; however, several published cases are reporting good outcomes with the use of adjuvant chemotherapy with or without radiotherapy [29, 62, 32]. Cisplatin combined with etoposide has been proposed as a regimen for adjuvant chemotherapy based on a review of the literature [63]. In a more recent report by Lewis *et al*. (2018), two patients underwent surgical treatment and they received adjuvant cisplatin-based chemotherapy for four cycles followed by thoracic radiation. Both patients achieved long-term survival [62].

Additionally, a few reports have described cases in which the patients received neoadjuvant therapy for downstaging before surgical resection. Bosch-Barrera *et al.* (2015) reported a 25-year-old patient with unresectable locally advanced pulmonary blastoma who received neoadjuvant chemoradiotherapy with two induction cycles of cisplatin plus etoposide, followed by concurrent weekly cisplatin and radiotherapy treatment. The tumor size significantly decreased, allowing for complete resection by pneumonectomy [59]. In another case, a 17-year-old male with a large tumor (12cm) with adjacent chest wall infiltration, which was considered unresectable initially, received preoperative chemotherapy with cisplatin plus etoposide. The reevaluation with chest CT scan after 3 cycles of chemotherapy demonstrated good regression of the mass. Therefore, the man underwent right upper and middle lobectomy followed by adjuvant local irradiation [57]. Moreover, in a patient who presented disease recurrence with a large mass, and although the original plan was for definitive radiation therapy with concurrent cisplatin and etoposide, the tumor regressed considerably after 2 weeks of treatment. Therefore, a preoperative course of radiation therapy and chemotherapy was decided and three weeks after completing therapy, he was reassessed with a chest CT showing impressive regression of disease, allowing for surgical treatment with right pmeumonectomy [67].

Regarding metastatic disease, treatment mainly includes chemotherapy; however, guidelines on regimens do not exist. Cutler *et al*. (1998) [63] and more recently Lewis *et al*. (2018) [62] have reviewed reports of patients who received chemotherapy. Historically, single-agent chemotherapy was initially tried with no clinical or objective response [62]. Vila *et al*. were the first to use combination chemotherapy with chlorambucil plus methotrexate in 1973 [33]. Over the following decades, oncologists applied various cytotoxic regimens, namely cisplatin-etoposide with or without ifosfamide and cyclophosphamide- and vincristine-based regimens. Other chemotherapeutic drugs that have been commonly used are carboplatin, doxorubicin, and paclitaxel [34, 52, 58, 65]. Moreover, two reports have been published of patients who received sorafenib; in one case the patient had a renal metastasis which responded well to sorafenib allowing for surgical treatment with radical nephrectomy [29, 50]. Interestingly, other four cases of metastasectomy have been reported, two of them involving metastatic tumors in the brain, in one case, a metastatic lesion in the breast, and finally, a case of metastatic PB to the ovary [48, 34, 62].

Only a few reports exist on the molecular alterations detected in PB, and even fewer that qualify for targetable therapies. Two cases have been published in which the tumor carried a ROS1 rearrangement. In the first case, fluorescence *in situ* hybridization (FISH) demonstrated a *ROS1* rearrangement in 7/50 tumor cells (14%) [20]. In the other case, the patient had a detectable CD74– ROS1 rearrangement and responded to crizotinib, providing a novel option for the treatment of PB [66]. The evidence remains scarce with regards to other molecular alterations; however, in the absence of established therapies and given the adenocarcinoma component of the tumor, it is reasonable to search for possible targetable mutations [26]. Finally, regarding immunotherapy, high expression of PD-L1 has been reported in some cases of PB, but no study has been published yet with the use of an immunotherapeutic agent [59].

Our literature review of recent (2000–2020) cases of patients with pulmonary blastoma who received chemotherapy in any setting (neoadjuvant, adjuvant, or metastatic) is shown in Table 2 [26, 28–30, 45, 47, 49, 50, 64, 66–71, 52, 54, 57–59, 62, 72–75]. Only English literature is included. Demographics characteristics, chemotherapeutics regimens, as well as reported survival, are summarized in the table.

Conclusion

Pulmonary blastoma is a rare tumor with unknown pathogenesis and aggressive behavior. It is diagnosed at a relatively young age, and it is frequently non-metastatic at diagnosis, allowing for surgical treatment. No guidelines exist regarding neoadjuvant or adjuvant therapy and concerning the optimal management of metastatic tumors. Due to the rarity of the cases, multicenter

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Bini *et al*. [67]	2001	53/M	LL Lobectomy	After recurrence: Chemotherapy cisplatin-etoposide × 3 cycles	12 m
Zaidi *et al*. [68]	2002	24/F	LU Lobectomy	Neoadjuvant vincristine, dactinomycin, ifosfamide, doxorubicin, etoposide, carboplatin	Alive at 35 m
Zaidi *et al*. [68]	2002	23/M	No	Vincristine, dactinomycin, cyclophosphamide, cisplatinum, doxorubicin	8 m
Walker *et al*. [45]	2005	21/F	Thoracotomy with decortication	Chemotherapy due to residual disease after surgery	6 m
Liman *et al*. [47]	2006	27/F	RU Lobectomy	Vincristine and cyclophosphamide followed by ifosfamide and etoposide	17 m
Liman *et al*. [47]	2006	54/M	RL Lobectomy	Vincristine and cyclophosphamide	10 m
Oshika *et al*. [49]	2007	58/M	RU Lobectomy and mediastinal LN dissection	Adjuvant chemotherapy with cisplatin and etoposide; Radiation after recurrence	Alive 70 m postop

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Mulamalla *et al*. [50]	2007	37/F	RU Lobectomy with LN dissection; Resection of local recurrence; Laparoscopic radical nephrectomy after response to sorafenib	Pemetrexed and bevacizumab × 3 in combination with radiation (4800 cGy) Sorafenib	NA
He *et al*. [69]	2008	47/F	The mass was removed en bloc through radical left intrapericardial pneumonectomy	Adjuvant chemotherapy (carboplatin/etoposide/isofosfamide) × 3 ;radiotherapy	3 y postop alive- disease free
Yu *et al*. [70]	2009	38/F	Lobectomy, metastasectomy (abdominal hysterectomy and bilateral salpingo-oophorectomy)	Adjuvant radiotherapy and chemotherapy (cisplatin and etoposide)	NA
Zagar *et al*. [64]	2010	24/M	RU Lobectomy, R pneumonectomy	Five years after lobectomy: Neoadjuvant radiation (60 Gy) followed by concurrent chemo-RT with cisplatin and etoposide (50 Gy total) in 2 Gy daily fractions; followed by adjuvant cisplatin and etoposide × 2 cycles	NA
Schwitter *et al*. [71]	2011	28/F	LU Lobectomy and LN dissection	Adjuvant Chemotherapy (initially ifosfamide, vincristin, actinomycin D and doxorubicin, later ifosmamide/cisplatin) Stereotactic Radiosurgery and whole brain RT (30 Gy)	Alive at 18 m
Van Loo *et al*. [29]	2011	77/M	RU Lobectomy with LN dissection	After recurrence: Sorafenib	12 m
Lindet *et al*. [52]	2011	22/F	R Pneumonectomy, pericardiectomy	After recurrence: 1st line: Ifosfamide, doxorubicin × 6 cycles then doxorubicin × 2 cycles followed by stereotactic radiotherapy (40 Gy); 2nd line: carboplatin, vincristine, 3rd line: cyclophosphamide; actinomycin-D, 4th line: docetaxel/gemcitabine	18 m
Sharma *et al*. [54]	2013	63/M	RL Lobectomy	After recurrence: Four cycles of cyclophosphamide, doxorubicin and vincristine (CAV)	NA
Muthu *et al*. [57]	2014	17/M	RU/RM Lobectomy; Tumorectomy along with excision of segments of fourth and fifth ribs	Neoadjuvant chemo with 3Cy Cis-VP Adjuvant RT, declined adjuvant chemo Declined chemo after 1st recurrence After 2nd recurrence → Cis-VP. The tumor was then de-bulked and its residue was irradiated; palliative radiation to the spine	24 m
Gallo *et al*. [72]	2015	43/M	No	Four cycles of cisplatin, ifosfamide, and etoposide (VIP) concurrently with 40 Gy external-beam radiation in 20 fractions	NA
Sakata *et al*. [58]	2015	63/M	LU Lobectomy and LN dissection	After recurrence: Carboplatin, Paclitaxel and bevacizumab	9.5 m
Bosch-Barrera *et al*. [59]	2015	25/F	Pneumonectomy (after neoadjuvant}	Neoadjuvant chemoradiotherapy based on two induction cycles of cisplatin plus etoposide, followed by concurrent weekly cisplatin to 50.4 Gy radiotherapy	Alive 8 m postop
Kilic *et al*. [73]	2016	68/M	LUL lobectomy, Cranial metastectomy	After recurrence: Radiotherapy and chemotherapy	6 m
Liu *et al*. [28]	2017	53/M	Left lobe resection plus mediastinal LN dissection	Adjuvant: Paclitaxel combined with nedaplatin × 4 Recurrence: RT 42 Gy/21 f pemetrexed + cisplatin + bevacizumab	18 m

Table 2. Summary of published cases since 2000 of patients with pulmonary blastoma who received chemotherapy and kinase inhibitors in any setting (neoadjuvant, adjuvant, or metastatic)

Author	Year	Age/sex	Surgery	Chemo or radiation	Survival
Caer *et al*. [74]	2018	71/F	RL Lobectomy	1st: Cisplatin-vepesid, 2nd: Carbo-etoposide; RT; Carbo-etoposide	Alive at 7 y postop
Meng *et al*. [66]	2018	44/F	No	Crizotinib first time used for PB (CD74–ROS1 rearrangement) → reduction in pleural effusion and 34.4% shrinkage of tumor size and improvement of symptoms, after 3m PD with enlarged L lung lesion and L pleural effusion	3 m PFS
Lewis *et al*. [62]	2018	38/F	LU Lobectomy with chest wall resection and mediastinal LN dissection, right parietal craniotomy, gamma knife radiosurgery (GKRS)	Adjuvant chemotherapy with cisplatin and vinorelbine , thoracic radiation with 50.4 Gy in 28 fractions.	Alive at 10 y postop
Lewis *et al*. [62]	2018	29/F	Thoracotomy and resection of the tumor Resection of the ovarian masses	Cisplatin, ifosfamide, vepesid, 59.49 Gy of radiation in 33 fractions	Alive at 10 y postop
Yang *et al*. [30]	2019	29/F	RM Lobectomy with LN dissection	Adjuvant Radiotherapy and nedaplatin	Alive at 6 m postop
Vossler *et al*. [75]	2019	66/F	Left Lobectomy	Palliative radiation and chemotherapy (cisplatin and etoposide)	6 m
Luo *et al*. [26]	2020	58/M	RU Lobectomy	Adjuvant: Nedaplatin plus paclitaxel After recurrence: two cycles of etoposide-cisplatin and six cycles of pemetrexed, bevacizumab, and carboplatin. The chemotherapy was stopped due to toxicity. The patient was finally administered anlotinib, a new oral multikinase inhibitor	Alive at 4 years

F — female; M — male; R — right; L — left; RU — right upper; RM — right middle; RL — right lower; LU — left upper; LL — left lower; m — months; y — years; Gy — Grey; NA — not available

collaboration is sorely needed in order to provide databases, allow large clinical trials, and establish therapeutic guidelines.

Conflict of interest

None declared.

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VIA MEDICA

CASE REPORT

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Bronchoscopic extraction of multiple endobronchial broncholiths in a patient with active pulmonary tuberculosis

Abstract

Broncholithiasis is an unusual clinical condition characterized by the presence of calcified or ossified material within the airways. Multiple endobronchial broncholithiasis during active infection with tuberculosis is an extremely uncommon presentation. Bronchoscopy plays an important role in the diagnosis and management of broncholithiasis. Currently, there are no specific guidelines for the management of broncholithiasis. Here, we present a case report where multiple broncholiths were successfully removed in a staged manner via rigid bronchoscopy.

Key words: broncholiths, broncholithiasis, rigid bronchoscopy, flexible bronchoscopy, lithoptysis

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Introduction

The term broncholithiasis is used to denote the presence of calcified or ossified material within the bronchial lumen [1]. It is an unusual condition with an incidence of only 0.1–0.2% of all lung diseases [2]. Though calcification is often seen in chest imaging as a sequelae of mycobacterial, fungal granulomatous lymphadenitis and silicosis, symptomatic endobronchial broncholithiasis is uncommon [1]. Broncholiths are calcified peribronchial lymph nodes which usually impinge on the bronchus or erode into the airway lumen [3]. Broncholiths can be detected incidentally during routine bronchoscopy or during evaluation of hemoptysis, cough, or recurrent pneumonia. Asymptomatic patients can be managed conservatively, whereas surgical or bronchoscopic removal is required for symptomatic patients [2].

Broncholiths have been removed successfully using forceps, laser photocoagulation, or cryotherapy [4, 5]. Here, we present a case report about the successful bronchoscopic removal of multiple broncholiths in a staged manner via rigid bronchoscopy. Multiple endobronchial broncholithiasis during active infection with tuberculosis is an extremely uncommon clinical presentation. Bronchoscopy plays an important role in its management.

Case history

A 63-year man who had never smoked presented with progressive dry cough and dyspnea of six months duration. He also had low grade fever (sometimes reaching 101°F) for about a month. There was no chest pain, hemoptysis, or loss of weight or appetite. He did not have a history of infection with tuberculosis. He did not have any other comorbid conditions. At presentation, he was afebrile and tachypneic. Auscultation revealed decreased air entry in the left chest. His chest radiograph showed a left lung midzone consolidation with multiple calcified densities in bilateral paratracheal and parabronchial regions (Figure 1A). Contrast-enhanced computed tomography (CECT) of the chest showed bilateral areas of patchy consolidation (Figure 1B) with multiple calcified lymph nodes in pre-paratracheal, pre-vascular, subcarinal and right hilar regions (Figure 1C). There were also calcified nodes in the

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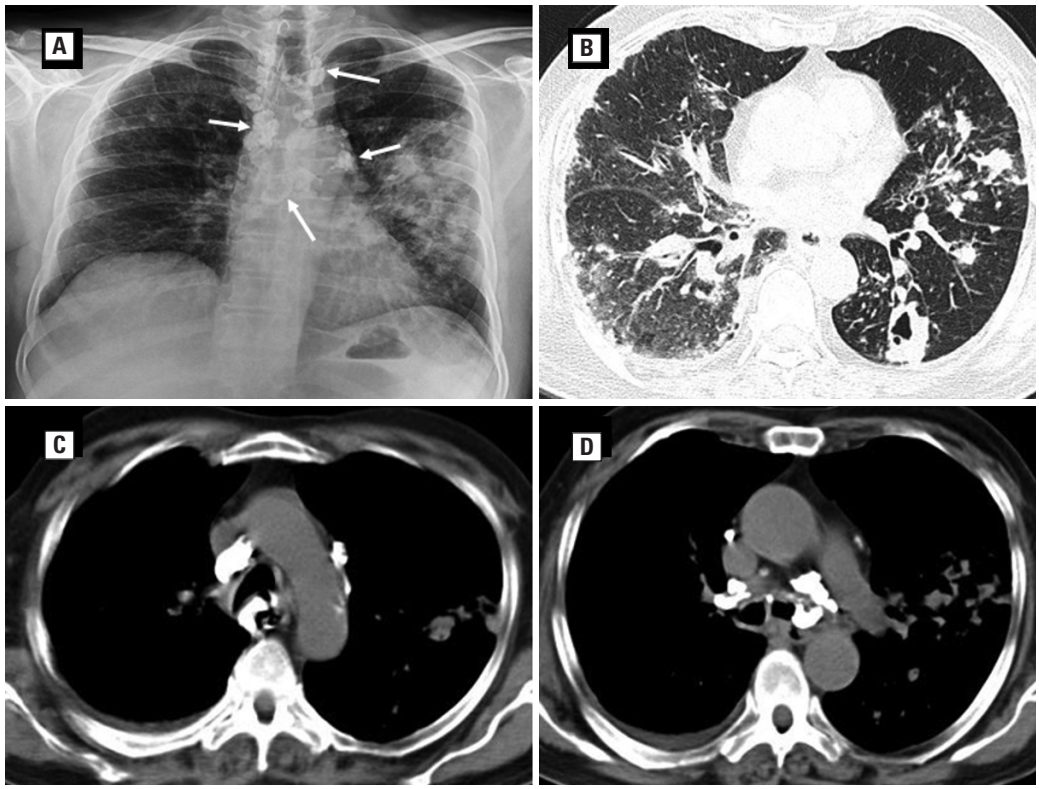

Figure 1. A. Chest radiograph showing multiple calcified opacities (broncholiths) in the paratracheal and peribronchial locations (white arrows) and a large patch of consolidation in the left mid zone; **B.** Lung parenchymal window of computed tomography (CT) of the chest showing multifocal patchy consolidation and cavities in bilateral lung fields; **C.** Mediastinal window of CT of the chest showing calcified subcarinal, paratracheal and para-aortic nodes in the mediastinum (extraluminal broncholiths); **D.** Mediastinal window showing an intraluminal broncholith in the left main bronchus as well as extraluminal broncholiths adjacent to both main bronchi

lumen of the left main bronchus (LMB) (Figure 1D). Bronchoscopy revealed edematous mucosa, granulation tissue, and two broncholiths occluding the lumen of the LMB (Figure 2A). Bronchial washings were positive for acid fast bacilli (AFB) on smear and gene Xpert MTB/Rif.

Rigid bronchoscopy was performed in order to remove the broncholiths. Under general anesthesia, the patient was intubated using a rigid tracheobronchoscope (Efer Dumon series III, 13 mm OD) The proximal granulation tissue was removed using a flexible cryoprobe (Erbe cryoprobe, 1.9 mm OD), and then the broncholiths were crushed with rigid forceps and removed piecemeal (as the broncholiths could not be removed in-toto). However, all broncholiths could not be removed in the first sitting. Post-procedure, the air entry to the left lung improved and the patient was started on anti-tubercular therapy (ATT). The patient spontaneously coughed out three broncholiths (lithoptysis) in the following month. Repeat bronchoscopy showed one residual broncholith causing partial occlusion of the LMB (Figure 2B). There was also a fistulous tract seen arising from the proximal left main bronchus and ending in the subcutaneous plane near the xiphisternum (broncho-subcutaneous fistula). In the second session, an entire broncholith was removed en masse using rigid forceps via the rigid bronchoscope. There was significant improvement in cough and breathlessness following the procedure. The patient is currently improving on ATT and repeat bronchoscopy showed no recurrence of endobronchial broncholiths (Figure 2C).

Discussion

Broncholiths are classified into two groups based on their origin: a) Intrinsic calculi, developed from lungs, bronchi, and lymph nodes; b) extrinsic calculi, developed from aspirated foreign bodies, secretions, and dusts. Broncholiths are usually gray-white and variable in size and shape with spur like projections or sharp edges. The chemical composition is of calcium phosphate (85–90%) or calcium carbonate (10–15%) [1]. The broncholiths are also classified based on their location in the tracheobronchial

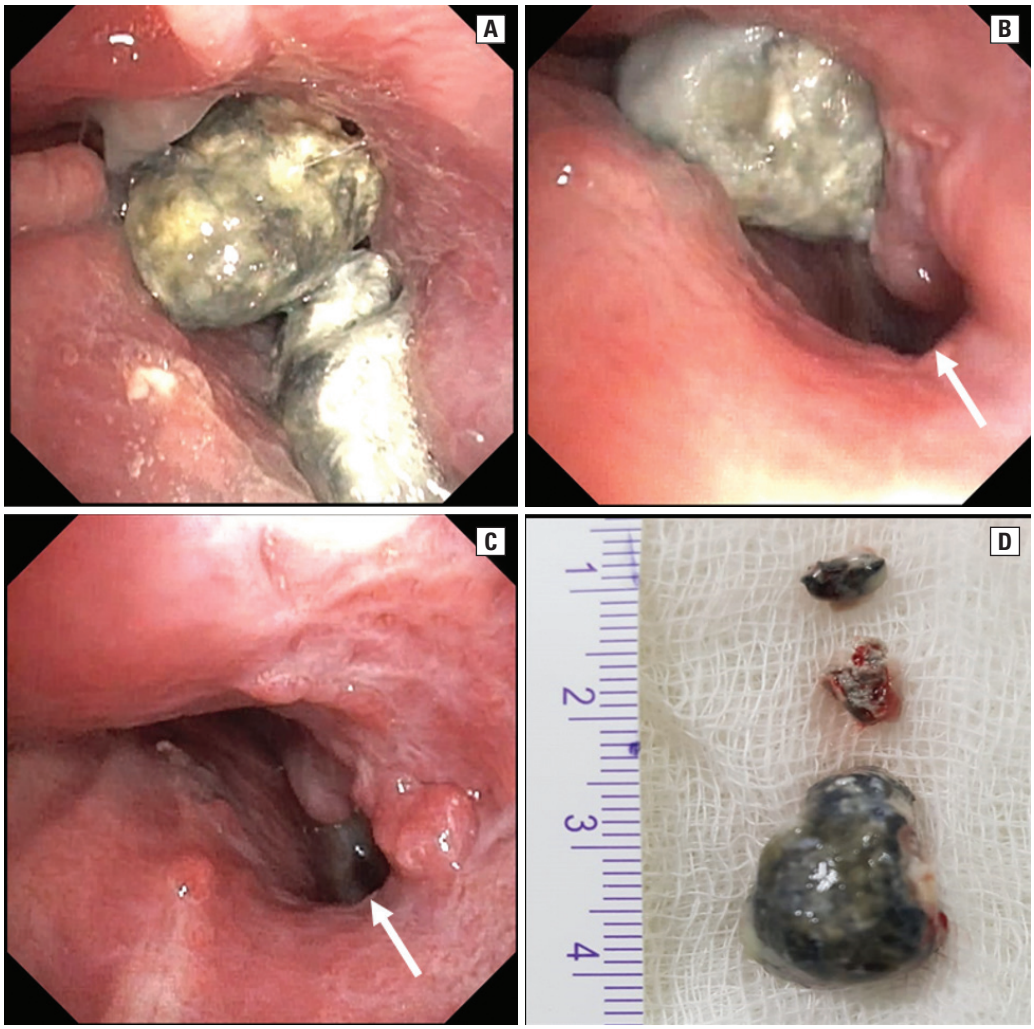

Figure 2. A. Bronchoscopic image showing two large broncholiths occluding the left main bronchus; **B.** Repeat bronchoscopy done after removal of one broncholith showing a fistulous opening, bronchial end of the bronchocutaneous fistula (white arrow); **C.** Image after removal of all intraluminal broncholiths; **D.** Broncholith after rigid bronchoscopic extraction

tree and can be intrabronchial, transbronchial, or extrabronchial [6]. The pathogenesis of broncholith formation can be explained by multiple mechanisms. A chronic long-standing infection or inflammation, usually of granulomatous etiology, brings calcium into airway walls or into adjacent lymph nodes. A calcified bronchial cartilage or a calcified necrotic lymph node then erodes into airways causing broncholiths. Another mechanism has been proposed to explain the presence of broncholiths without airway erosion/fistula formation. A necrotic/caseating lymph node discharges its contents in a liquid form into the bronchus and this caseating material calcifies on exposure to air leading to broncholith formation [1].

Broncholiths, by causing endobronchial obstruction, can lead to recurrent post-obstructive pneumonia and lung abscess formation [7]. They can also erode into airways causing fistulae and hemoptysis [8, 9]. Occasionally, they can be expectorated spontaneously leading to resolution of symptoms [10]. Most patients with broncholiths have a past history of tuberculosis, silicosis, or histoplasmosis. Occurrence of broncholithiasis during the acute phase of tuberculosis is less common, as was seen in the index case [11].

Treatment options include observation for asymptomatic cases, and bronchoscopic removal (flexible or rigid) or surgery in symptomatic cases depending on local expertise and resources [3, 12, 13]. With increasing experience in therapeutic bronchoscopy, most centers now recommend bronchoscopic extraction as the initial modality of therapy for patients with symptomatic endobronchial broncholithiasis [1]. Surgical removal is considered in cases of symptomatic purely extrabronchial broncholiths, fixed broncholiths

(when bronchoscopy fails), or when there are complications like massive hemoptysis and/or broncho-esophageal fistulae [3].

Various bronchoscopic methods have been described for the removal of broncholiths. Forceps, laser photocoagulation, and cryoprobe extraction have all been shown to help in extracting broncholiths [4, 14]. Laser-assisted broncholithotripsy has also been described for removing impacted broncholiths [15]. Flexible bronchoscopic removal appears favorable in cases with loose or partially eroded broncholiths [13]. Rigid bronchoscopy is preferred over flexible bronchoscopy in cases of symptomatic large or fixed broncholiths. The size and location of the broncholith, mobility, relation to surrounding vascular structures, and distal parenchymal pathology impact the decision on which modality to choose. Cerfolio *et al*. presented an algorithm for the management of broncholiths based on symptomology and relationship of the broncholith to the airway (extrabronchial versus endobronchial, fixed vs mobile) [3].

The ability of the clinician to choose wisely using a combination of both rigid and flexible bronchoscopes along with various accessories like forceps, cryotherapy, or lasers is essential for a successful outcome. It is always recommended to have a thoracic surgeon on standby before attempting broncholith removal.

Conclusions

Multiple endobronchial broncholiths during active tuberculosis is an uncommon clinical presentation. Bronchoscopy plays an important role in the diagnosis and management of broncholithiasis. Rigid bronchoscopic removal of symptomatic broncholiths is a feasible and safe option. When bronchoscopic removal fails, surgical extraction remains the treatment of choice.

Conflict of interest

None declared.

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A very unusual case of interstitial lung disease

Abstract

Cotton dust exposure has been implicated in causing diseases like byssinosis and obstructive airway diseases like COPD and asthma. Long-term exposure to cotton dust causing interstitial lung disease and pulmonary fibrosis has been sparsely reported in the literature. Here, we report a case of an individual with long-term cotton dust exposure who presented with typical symptoms of interstitial lung disease and was managed conservatively.

Key words: cotton dust, byssinosis, interstitial lung disease, pulmonary fibrosis

Adv Respir Med. 2021; 89: 524–527

Introduction

Long-term exposure to cotton fibres has been classically associated mostly with byssinosis and airway diseases like chronic obstructive pulmonary disease and asthma [1, 2]. The exposure constitutes of broken cotton fibres, bracts and pericarps, as well as to bacteria and fungi on the surface of these cotton products. Cotton-induced pulmonary fibrosis and pneumoconiosis has been rarely reported in the literature [3, 4]. Here, we report a case of a cotton mill worker who presented with an insidious onset of breathlessness and cough who was diagnosed with cotton-induced interstitial lung disease and was managed conservatively.

Material and methods

A 65-year-old male who was a non-smoker and had a history of working in a cotton mill for 30 years presented with a history of sudden onset, progressive breathlessness and dry cough that had been present for six months. His work history included working in a cotton mill for 8 hours per day, 5 days a week, for 30 years. He was initially evaluated at another hospital, was managed conservatively, and was even started on oral steroids. He had symptomatic improvement at first but later reported to our hospital with fever, increased cough, and breathlessness that had been present for a two-week duration. He stated that he used to feel better on holidays and weekends but that his symptoms had worsened as of late. There was no history of joint pains or any other connective tissue disease. Interestingly, he stated that he had noticed similar complaints in some of his co-workers. On examination, he was tachycardic (pulse — 110/min), tachypnoeic (respiratory rate — 30/min), and hypoxic (SpO_2 — 80% at room air). He had grade II clubbing in both hands. On auscultation, he had bilateral, symmetrical fine inspiratory crackles in the infrascapular and infra-axillary areas. There were no signs of any connective tissue disorders. On evaluation, his complete blood count, liver function tests, and renal function tests were within normal limits. His chest x-ray showed bilateral reticular opacities in both lower zones (Figure 1A). He underwent high-resolution computed tomography of the chest which showed multifocal areas of honeycombing with bi-basal predominance, extensive areas of interlobular septal thickening, a few areas of ground-glass attenuation in bilateral lung fields (Figure 1B, 1C), and discretely enlarged mediastinal lymph

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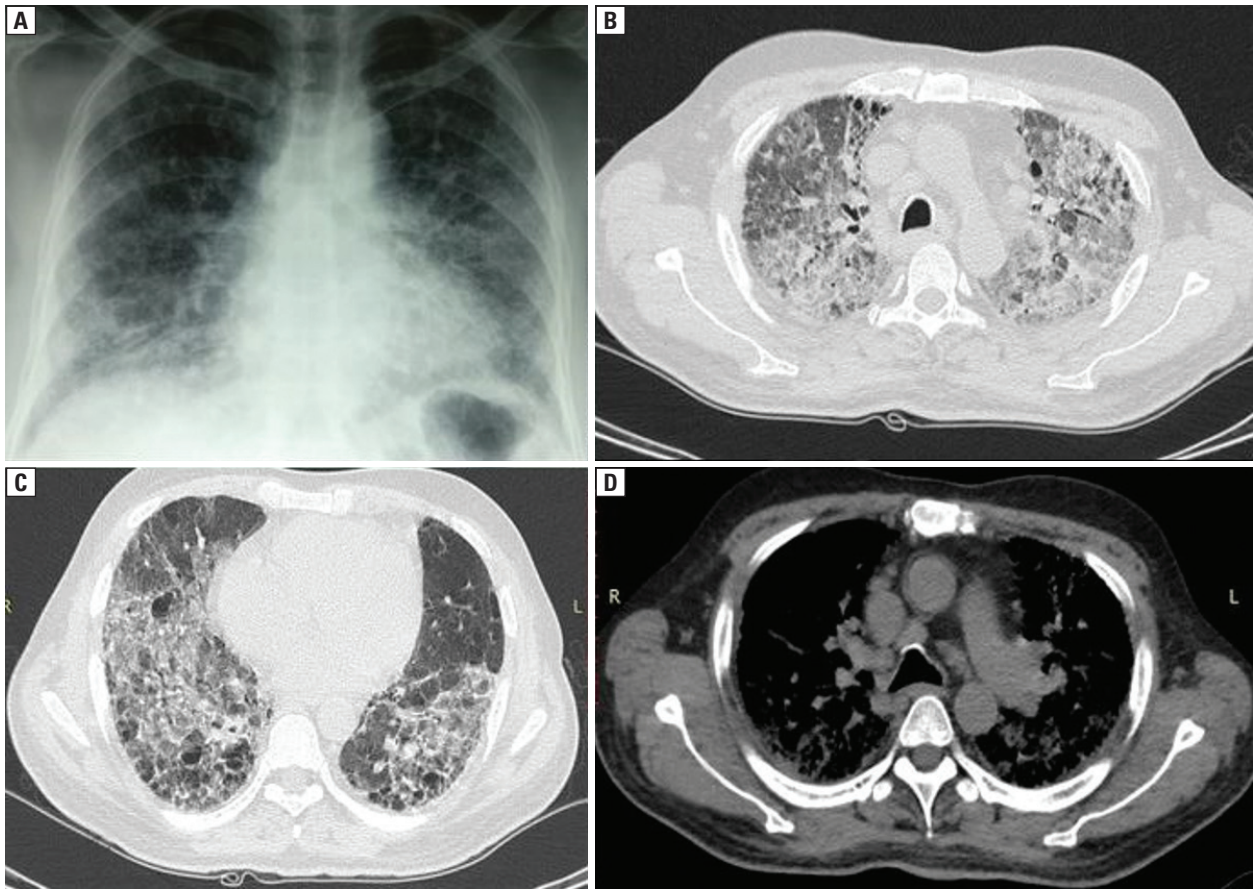

Figure 1. A. Chest x-ray of the patient showing bilateral reticular opacities; **B. C.** Extensive interlobular and intralobular septal thickening, traction bronchiectasis, microcystic and macrocystic honeycombing in bilateral lung fields. Extensive ground-glass opacities along with areas of air trapping also seen scattered in the lungs bilaterally giving mosaic attenuation throughout the lung fields; **D.** High-resolution computed tomography of the chest showing bilateral pleural involvement with a shaggy pleural outline. Multiple discrete enlarged mediastinal lymph nodes seen

nodes (Figure 1D). His spirometry results were as follows: forced expiratory volume in 1 second (FEV_1) — 1.55 litres (68% of the predicted), forced vital capacity (FVC) — 1.65 litres (54% of the predicted), and a normal ratio of FEV_1/FVC — 93.94%. There was no post-bronchodilator reversibility and there was evidence of small airway obstruction. His diffusion capacity of the lungs for carbon monoxide (D_{LCO}) showed a moderate diffusion defect (50%). The results of the 6 minute walk test showed that he had a decreased walk distance of 120 metres with significant desaturation (10% fall of SpO_2 from baseline) (Table 1). His arterial blood gas at room air showed hypoxemia (pH — 7.40, pO_2 — 50 mm Hg, and pCO_2 — 41 mm Hg). His connective tissue disorder profile (rheumatoid factor, anti-cyclic citrullinated peptide, anti-nuclear antibody, C-reactive protein, and extractable nuclear antigen antibody levels) was within normal limits. He was diagnosed with cotton dust-induced interstitial lung disease based on clinical, radiological, and spirometric criteria, and was managed with long acting bronchodilators and inhaled steroid inhalers with oxygen supplementation, while at the same time tapering the dose of oral steroids. He was advised and counselled about complete cessation of cotton dust exposure and even regarding potentially changing his profession. He is presently symptomatically better with improved exercise tolerance.

Discussion

Cotton dust exposure constitutes a major occupational health hazard in our country. The effect of cotton exposure can be varied and depends on the duration of exposure, site of exposure, effect of the specific component of cotton dust, presence of fungi, and presence of other factors such as smoking. The most common respiratory diseases associated with cotton dust exposure are byssinosis and airway diseases such as COPD and asthma [2, 4].

Table 1. The details of pulmonary function testing

Spirometry	Pre	Post
FEV_1	1.55 L (68%)	1.58 L (69%)
FVC	1.65 L (54%)	1.78 L (56%)
FEV_1/FVC	93.94%	88%
DLCO	50%	9.4 mL/min/mm Hg
6MWT	120 m	With significant desaturation (> 10% from baseline)

FEV_1 — forced expiratory volume in 1 second; FVC — forced vital capacity; D_{LCO} — diffusion capacity of the lungs for carbon monoxide; 6MWT — *6 minute walk test*

Byssinosis can be acute or chronic. It generally presents with a history of cough, chest tightness, and breathlessness after long-term exposure to cotton dust. It classically has a history of increasing severity of symptoms after returning to work after holidays/breaks (Monday asthma) and typically worsens as the day progresses. Acute byssinosis has been characterized by symptoms occurring after a short duration of exposure and by a fall in FEV1 of more than 30% [2, 7].

The other most common diseases associated with cotton dust exposure are airway diseases like asthma and COPD. Early stages of byssinosis can have features of asthma like reversible airflow limitation and airway hyperresponsiveness. There can be large changes in pre- and post-work FEV1, which is also termed 'cross-shift drop' in FEV_1 [2]. These symptoms can become more severe and frequent with long-term exposure and patients can develop progressive breathlessness and cough with expectoration resembling COPD. These patients can have a post bronchodilator FEV_1/FVC (forced expiratory volume in 1 second to forced vital capacity) ratio < 0.7 [2, 4, 5].

Cotton dust exposure has rarely been reported to cause pneumoconiosis/interstitial lung disease and pulmonary fibrosis except for some case reports and post-mortem reports [1, 3, 4, 6]. Pneumoconiosis due to cotton dust is different than pneumoconiosis due to inorganic dust as it is likely due to hypersensitivity pneumonitis secondary to organic dust inhalation produced during processing of cotton in cotton industries. The pathogenesis may also involve production of nitric oxide from alveolar macrophages and type-2 epithelial cells from lipopolysaccharides (LPS) present in cotton dust (component of outer membrane of various Gram-negative bacteria) [3]. This nitric oxide reacts with superoxide to initiate the cascade of inflammatory cytokine production which may cause structural damage and fibrosis. The endotoxin has been implicated in causing airway inflammation, hyperreactivity, and airflow obstruction causing byssinosis [4]. Patients with cotton dust-induced pneumoconiosis generally present with insidious onset breathlessness with dry cough and a retrospective history of prolonged exposure to cotton dust. On examination, they are hypoxic at room air. On auscultation, they have bilateral inspiratory crackles, as was the case in our patient [3]. The diagnosis can be confirmed radiologically and chest radiographs of these patients typically show bilateral basal interstitial infiltrates with reduced lung volumes. In these patients, computed tomography of the chest can show fibrosis with peribronchiolar distribution, centrilobular nodules with a 'tree in bud' appearance, and areas of ground-glass opacities [1, 3, 7]. Our patient also had features of diffuse fibrosis with ground-glass opacities in bilateral lung fields.

Byssinosis generally causes a reversible decrease in FEV_1 but as the disease progresses, the changes can become irreversible. Patients with pneumoconiosis generally show a mixed defect. Our case also had a mixed defect on spirometry and had a diffusion defect which indicated the severity of the disease. These patients generally have exercise-induced hypoxemia. On the other hand, resting hypoxia indicates severe disease and fibrosis [2, 7].

Bronchoalveolar lavage (BAL) and lung biopsy have major roles in this disease as they can confirm the diagnosis. BAL differential cytology can help differentiate byssinosis from other differential diagnoses such as hypersensitivity pneumonitis (lymphocyte predominant). The cotton fibres deposited in the lungs can form byssinosis bodies which causes a foreign body reaction of the lung tissue [3, 4, 6, 7]. In our case, the diagnosis of cotton dust-induced interstitial lung disease was made on the basis of clinical, radiological, and pulmonary function tests. We did not perform a bronchoscopic procedure as the patient was hypoxemic at room air and had a significant history of exposure to cotton dust. Clinical findings and computed tomography of the chest confirmed interstitial lung disease. All secondary causes were excluded.

The treatment of pneumoconiosis consists mainly of cessation of exposure [3, 8]. According to a prospective cohort study consisting of 447 cotton textile workers and 472 unexposed silk textile workers with 25 years of follow-up and based on spirometry and respiratory questionnaire data, the authors confirmed that ces-

sation of cotton dust exposure is associated with improvement in lung function and respiratory symptoms [8]. Patients should also be counselled about changing their profession. Corticosteroids also have a role in reducing inflammation. Supportive treatment includes supplementary oxygen, bronchodilators, and prompt treatment of secondary bacterial infections [3, 7, 8].

Conclusion

Cotton dust exposure-related diseases are a major cause of increased morbidity in developing countries. The manifestation of disease also depends on duration of exposure, site of exposure, effect of the specific component of the cotton dust, presence of fungi, and presence of other factors like smoking. The most common respiratory diseases associated with cotton dust exposure are byssinosis and airway diseases like COPD and asthma. Cotton dust-related interstitial lung disease has rarely been reported on in the literature and should be kept in mind by treating pulmonologists while managing patients with similar clinical presentations.

Conflict of interest

None declared.

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VIA MEDICA

CASE REPORT

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Nintedanib-mediated improvement in CT imaging in pulmonary fibrosis associated with systemic scleroderma

Abstract

Nintedanib is an antifibrotic drug that has an inhibitory effect on growth factor tyrosine kinases. In patients with idiopathic pulmonary fibrosis and systemic scleroderma-associated interstitial pneumonia (SSc-IP), nintedanib has been effective in suppressing the decline in forced vital capacity over time and the onset of acute exacerbation of interstitial pneumonia. Here, we report a SSc-IP patient who showed an improvement on CT images following nintedanib treatment. To our knowledge, this is the first report of such a case. Although SSc-IP patients are very rare, additional clinical experience and understanding will be required to prove the therapeutic benefit of nintedanib in these cases in relation to improved chest images.

Key words: systemic scleroderma, pulmonary fibrosis, nintedanib, computed tomography

Adv Respir Med. 2021; 89: 528–531

Introduction

Systemic scleroderma-associated interstitial pneumonia (SSc-IP) is a collagen disease. It is characterized by organ fibrosis due to fibroblast proliferation and impaired blood circulation due to vascular endothelial cell proliferation in the skin and organs, such as the lung and kidney [1]. More than half of patients with SSc develop interstitial pneumonia (IP) due to inflammation and fibrosis in the lung interstitium [2, 3]. Acute or subacute progression of IP and pulmonary hypertension are serious pathological conditions that determine the prognosis of SSc patients [3].

The antifibrotic drug nintedanib has been shown to suppress the gradual decline in forced vital capacity (FVC) and the onset of acute exacerbation in idiopathic interstitial pneumonia (IPF) patients, and as such, has become one of the most reliable drugs for the treatment of IPF [4–6]. Similar clinical effects have recently been confirmed in patients with SSc-IP in a large-scale clinical trial [7]. While nintedanib-mediated suppression of progression and advance in prognosis have been broadly shown, an improvement on computed tomography (CT) imaging, however, has been reported in only a few IPF patients [8–10]. To the best of our knowledge, there have been no reports of a SSc-IP patient showing improvement on CT images. Here, we report on our treatment with nintedanib of a patient who exhibited improved CT imaging . Although this type of case is extremely rare, reporting it provides valuable suggestions for future treatment plans involving nintedanib.

Material and methods

A 73-year-old woman was referred to our hospital with ground-glass opacities in both lower lobes in a chest radiograph taken at mass screening. She had had slight dyspnea on exertion for several months. She was diagnosed as having SSc due to symmetrical thickening, tightening and induration of the skin of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joints, reticular densities most pronounced in the basilar areas of the lungs on chest radiograph, and the presence of anti-centromere antibody. She had no smoking habit. The patient was pathologically diagnosed with primary biliary cholangitis 25 years ago.

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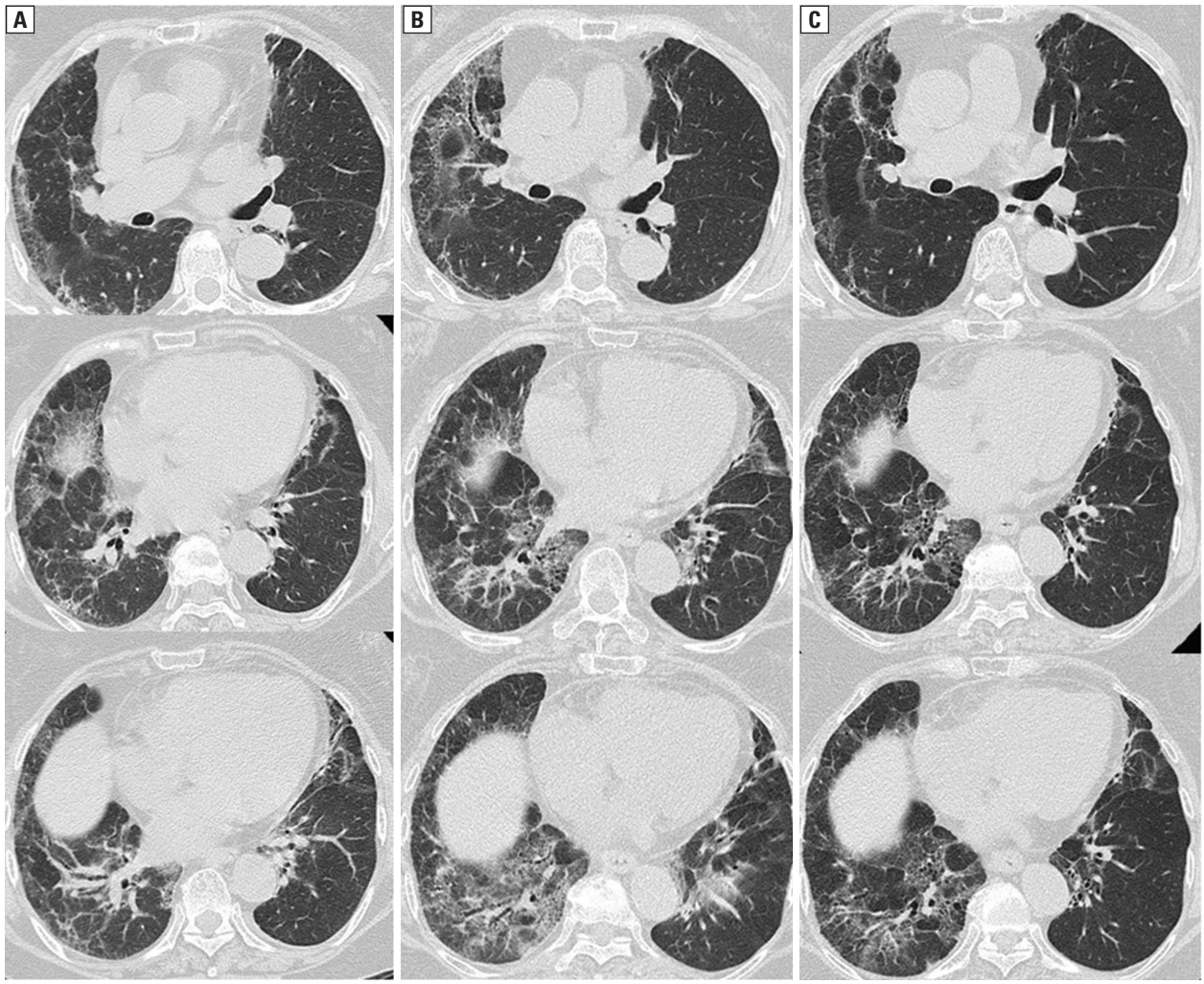

Figure 1. Chest computed tomography (CT) scan 10 months (**A**) and 26 months (**B**) after the initial visit to our hospital showed expansion of subpleural ground-glass opacities with thickening of vascular bundle in bilateral lower lobes of the lung. Chest CT scan taken 8 months after the initiation of nintedanib revealed an improvement of diffuse subpleural ground-glass opacities (**C**)

Computed tomography taken at the first visit showed traction bronchiectasis, bronchial bundle thickening, and ground-glass opacities in the lower lobes of both lungs. Blood examination at the first visit revealed thrombocytopenia, which was refined to idiopathic thrombocytopenia after more testing results.

Therapy with prednisolone and tacrolimus was started as a treatment for idiopathic thrombocytopenic purpura. The tacrolimus dose was 2 mg/day, commencing two years before the initiation of nintedanib. Prednisolone was reduced to 5 mg/day four months before the initiation of nintedanib, with this dose remaining constant ever since. Chest CT images taken 10 months and 26 months after the initial visit to our hospital showed the range of ground-glass opacities expanded and exacerbation was confirmed (Figure 1A and 1B).

At that time, nintedanib was reimbursed through health insurance in our country. Patients were thoroughly informed on the benefits and adverse effects of nintedanib before starting nintedanib treatment. In particular, the dose of nintedanib was explained in relation to the results of the SENSCIS study. Treatment started at 2×100 mg of nintedanib daily. One month after the administration of nintedanib, the patient noticed an improvement in her dry cough and dyspnea, and due to this amelioration in clinical symptoms and imaging, desired to continue on the same nintedanib dose. As a result, there was no dose increase. There were no side effects such as loss of appetite or nausea. After commencing nintedanib treatment, the patient was asked several times about the presence or absence of diarrhea, but there were no side effects of diarrhea, probably because the patient was taking codeine

phosphate as an antitussive. Blood sampling examinations including liver function were performed regularly, but no abnormal values due to nintedanib were found. Chest CT was performed eight months after the start of nintedanib, and a regression of ground-glass opacities on chest CT scan was confirmed (Figure 1C). An improvement on chest CT scan was accompanied by a decrease in dry cough and dyspnea on exertion. One year after the start of nintedanib, treatment is ongoing.

Discussion

In many pulmonary fibrosis cases, including IPF and SSc-IP, fibrosis progresses due to an abnormal repair reaction to damage to the alveolar epithelium. During this abnormal fibrosis, alveolar epithelial cells differentiate into fibroblasts and myofibroblasts [11]. Lung fibroblast proliferation and migration is stimulated by fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and fibroblast transformation is induced by transforming growth factor-β2 [11]. Nintedanib inhibits the action of growth factors on tyrosine kinases, mainly FGF, VEGF, and platelet derived growth factor (PDGF). In a phase III trial in IPF patients, nintedanib was effective in suppressing the decline in FVC over time and the onset of acute exacerbation of IP [4–6]. In SSc-IP patients, a large-scale clinical trial has recently been conducted [7], and the clinical effects observed in these subjects are similar to that observed in IPF patients [12]. There are only a few reported cases that show an improvement on CT images with nintedanib therapy, and all are patients with IPF [8–10].

A recent sub-study analysis of the SENSCIS trial examined the effect of nintedanib on HRCT markers of fibrosis [13]. It found only nine out of 52 SSc-ILD patients treated with nintedanib had a notable improvement in fibrotic changes on HRCT analysis, and none were classified as 'much better', which was defined by the authors as 'a moderate decrease in honeycombing and/or reticulation and/or fibrotic ground-glass opacity; a decrease was more than 10%'. According to this sub-study analysis, an improvement on CT was extremely rare.

To the best of our knowledge, no similar cases of HRCT improvement in SSc-ILD after nintedanib therapy have been published to date. Therefore, this is the first SSc-IP case who has showed an amelioration in CT images following nintedanib treatment, defined by a regression of ground-glass opacities and septal thickening on the chest CT scan. Our patient also showed an improvement in her dry cough as well as dyspnea on effort.

It is important to consider the possibility that mechanisms other than nintedanib might have contributed to the patient's improved CT images. Firstly, there is the possibility of spontaneous changes in SSc cases [14]. Spontaneous changes in skin lesions have been reported in SSc patients, but there have been no reports of improvement in opacities on chest CT images. Secondly, there is the potential effect of drugs other than nintedanib. The patient was also receiving corticosteroids and tacrolimus, which both commenced three years before the initiation of nintedanib. The dose of tacrolimus had been constant for two years before the initiation of nintedanib. The dose of prednisolone was reduced four months before the introduction of nintedanib, and had not changed since. Chest CT scans were taken several times during the administration of these drugs, which showed a gradual exacerbation of ground-glass opacities over time, but no improvement. Therefore, the possibility of these drugs contributing to the improvement on CT images is low, and it was instead considered to be due to the effect of nintedanib.

Nintedanib has been reported to have gastrointestinal adverse effects (AEs) such as appetite loss, nausea and liver dysfunction [4–6]. In our patient, frequent examination did not find any severe AEs to prevent continuing treatment. In addition to CT images, therapeutic effects in SSc-IP patients can be observed in respiratory function and pathological evaluations. On exertion, there was no decrease in oxygen saturation, and an improvement in subjective symptoms such as dry cough and dyspnea was observed. However, as the patient did not wish to be examined, there were no assessment on pulmonary function and histopathological evaluation.

This case report has some limitations. One of them is the lack of pathological examination. The pattern shown on CT scans was probably nonspecific interstitial pneumonia, and this pattern might be reversible, if cellular component was present. Evaluation of tissue specimens obtained by transbronchial lung biopsy (TBLB) would be useful. If performing TBLB was difficult, analysis of bronchoalveolar lavage fluid would be helpful to understand why these changes were reversible. The other serious disadvantage was the lack of lung function data before and after treatment. Results of pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide, and six-minute walk test before and

after eight months of therapy with nintedanib, would be important to confirm a functional improvement corresponding to a CT amelioration of fibrotic changes. However, due to patient's refusal to perform any of these tests, as well as the circumstances associated with the outbreak of coronavirus disease in 2019 (COVID-19), they were not performed.

Conclusions

In conclusion, our observation suggests that nintedanib contributes to reducing regression of ground-glass opacities in SSc-IP patients. This indicates these rare patients could be expected to exhibit improved CT images with nintedanib therapy. It remains to be elucidated what characteristics of SSc-IP patients are related to improvement of the CT image, and the precise mechanism of action of nintedanib noting its inhibitory action on growth factors such as FGF, VEGF, and PDGF. Although careful consideration of side effects is required, if nintedanib can improve CT images in addition to the previously confirmed effects, it would be a desirable treatment option for SSc-IP patients. Additional clinical experience and knowledge will be required to prove our observation of the therapeutic effect of nintedanib on improving chest images.

Statement of ethics

This study was approved by the institutional ethics committee of each Hospital (Project approval number: NO16-66). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Conflict of interest

None declared.

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Pulmonary actinomycosis complicated by fistula of the chest wall

Abstract

Actinomycosis is a rare disease caused by *Actinomyces* spp. The clinical and radiological picture of the disease is uncharacteristic, which delays the diagnosis and can lead to complications. We present a case of pulmonary actinomycosis complicated by a chest wall fistula in a 43-year-old man with advanced tooth decay. The patient was admitted to our Department due to a chest wall fistula with bloody discharge. A few months earlier, he was treated with antibiotics for pneumonia. Since then, weakness, exertional dyspnoea, and weight loss had been observed. On admission, increased inflammatory markers were found in laboratory tests. Chest computed tomography (CT) revealed right-sided encapsulated pleural fluid collection containing gas bubbles, pleural thickening, anterior thoracic wall soft tissues thickening and subcutaneous fat stranding. CT suggested an empyema or a breast either pleural malignancy. The picture suggested a breast or pleural tumour to differentiate with an empyema. Videothoracoscopy was performed, the histological examination of the collected samples revealed granulation tissue and bacterial colony of a morphology corresponding to *Actinomyces* spp. Pulmonary actinomycosis was diagnosed. Antibiotic therapy according to the guidelines was initiated and dental treatment was recommended. Healing of the fistula and significant regression of lesions in the right lung were achieved. Although it is a rare disease, actinomycosis should be considered in the differential diagnosis of any chronic infiltrative lung lesions.

Key words: actinomycosis, tooth decay, fistula of the chest wall, antibiotics

Adv Respir Med. 2021; 89: 532–537

Introduction

Actinomycosis is a rare disease caused by *Actinomyces* spp., gram-positive anaerobic bacteria that normally live in the human oral cavity, digestive tract and urogenital system as commensals. *A. israelli* is considered to be the most common cause of the disease, followed by *A. naeslundi* and *A. mayeari* [1]. These bacteria usually coexist with other microorganisms that reduce the oxygen concentration in the environment and weaken the body defences, allowing *Actinomyces* to grow [2]. The disease can affect many organ systems. Infections of the craniofacial area are the most common, followed by gastrointestinal and respiratory disease [3]. It may also involve the central nervous system, bones and joints and the genitourinary system [4]. Lung infection occurs as a result of aspiration of infected contents from the oral cavity and the gastrointestinal tract [5]. Risk factors include lack of proper oral hygiene, alcoholism, chronic respiratory diseases such as chronic obstructive pulmonary disease, bronchiectasis, history of pulmonary tuberculosis, immunosuppression in the course of other diseases or treatment [4]. Males are more likely to be affected than females, which may be associated with less hygiene and more frequent facial injuries. Infection can occur at any age, but most often occurs in people aged 20–50 [5]. We present the case of a 43-year-old man suffering from actinomycosis complicated by a fistula of the chest wall. The aim of the study is to draw doctors' attention to the need for considering this disease at an early stage of differential diagnosis of ambiguous clinical cases.

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Case report

A 43-year-old smoking man with no history of chronic diseases was admitted to the National Tuberculosis and Lung Diseases Research Institute due to a chest wall fistula. His problem started five months earlier with dyspnoea and chest pain, for which he was evaluated in a different hospital. Tests performed at that time revealed significantly increased blood inflammation markers and right-sided pleural effusion up to the 8th rib with accompanying lung consolidations on chest x-ray. Community-acquired pneumonia was diagnosed. The patient refused hospital admission, so ambulatory antibiotic therapy was initiated (amoxicillin with clavulanic acid and clarithromycin). Despite treatment, mild chest pain persisted, deterioration of exercise tolerance and gradual weight loss developed. A fistula appeared with time in the right nipple area, oozing bloody discharge. Fever was not observed.

On admission to the Department, the patient's blood pressure was 140/95 mm Hg, heart rate regular 104/min, oxygen saturation 98% on room air. Chest auscultation revealed a decrease in breathing sounds at the base of the right lung, no adventitious sounds were heard. There were two striking findings from inspection: advanced tooth decay and cellulitis with fistula in the right mammary area. Blood tests revealed increased inflammatory markers and abnormal coagulation parameters (Table 1). Chest X-ray showed a large amount of fluid in the right pleural cavity (Figure 1). Contrast enhanced CT with pulmonary angiogram excluded pulmonary embolism. It revealed right-sided encapsulated pleural fluid collection containing gas bubbles, pleural thickening and contrast enhancement and features of anterior thoracic wall involvement: soft tissues thickening, discreet rib destruction and subcutaneous fat stranding (Figure 2). CT suggested a pleural empyema or a breast either pleural malignancy. Thoracentesis was performed and trace amount of bloody fluid was obtained — pH 8, brown colour, erythrocytes 3.85 x 1012/L; haemoglobin 11,8 g/dL; the smear was dominated by leukocytes — 77%. The fistula swab cultures yielded the growth of *Acinetobacter baumani complex*. For diagnostic and therapeutic reasons, the patient was referred for video-assisted thoracoscopic surgery (VATS). A pleural empyema was evacuated, and the anterior chest wall was incised. Material for microbiological tests and histopathological evaluation was collected. *Parvimonas micra* was cultured on the pleural effusion in anaerobic conditions, and the culture was sterile under aerobic conditions. The smear of pleural fluid was negative for acid-fast bacteria (final cultures were also negative), and there was no fungal growth. The patient was managed with pleural drainage and antibiotic therapy in accordance with antibiogram. Clinical improvement was achieved. As results of the histopathological examination of the chest wall phlegmon became available, they revealed a nonspecific granulation tissue with massive inflammatory infiltrate rich in neutrophils and plasma cells and with multiple colonies of densely packed bacteria. The colonies were covered by eosinophilic proteinous deposits (Splendore-Hoeppli reaction). Grocott methenamine-silver stain (GMS) revealed the filamentous structure of the bacteria. Morphology of microorganisms corresponded with *Actinomyces* spp. (Figure 3). The culture targeted at *Actinomyces* spp were negative. Based on histopathological analysis and corresponding clinical picture, the diagnosis of actinomycosis complicated by fistula of the chest wall was established. The antibiotic therapy was started in accordance with the guidelines for treating actinomycosis (intravenous therapy with amoxicillin with clavulanic acid for 2 weeks during hospitalisation followed by oral treatment with amoxicillin 3g/day at home) and dental treatment was recommended. During the initial treatment, the fistula was healed and the lesions in the right lung regressed significantly. In good general condition, the patient was discharged home. A follow-up hospitalisation was planned, but for economic reasons, it was not performed, and antibiotic therapy was discontinued approximately 3 weeks after discharge. The further course of the disease remains unknown.

Table 1. Laboratory tests results

Parameter	Result	Norm
Leukocytes [$\times 10^3/mm^3$]	12	4.23–9.07
C-reactive protein (CRP) [mg/L]	122	< 10
D- dimers [ng/mL]	1242	< 500
Activated partial thromboplastin time (APTT, formerly kaolin--cephalin time) [s]	38	24–35
INR	1.45	0.8–1.2

INR — international normalized ratio

Discussion

The clinical presentation of the respiratory system actinomycosis is not characteristic,

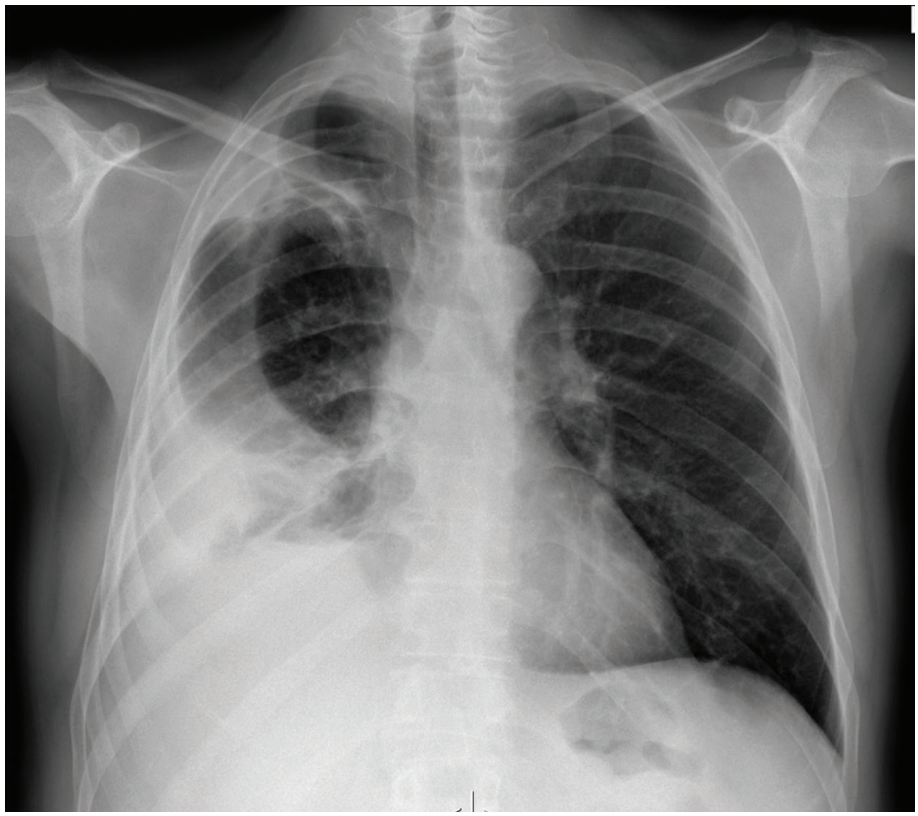

Figure 1. Posteroanterior chest radiograph shows a large amount of fluid in right pleural cavity

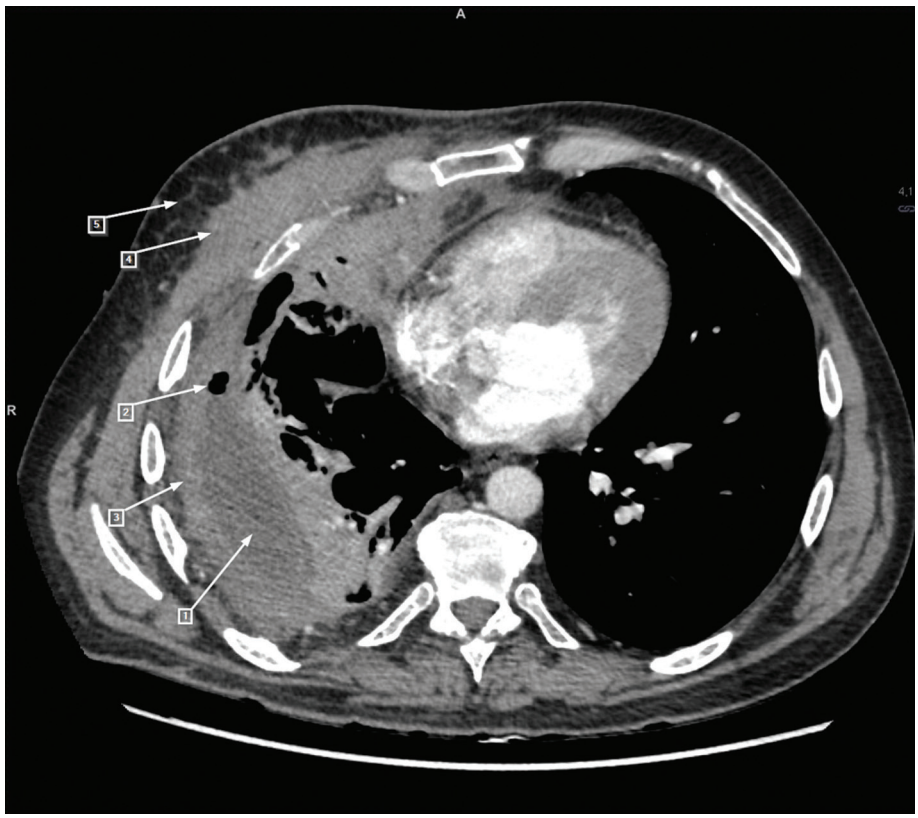

Figure 2. Axial contrast-enhanced CT image reveals right-sided encapsulated pleural fluid collection (arrow 1) containing gas bubbles (arrow 2), pleural thickening and contrast enhancement (arrow 3), anterior thoracic wall soft tissues thickening (arrow 4), subcutaneous fat stranding (arrow 5)

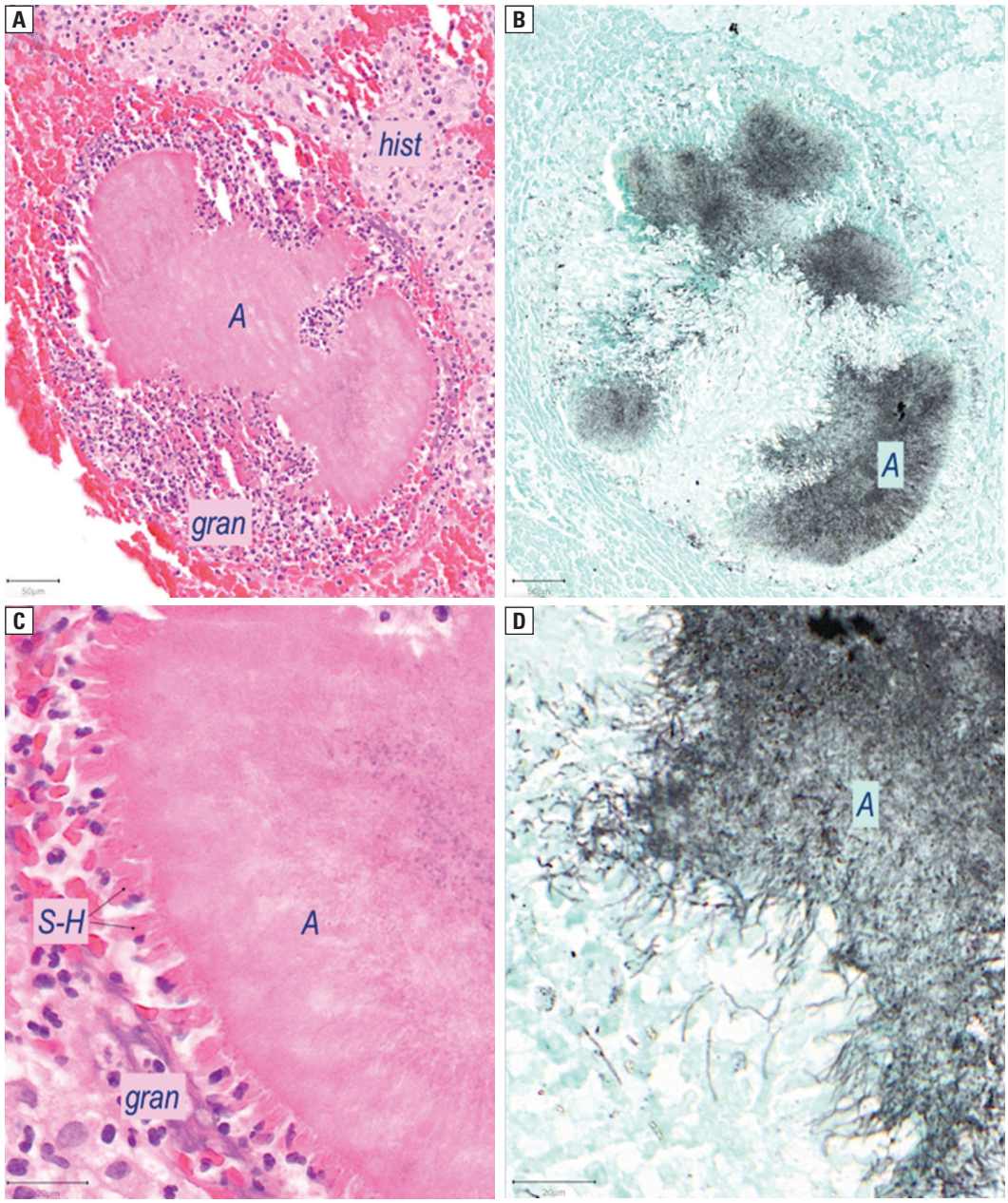

Figure 3. Microphotography of a colony of *Actinomyces*. **A, B**. Low-power of densely packed tangles of bacterial colony (*A*) surrounded by granulocytes (*gran*) and histiocytes (*hist*). **C.** High-power of bacterial colony (*A*) with eosinophilic deposits of proteinous exudate at the edge - so-called Splendore-Hoeppli phenomenon (*S-P*). **D**. GMS stain highlighted the filamentous structure of bacteria at the periphery of the colony (A and C — hematoxylin and eosin stain, magn. × 100 and 400; **C** and **D** — grocott methenamine silver stain — GMS, magn. × 100 and 400)

which is responsible for diagnostic difficulties and mistakes. It has been estimated that it takes approximately 3 months to make a proper diagnosis of pulmonary actinomycosis [6]. Initially, the disease may be asymptomatic. Later on, chronic cough, dyspnoea, chest pain, fever or low-grade fever, deterioration of exercise tolerance, weight loss, sweating, and recurrent respiratory infections appear. There are reports of massive or recurrent haemoptysis requiring pulmonary embolisation as the main clinical manifestation [7, 8]. In our case, the first symptoms of the disease were dyspnoea and chest pain. On the basis of performed tests, pneumonia was diagnosed and antibiotic therapy was initiated. Despite the treatment, the patient observed a deterioration of exercise tolerance, weight loss and local chest skin changes, which prompted him to seek further medical assistance. First, chest CT was performed 5 months after the first symptoms. It indicated right-sided empyema and/or breast or pleural neoplasm. According to the literature, pulmonary

nodular infiltrates are the most frequent radiological findings at the initial stage of the disease. Other observations include cavitation within the nodular infiltrates, central necrosis, ground-glass opacities, subpleural consolidation, mediastinal lymph nodes enlargement, pleural thickening and effusion [1, 7]. At that stage, it is very difficult to differentiate actinomycosis from pulmonary tuberculosis, neoplasms, lung abscesses or fungal lesions. In further course of the disease, the lesions may progress locally and involve adjacent structures. The formation of fistulas (e.g., into the oesophagus or through the chest wall) and abscesses within the respiratory system is a rare form of the disease and it appears most commonly at the late stage when not properly treated [4]. For this reason, the presented case deserves special attention. Five months elapsed between first symptoms and the diagnostic work-up in our Department. This time was sufficient for the development of complications. This shows how important it is to consider actinomycosis at an early stage of the differential diagnosis, especially if no improvement is achieved with treatment targeted at the most common respiratory infection agents.

Diagnosis of the disease is based on the presence of *Actinomyces* spp in the microbiological examination and/or findings in the histopathological test. Bronchoscopy may be helpful, however, there is no bronchoscopic pattern characteristic of actinomycosis. Samples collected during the examination can be considered diagnostic only in the presence of pulmonary cavities [3, 4]. Otherwise, it is difficult to decide whether the bacteria are the causative factor or just a contamination. Suzuki *et al*. [7] reported a case where pulmonary actinomycosis was diagnosed by transbronchial lung biopsy, but it is to remember that the diagnosis was made based on the tissue histopathological examination, not the cultures. Ding *et al.* [5] and Tabarsi *et al.* [8] presented similar cases. In our patient, bronchoscopy was not performed because the disease process seemed to originate from the chest wall. Instead, urgent VATS was undertaken. The surgical intervention was the most appropriate, both for diagnostic and therapeutic reasons. Surgical or CT-guided lung biopsy is also recognised as an appropriate diagnostic tool for pulmonary actinomycosis [4]. Pleural fluid testing is reasonable, but it rarely yields positive results [3, 9]. Samples for *Actinomyces* spp cultures should be collected under anaerobic conditions and growth should last 15–20 days. However, positive results are obtained in less than 50% of cases. Reasons include recent antibiotic therapy, abundant growth of other microorganisms, complicated procedure of specimen collection and the necessity to use non-standard conditions [3, 8]. In our case, cultures for *Actinomyces*, collected during thoracentesis and VATS, were negative. It is difficult to say which of the above-mentioned reasons played a role here. Perhaps it was influenced by other microorganisms' growth (*Acinetobacter baumani complex, Parvimonas micra*). In the presented case, histopathological findings were crucial for the final diagnosis. Characteristic lesions in the histological examinations include inflammatory granulation tissue with necrotisis and colonies of gram-positive filamentous bacteria. Macroscopically, bacterial colonies form yellowish clumps, so-called sulfur granules of a diameter of 0.1–1 mm. It is important not to consider them pathognomonic as they can also occur in other diseases such as nocardiosis or mycoses [4]. The possibility of using molecular techniques in the diagnosis of actinomycosis has been reported [6].

The treatment scheme of pulmonary actinomycosis remains controversial. Antibiotics penetration to the infection site is poor due to low vascularisation of the lesions and a large number of fibrous lesions [6]. Therefore, high doses of antibiotics and prolonged time of treatment should be applied. Standard treatment regimen includes the use of intravenous penicillin (18–24 mln units/day) for 2 to 6 weeks followed by oral treatment for 6 to 12 months (amoxicillin 3 g/day) [1, 4, 10]. Alternative treatments are based on the use of clindamycin or macrolides. [2, 4, 11]. *Actinomyces* spp do not produce β-lactamase, so there is no need to use their inhibitors, however, some authors describe effective therapy with them [12]. The treatment should be continued for at least 3 months to prevent local complications like fistulas or phlegmon of the chest wall and disease recurrence [4]. However, some authors advocate shortening the therapy to less than 6 months, including reducing the intravenous treatment phase to less than 14 days [10]. The argument for such approach is earlier detection of the disease nowadays than it was in the past, when the disease was often diagnosed at the late stage, with complications [10]. Zhang *et al*. [3] analysed 145 cases of actinomycosis and reported an average treatment duration of 4.5 months. All patients were considered cured. Kinner *et al*. [13] described 19 patients who were considered cured after an average treatment duration of 6 weeks. It is suggested to consider discontinuation of antibiotic therapy 1–2 months after disappearance of

clinical and radiological symptoms of the disease. Surgical treatment may also allow for shortening the antibiotic therapy [10]. Indications for surgery are massive/recurrent haemoptysis, no improvement after antibiotic therapy or the need to supplement it in case of abscesses, fistulas or phlegmon. In addition, invasive procedures are performed to rule out neoplasms. In case of massive pleural effusion, drainage should be used [6]. Quickly applied, it can also shorten the time of antibiotic therapy. However, the small number of described cases does not allow to confirm this unequivocally.

Conclusions

Pulmonary actinomycosis is a rare disease, but it should be considered in all patients with progressing infiltrative lung/pleural pathology. Once the diagnosis is made, proper antibiotic therapy should be started immediately. Delay in diagnosis or incorrect treatment may lead to severe complications.

Conflict of interest

None declared.

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Characteristic imaging finding and spot radiological diagnosis in a young man with acute breathlessness and chest pain

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Septic pulmonary embolism (SPE) is a serious complication of fulminant bacteraemia, usually seen in immunocompromised persons or intravenous drug abusers. Prompt recognition is usually possible through classic imaging appearance in the relevant clinical background.

A 26-year-old, previously-healthy, immunocompetent male presented to the pulmonology outpatient centre with sudden onset of breathlessness, chest pain, dry cough and burning micturition of three days' duration. A week earlier he had consulted the orthopaedic outpatient centre for acute high-grade fever with a painfully swollen left knee, and was diagnosed as left distal femur acute osteomyelitis. Immediately prior to this presentation, he had developed a furuncle in the left external nostril that went unattended. There was no history of trauma, intravenous drug abuse or other addictions. Examination revealed a temperature of 101°F, blood pressure 126/82 mm Hg, pulse rate 124/min, respiratory rate 28/min and SPO_2 89% on ambient air. The left knee joint was swollen and tender. Investigations were remarkable for a total leukocyte count of 29,100/mm^3 and C-reactive protein 151 mg/dL. Blood and urine cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA), while sputum and synovial fluid cultures were sterile. Echocardiography was unremarkable, and chest radiograph showed bilateral ill-defined nodules (Figure 1A). Computed tomogram of the chest (Figure 1B) revealed multiple, bilateral, variably-sized, pleural-based and parenchymal nodules, few of them with cavitation. Some of the nodules had a distinct vessel branch directly entering it, suggestive of the classical feeding vessel sign (FVS).

The clinical picture and pathognomonic imaging features suggested a diagnosis of SPE secondary to left distal femur acute osteomyelitis-induced MRSA septicaemia. The patient was initiated on linezolid and cefepime intravenously as per the culture-sensitivity reports, which was followed by respiratory stabilization within 72 hours and complete clearing of pulmonary nodules after two weeks. He was subsequently transferred to orthopaedics for further care of his joint complaints.

SPE is an uncommon, potentially fatal complication of fulminant bacteraemia. It is usually seen in patients with right-heart infective endocarditis, indwelling devices and catheters, skin or soft tissue or bone infections, septic abortions, oro-dental infections and in immunocompromised persons. The occurrence of septic embolism in an immunocompetent host indicates severe infection that fails to remain contained at the primary focus and spreads to other sites. SPE arises due to hematogenous dissemination of infected microthrombi from an extrathoracic nidus. The thromboemboli produce microvascular occlusion within the lungs resulting in a host of insults that include ischaemic lung parenchymal damage, infarction, infective and inflammatory changes, and microabscess formation. These pathophysiological processes manifest as lung nodules on chest imaging.

A high clinico-radiologic index of suspicion is required as the diagnosis of SPE can be challenging due to diverse presentations and varying aetiologies. The most commonly reported clinical features include chest pain, dyspnoea and cough occurring in a febrile patient with a known extrathoracic site of bacteraemia. Blood cultures, chest imaging and echocardiography form the cornerstone of diagnosis of suspected SPE. Diagnosis relies greatly on the classical chest CT findings in an appropriate clinical setting. Typical CT imaging characteristics include bilateral, peripheral nodules (with or without cavitation), wedge-shaped pleural-based infarcts, FVS, pleural effusion, and mediastinal and/or hilar lymphadenopathy [1–3]. FVS is considered a highly suggestive imaging sign of SPE, with a reported prevalence of 67–100% [4]. It is also known as the feeding artery sign or fruits on the branch sign, and indicates a pulmonary artery branch that leads directly to the nodule. Other conditions where it may be commonly seen are lung metastases, pulmonary infarcts, vasculitis, and pulmonary arteriovenous malformations [5].

Management of SPE involves adequately addressing the primary focus of infection, prolonged course of broad-spectrum antibiotics, and other supportive measures as appropriate. Complications depend upon the

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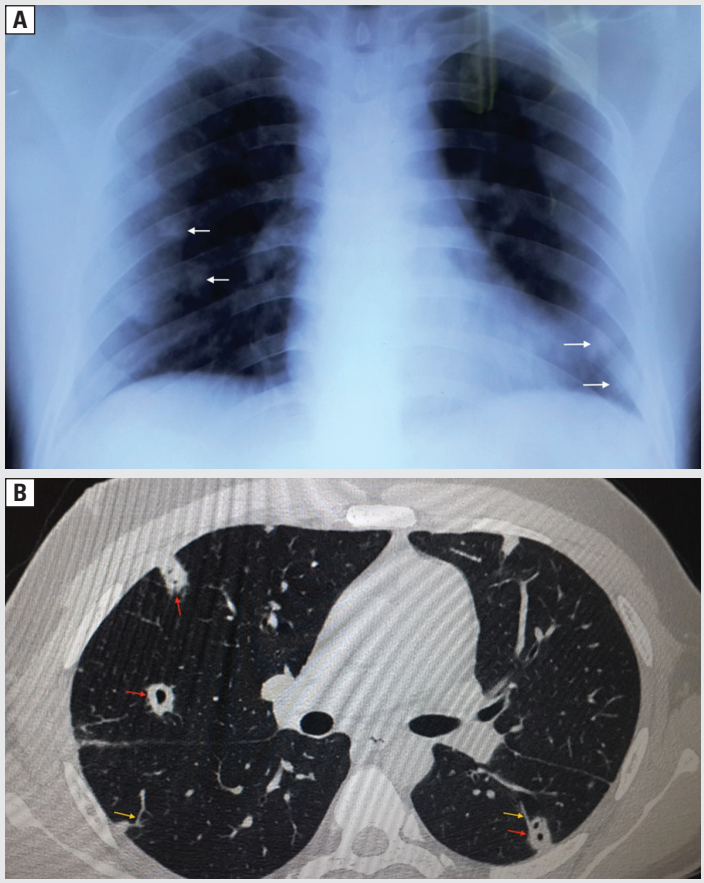

Figure 1. A. Chest radiograph (posteroanterior view) showing bilateral, ill-defined, nodular parenchymal opacities, mainly in mid and lower lung zones (white arrows). **B.** Chest computed tomogram scan (axial section, lung window) showing multiple, bilateral, peripheral parenchymal nodules, few showing cavitation (red arrows), and some having a distinct vessel branch directly entering the nodule — the feeding vessel sign (yellow arrows)

quantum of lung parenchymal damage inflicted, and include empyema, lung abscess, chronic cavitary lung disease, pneumothorax, and acute hypoxemic respiratory failure.

To conclude, SPE is a serious condition that must be strongly considered in the appropriate clinical context. Thoracic CT imaging plays an invaluable role in diagnosis especially when characteristic imaging findings are present. Timely diagnosis and aggressive treatment of this entity can be life-saving. This clinical vignette is being reported to highlight the pathognomonic FVS that facilitates clinching of the diagnosis of this uncommon entity, and must incite its consideration even in young immunocompetent individuals without any comorbidities or risk factors.

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Sclerosing pneumocytoma accompanied with dilated air-containing space

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Sclerosing pneumocytomas are one of the most common benign lung tumors. Although rare [1–4], some of them can be accompanied by dilated air-containing space.

A 61-year-old woman was referred to our hospital because of a nodule in the left lung detected in a chest radiograph mass screening program (Figure 1A). Chest computed tomography (CT) showed a well demarcated nodule with a peritumoral air-lucent zone in the lower left lobe. In chest radiograph taken at another medical institution 7 years ago, a nodule was detected in the left lung, which was diagnosed as a sclerosing pneumocytoma (Figure 1B). However, the patient did not wish further evaluation because she was asymptomatic. Eighteen months after the first visit to our hospital, she came to our institution because of hemoptysis. Chest CT taken at that time confirmed that the nodule with peritumoral air-lucent zone increased by a maximum diameter of 7 mm at this interval (Figure 1C). With the advent of hemoptysis, surgical resection was performed. The patient was pathologically diagnosed as having a sclerosing pneumocytoma, and the presence of a dilated air-containing space corresponding to the peritumoral air-lucent zone seen on CT was pathologically confirmed. When calculated using Schwartz's formula, the tumor doubling time was 5.9 years, and its onset was estimated to be more than 10 years ago.

Pulmonary sclerosing pneumocytoma is one of the most common benign tumors of the lung. It is pathologically composed of several components such as cartilage, connective tissue, muscle, fat, and bone. The tumor usually occurs at the age of 40 and 50. The majority of lung sclerosing pneumocytomas develop in the periphery of the lung [1–5]. They are typically well-circumscribed nodules or masses with either smooth or lobulated margins. Although rare, however, some of the patients with sclerosing hemangioma could be accompanied by dilated air-containing space [1–4]. Patients with this tumor are usually asymptomatic and they are found incidentally when imaging the chest for other reasons. However, it can occasionally present with hemoptysis, bronchial obstruction, and cough. It has been estimated that these benign tumors grow very slowly, however, to the best of our knowledge, there has been no report to reveal their volume doubling time.

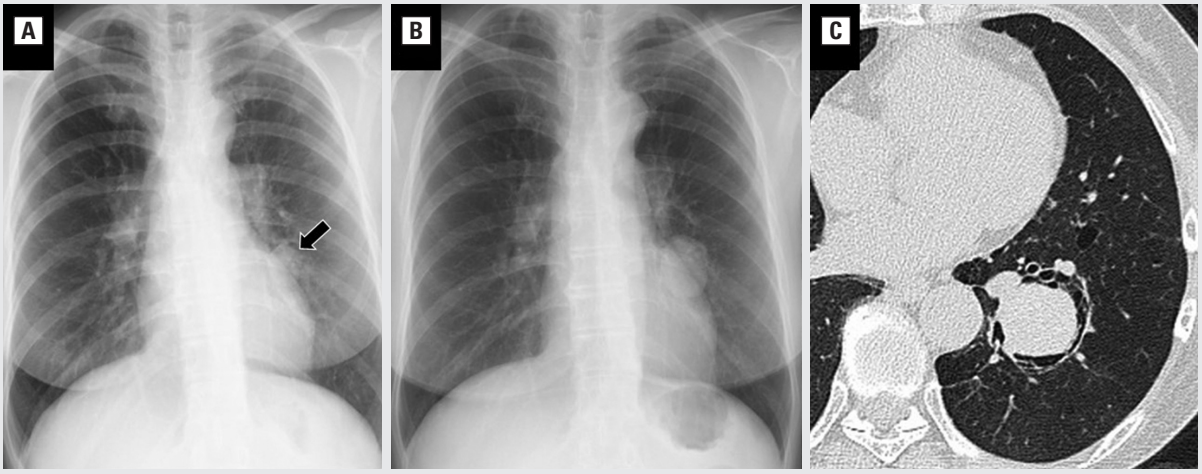

Figure 1. A nodule in the left lung (arrow) in plain chest radiograph taken 7 years ago (**A**), and that taken at the first visit to our hospital (**B**). The nodule in chest computed tomo taken 18 months after the first visit (**C**)

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No studies have examined the volume doubling time of this tumor with dilated air-containing space. Although rare, sclerosing pneumocytoma is showing CT images similar to "halo sign" and 'meniscus sign'that have been observed in our patient too. There have been reports suggesting the involvement of tumor-related bleeding in the pathological findings of such signs and space formation around the tumor. The current report presents the natural history of such a type of lung sclerosing pneumocytoma that presented as a slow-growing mass, which was determined by calculating its doubling time and volume changes.

This study was approved by the institutional ethics committee in our Hospital. Written comprehensive informed consent at the time of admission for obtaining pathological specimens was acquired from the patient.

Conflict of interest

No conflict of interest was declared by the authors.

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Unilateral multiple thoracic hydatid cysts: a rare presentation

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Hydatidosis, when present in multiple thoracic locations, requires a synchronous or successive approach, which can lead to an increased risk of complications.

A 50-year-old female with a history of hepatic hydatid cyst surgery 30 years ago presented with chest pain and dyspnea. Chest X-ray revealed multiple homogeneous opacities of the right hemithorax (Figure 1A). Thoracic and abdominal computed tomography (CT) scans (Figure 1B, 1C, and 1D) showed multiple hydatid cysts in the right hemithorax [2, 3]. Hydatidosis serology (ELISA) was positive. After 2 weeks of preoperative Albendazole treatment, the patient underwent a posterolateral thoracotomy. Protection of the surgical field was maintained with packs immersed by a scolicidal solution and difficult pneumolysis. All the cysts were treated via cystectomies or pericystomies with capitonnage. There was no trans-diaphragmatic fistulation. The diagnosis was confirmed by pathological examination. The patient was discharged uneventfully on the 7th postoperative day. No further complications or recurrence occurred during 12 months of follow-up.

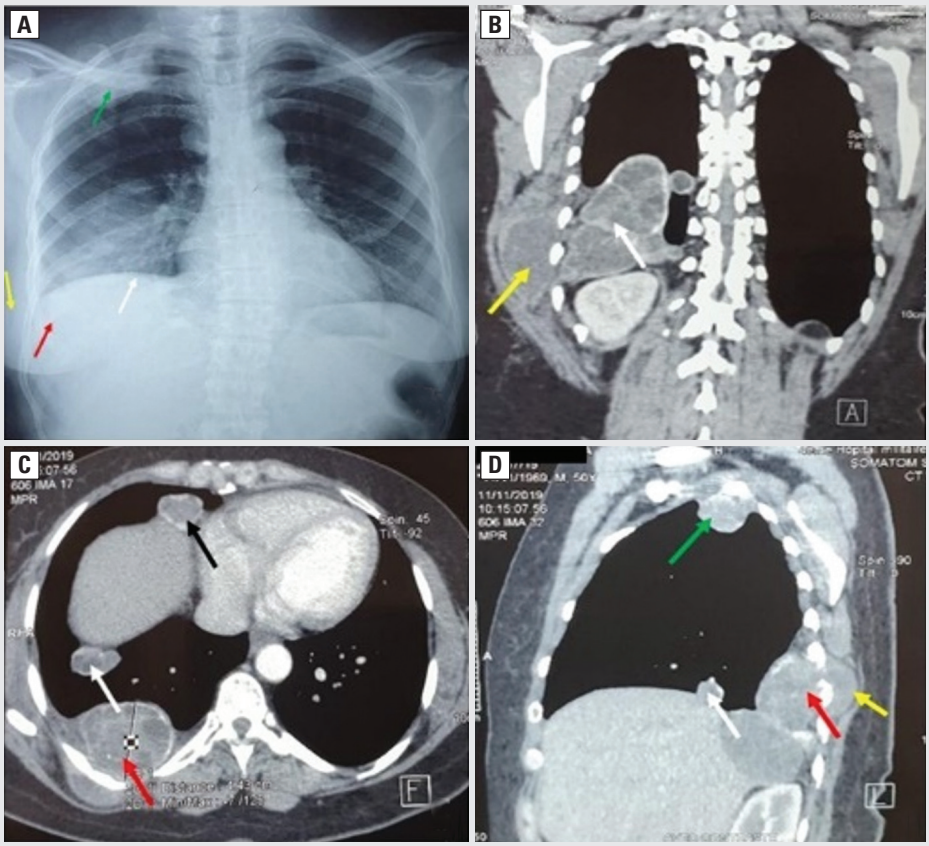

Figure 1. A. Chest x-ray showing multiple right thoracic opacities; **B–D.** Chest computed tomography showing multiple right thoracic hydatid cysts: chest wall (yellow arrow), diaphragmatic (white arrow), pericardial (black arrow), pleural (red arrow), and pulmonary (green arrow) regions

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Multiple thoracic hydatid disease is usually secondary to dissemination after spontaneous or preoperative rupture of the hepatic cyst into the thorax. Therefore, the right hemithorax is the most affected region [1, 2].

In terms of thoracic spread, the diaphragm is the first location affected. This occurs most often secondary to intraoperative contamination of the hepatic location due to precautions taken during surgery. This complication is usually asymptomatic, although symptoms can occur in complicated forms such as rupture or infection of the cyst or by compression of the neighboring organs. Imaging with CT gives important diagnostic information about the cysts (location, size, character, and relationship to surrounding vital structures) [2–4]. The treatment is based on successive or simultaneous surgery via excision of hydatid cysts. Preoperative medical treatment with albendazole is recommended by some authors because it sterilizes the contents of the cyst and prevents postoperative spread. Strict precautions and careful handling of the cyst are essential during surgery. Therefore, the operating field must be absolutely protected with scolicidal solutions such as hypertonic saline, povidone iodine, or hydrogen peroxide in all cases [1, 4]. Conservative treatment options such as cystotomy and pericystectomy with capitonnage of the residual cavities are the most effective procedures [3, 5], whereas radical surgery (lobectomy or more) is rarely indicated. The recurrence rate is reported to be higher with conservative surgery rather than radical surgery [4] due to failure to totally remove the smallest cysts and/or prevent spread during surgery. The follow-up after surgery must be extended to detect any recurrence or dissemination; this is especially true is for endemic areas of hydatidosis [2].

We concluded that a CT scan gives important diagnostic information and aids in therapeutic management of the cysts. The treatment is based on surgical conservative procedures associated with medical therapy.

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Antitubercular therapy — an uncommon side effect

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A 43-year-old female presented with complaints of chest pain, non-productive cough, shortness of breath, diarrhoea, loss of weight and appetite, and generalised malaise for a period of one month [3]. The chest X-ray demonstrated a massive right-sided pleural effusion. Subsequently, pleural fluid reports revealed an exudative effusion with predominantly mononuclear cells, negative malignant cytology and no growth in pyogenic culture as well as a Mycobacteria Growth Indicator Tube (MGIT) culture. Contrast-enhanced computed tomography (CECT) demonstrated a loculated pleural effusion with right middle lobe pneumonia. CECT of the abdomen revealed diffuse circumferential enhancing thickness of the terminal ilium and ileocecal junction with enlarged lymph nodes. The Mantoux test was positive (30 mm). The baseline haematologic and organ function tests were within normal ranges. The absence of sputum production and failure to induce sputum led to a request for bronchoscopy in order to obtain a microbiological diagnosis. Unfortunately, the patient did not provide consent to have this procedure. Thus, based on the clinic-radiological profile and the fact that the region was TB endemic, the patient was initiated on weight-based Antitubercular therapy (ATT) comprising of isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (1600 mg), and ethambutol (1100 mg). However, within two days of therapy, the patient complained of general pruritus, especially over all four limbs, and exanthematous lesions in the extensor aspects. Symptomatic therapy comprising oral antihistaminic drugs and topical steroids provided partial relief. Investigations revealed a haemoglobin (Hb) level of 12.3 gram %, a total leucocyte count (TLC) of 9200/mm^3 (comprising 36% eosinophils), and an absolute eosinophil count (AEC) of 3312/mm. A detailed work-up as a result of eosinophilia revealed normal spirometry results (testing for asthma) and a normal stool examination (testing for helminthic infection). Liver function tests also revealed transaminitis (Aspartate transaminase — 252 IU/L; Alanine transaminase — 240 IU/L). A diagnosis of ATT-induced drug rash with eosinophilia and systemic symptoms (DRESS) was made. On discontinuing ATT, the AEC decreased to 380/mm^3. The patient was also provided with symptomatic relief.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug reaction characterized by an extensive skin rash associated with visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis [1]. The syndrome is characterized by a latency period ranging from 3 weeks to 3 months after the introduction of the offending drug. The range of eosinophilia may determine the involvement of internal organs with pulmonary infiltrates. In general, eosinophilia may be observed about 1 to 2 weeks after the onset of the syndrome, or can even occur after the increase in liver enzymes has normalized [2]. Multiple diagnostic criteria have been proposed for the diagnosis of DRESS syndrome by organizations including the European Registry of severe cutaneous adverse reactions (*RegiSCAR)*, the Japanese research committee on severe acute cutaneous reactions (*J-SCAR),* and by Bocquet et al. [3], which require that the three criteria of cutaneous involvement, eosinophilia, and systemic involvement (lymphadenopathy, transaminitis or nephropathy) are fulfilled. The index case had cutaneous eruptions, eosinophilia, and systemic manifestations (increased liver enzymes > 2 times greater than normal). There are only a few case reports of DRESS syndrome developing after taking ATT which all improved on cessation of therapy [4]. All ATT drugs have been implicated in causing DRESS, with isoniazid and rifampicin being most common [5]. The index case also demonstrated a reappearance of a rash and eosinophilia on attempted reintroduction of both drugs. As a result, the patient was eventually shifted to a modified therapy as per national guidelines. A large case series conducted over ten years documented only 67 cases of DRESS syndrome due to ATT with mortality in two patients [6]. Thus, DRESS is rare, but can also be life-threatening.

To conclude, a high index of suspicion and regular follow-up are the keys to an early diagnosis of DRESS syndrome in order for the offending drugs to be stopped early.

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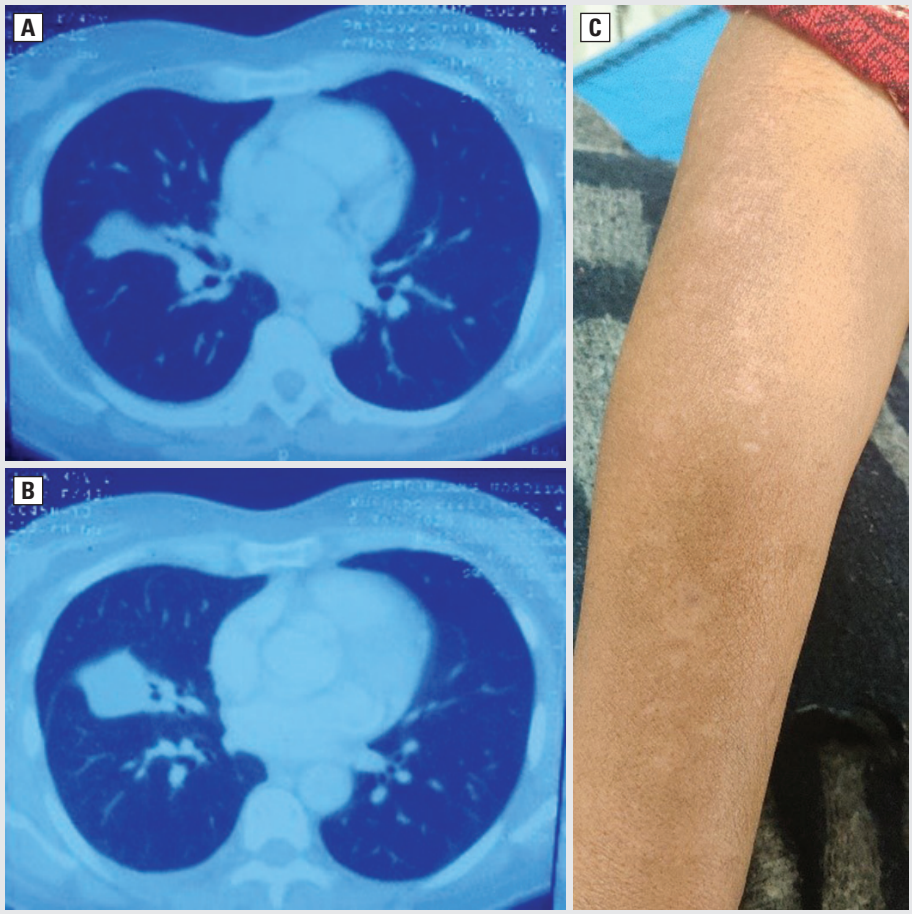

Figure 1. A, B. Computed tomography of the chest showing right middle lobe consolidation; **C.** Exanthematous rash over the right leg

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A young female with polycythemia: Pearls in the lung

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A 35 year-old female presented to the Pulmonary Medicine OPD with a history of progressive dyspnea, malaise, weakness and easy fatigability for the last 5–6 months. On examination, she had clubbing and redness on her face. She had stable vitals but low room air oxygen saturation on pulse oximetry (SpO_2 of 85%). Chest examination was normal. Laboratory parameters showed Hb — 19.2g/dl and hematocrit — 57%. Other hematologic and biochemical parameters were within normal limits. Her chest X-ray showed right upper lobe infiltrates (Figure 1A–B) and she was prescribed empirical anti-tubercular therapy (ATT) by an outside practitioner based on clinical and radiological findings. Echocardiography (ECHO) and an ultrasound of the abdomen were normal. Screening for polycythemia conducted during the initial evaluation revealed high erythropoietin levels, absent Jak-2 mutation, and no findings to suggest plasma volume contraction. She had no improvement of symptoms after 1 month of ATT. As a result, the patient was evaluated further. ABG measurements showed ph — 7.41, pCO_2 — 39, pO_2 — 49, and HCO_3 — 23. A contrast ECHO was ordered to rule out any blood shunting as infiltrates on chest X-ray were inconsistent with the degree of hypoxemia and polycythemia. ECHO revealed appearance of air bubbles in the left atrium after 3 cycles of heart beats. A subsequently performed contrast-enhanced computed tomography of the chest along with CT pulmonary angiography (Figure 1C–F) showed pulmonary arteriovenous malformations. A CT scan of the brain was normal. A colour doppler of bilateral upper and lower limbs (arterial and venous) did not show any thrombi. Hence, the final diagnosis was pulmonary arteriovenous malformations (PAVMs).

Pulmonary arteriovenous malformations are rare pulmonary vascular anomalies and are mostly asymptomatic but can cause dyspnea based on the degree of left-to-right shunting and the severity of hypoxemia [1]. Although uncommon, polycythemia can be a presenting manifestation of PAVMs due to chronic hypoxemia [2]. Paradoxical emboli can cause stroke or cerebral abscesses, particularly if previously undiagnosed. The most common cause of PAVMs is HHT (hereditary hemorrhagic telangiectasia). PAVMs may be solitary or multiple and lower lobes are most commonly affected. The right upper lobe is rarely involved [1]. In our case,

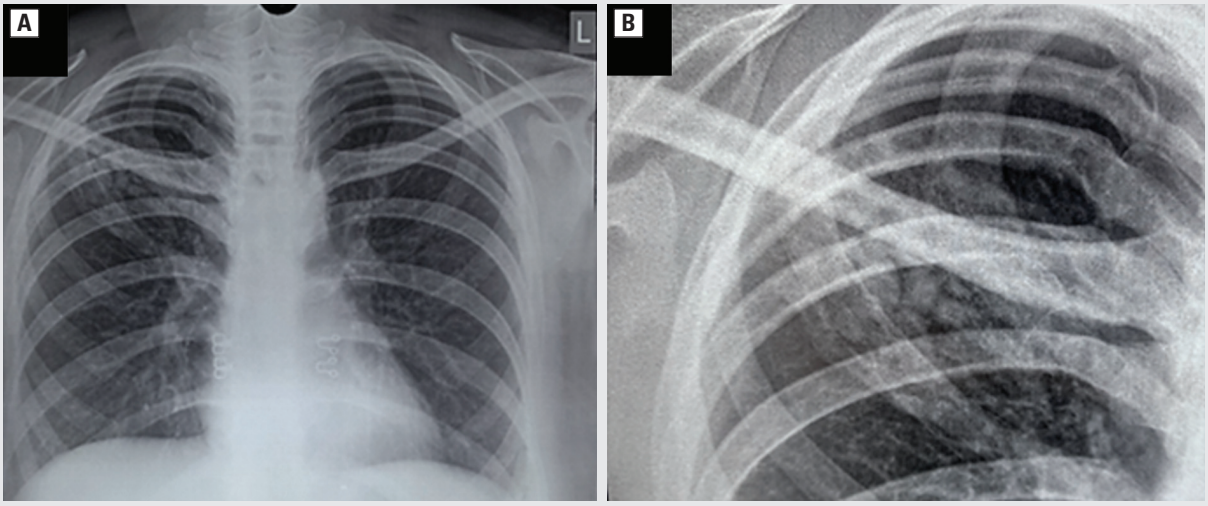

Figure 1. A. Chest X-ray posteroanterior view showing a lobulated opacity in the right upper zone. **B.** Magnified view showing curvilinear opacities extending from the hilum suggestive of a pulmonary arteriovenous malformations (AVM)

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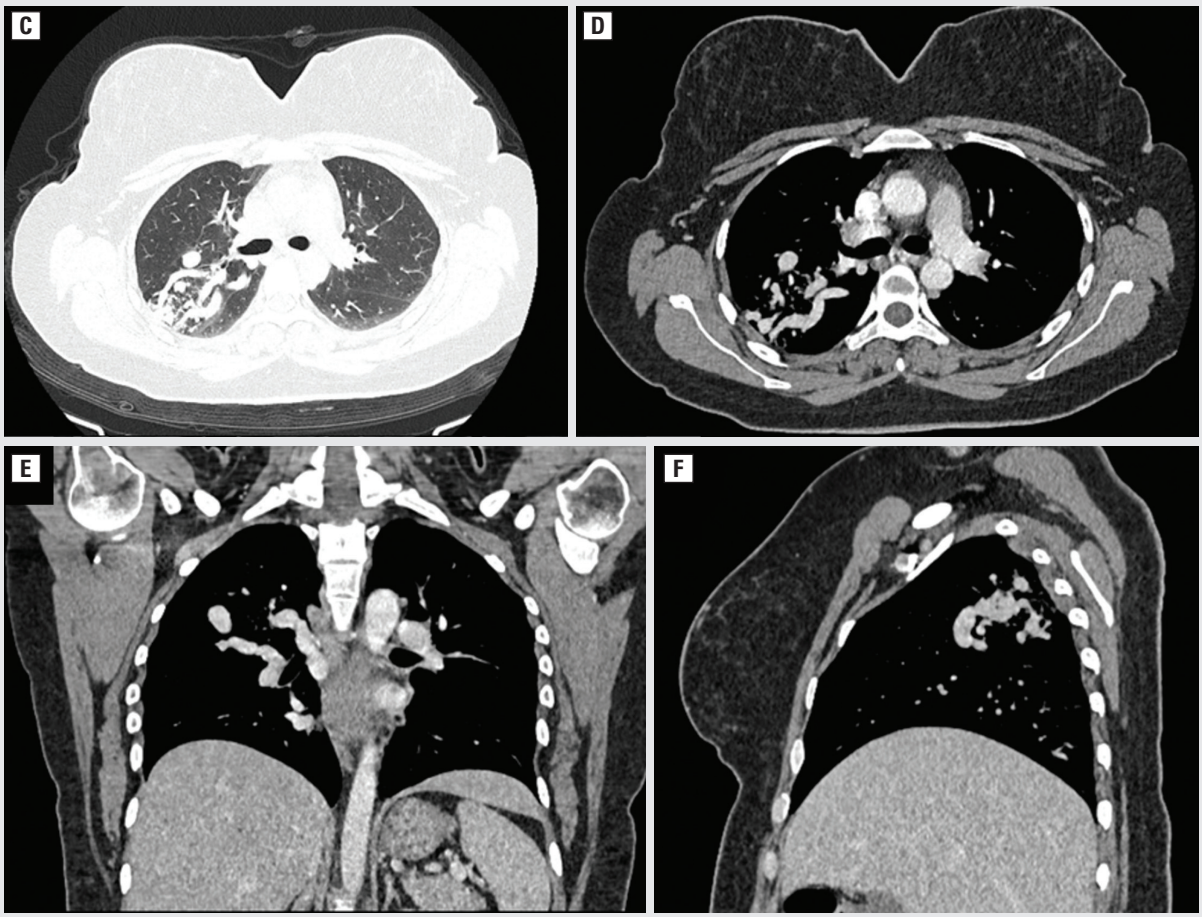

Figure 1. C. Axial chest computed tomography (CT) pulmonary window showing tubular branching opacities in the posterior segment of the right upper lobe. **D.** Axial CT mediastinal window showing a tuft of vessels. **E.** Coronal CT showing a pulmonary AVM with a feeding artery and draining vein. **F.** Sagittal CT showing a pulmonary AVM

the unusual location of this rare entity led to a false diagnosis of pulmonary tuberculosis. Chest radiographic features classically present are sharply defined non-specific round to oval opacities of uniform density that are frequently lobulated and range in size from 1–5 cm [3]. Contrast echocardiography is a highly sensitive tool for diagnosis, but CT pulmonary angiography remains the gold standard [4]. Treatment options include embolization and surgical excision [5].

The diagnosis of PAVM as a cause of polycythemia in a young female and its unusual location in the lungs leading to an incorrect diagnosis of pulmonary tuberculosis makes this case rare and interesting.

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Clinical studies regarding COVID-19 in Belgium

To the Editor

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), arrived in Belgium early February 2020 [1]. This was the start of an epidemic that, by May 2nd, 2021, would be responsible for 993,434 confirmed cases; 70,384 hospitalisations and 24,258 fatalities [2]. After more than one year of research into the disease and its causative agent, a lot of progress has been made in management and treatment of COVID-19 [3]. As of December 21st, 2020, the Belgian Federal Agency for Medicines and Healthcare products (FAHMP) reported that 32 clinical drug trials, 6 clinical vaccine trials and 5 clinical studies with medical devices and/or in vitro diagnostics were authorized [4]. Continued research efforts are essential to tackling the persisting pandemic.

To obtain an insight into the clinical studies already performed in Belgium, the clinical trials database of FAHMP was searched for "covid-19". To identify additional studies not involving investigational medicinal products (IMPs), the clinicaltrials.gov database was searched for "COVID-19", "COVID" and "SARS-CoV-2". The results were filtered for studies in Belgium that were completed, suspended or terminated.

Thirty-three unique studies were retrieved from the FAHMP register (Supplementary materials, Table S1). Of these studies, 23 (69.70%) were being conducted at multiple sites in Belgium. This means that in a large majority of the studies, there was a cooperation between different institutions. Monocentric studies were often carried out in centres with specific expertise. Twenty-six (78.79%) studies utilized randomisation. Despite being only part of study design, this observation suggests that the urgency by which knowledge about COVID-19 is needed, did not negatively impact the scientific rigor of the research performed.

The number of studies per phase of development studies are shown in Figure 1. Five of the extracted studies (15,15%) were in phase I (human pharmacology). Most of these studies investigated the safety and immunogenicity of vaccine candidates. Nine (27.27%) studies were only in phase II (therapeutic exploratory). These studies investigated a wide variety of treatment strategies to tackle COVID-19, ranging from antiviral drugs to cell therapy. Phase III (therapeutic confirmatory) studies accounted for 6 (18.18%) of the total number of studies. These studies looked into the safety and efficacy of several treatments for disease management and prevention. Five (15.15%) studies were described being both phase II & III. Finally, 8 studies were in phase IV (therapeutic use). Based on these observations, it can be stated that COVID-19 research in all phases of the development process is being conducted in the Belgian territory.

Twenty-eight completed or terminated studies were conducted in Belgium according to the clinicaltrials.gov database (Supplementary materials, Table S2). Completed studies numbered 25 (89.29%) and terminated studies 3 (10.71%). The three terminated studies investigated hydroxychloroquine as a treatment, a COVID-19 vaccine and the performance of three sampling methods. Unfortunately, none of the completed studies had results available. From the identified studies, it is clear that a lot of different research interventions have been used for COVID-19 research, including ques-

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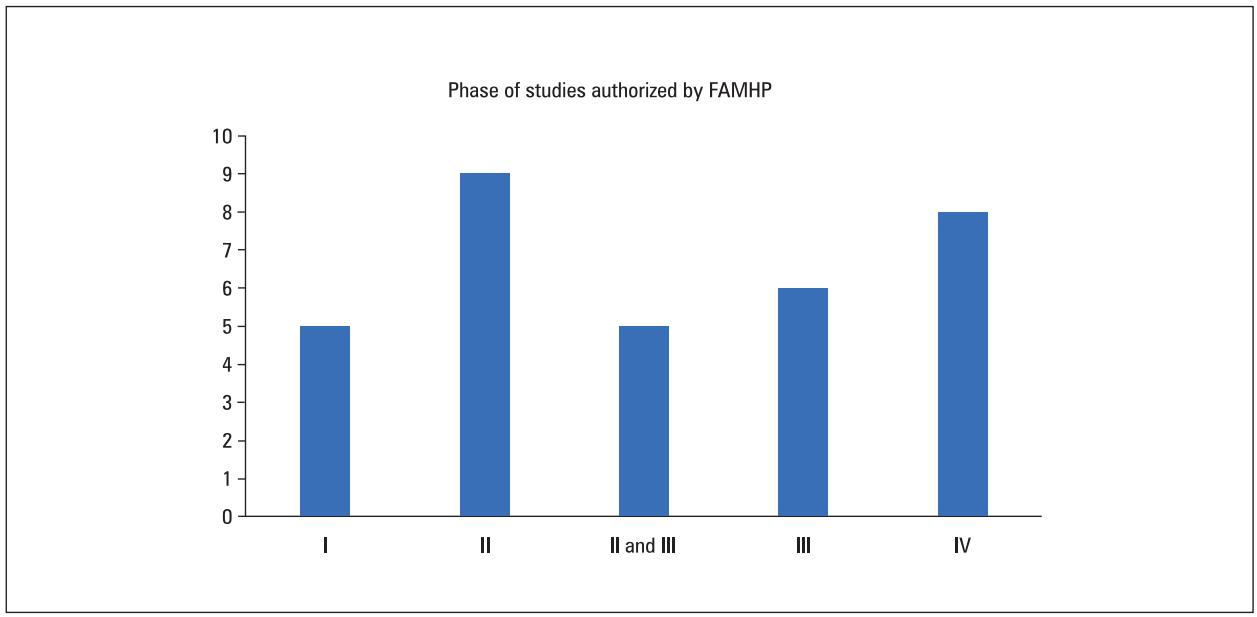

Figure 1. Number of studies approved by Federal Agency for Medicines and healthcare products (FAMHP) per phase

tionnaires and drug treatment. This is linked to the wide range of research topics of the studies, which ranged from discontinuation of fertility treatment to quality of life of oncology patients during the pandemic. A lot of aspects besides the purely medical and virological questions about the pandemic are being investigated.

Eleven (39.28%) of the studies were interventional while 17 were observational (60.71%). This means that several types of study design are used to investigate the COVD-19 pandemic.

In general, it is clear that a lot of research on COVID-19 has been conducted in Belgium. The studies are diverse in scope and methods. A more comprehensive analysis of the research conducted, could provide directions for further research. Additionally, systematic reviews and meta-analyses could synthesize the different studies already conducted.

Conflict of interest

The authors do not have a conflict of interest.

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High-dose steroids for the treatment of severe COVID-19 pneumonia: the need of the hour?

To the Editor

Ever since the results of the RECOVERY trial [1] were made public, steroids became the mainstay of the treatment of patients with moderate to severe COVID-19 pneumonia needing oxygen support. As the pandemic progressed and patients with moderate to severe disease requiring oxygen were treated with 6 mg dexamethasone for 10 days, it soon came to light that the recommended dose did not show a significant mortality benefit. In clinical practice, high-dose steroids are used in disease processes involving high inflammatory activity such as auto-immune diseases, septic shock unresponsive to fluid resuscitation and vasopressors, chronic obstructive pulmonary disease (COPD) exacerbation, severe asthma, and allergy. Therefore, to consider high-dose steroids for the management of severe COVID-19 pneumonia is not a novel concept.

Edara *et al*. [2] published a case series where they treated two patients who were deteriorating on conventional regimen of steroid therapy with high doses of methylprednisolone reaching up to 500–750 mg/day and reported a positive outcome. So *et al*. [3] treated seven patients with COVID-19 intubated secondary to acute respiratory distress syndrome with high-dose methylprednisolone 500–1000 mg/day and reported a positive recovery in all seven patients. A study from Iran [4] randomised sixty-eight hospitalised patients with confirmed severe COVID-19 into two groups with a ratio of 1:1, with one group receiving standard care with the addition of methylprednisolone pulse (intravenous injection, 250 mg/day^{-1} for 3 days) and the second group receiving standard care alone (which included the conventional dose of the steroid). The number of patients with a clinical improvement was higher in the group receiving methylprednisolone pulse therapy as compared to the group receiving standard care (94.1% *vs* 57.1%), and the mortality rate was lower in the methylprednisolone group (5.9% *vs* 42.9%; $p < 0.001$). These studies, though not adequately powered, do raise a possibility of benefit to patients with severe disease when treated with high doses of steroid.

A question now arises on defining the subset of patients who would qualify for the high-dose steroid therapy. This query was answered by a recent study published by Spanish authors [5] to test whether high-dose corticosteroid pulse therapy (1.5 mg/kg/24h of methylprednisolone or dexamethasone equivalent) was associated with increased survival in Covid-19 patients at risk of hyper-inflammatory response. The group provided with the initial criteria using laboratory markers to stratify these patients. The parameters proposed were (IL-6 ≥ 40 pg/mL, and/or two of the following: C-reactive protein ≥ 100 mg/L, D-dimer ≥ 1000 ng/mL, ferritin ≥ 500 ng/mL and lactate dehydrogenase ≥ 300 U/L) and a positive outcome was noted in the subjects receiving the higher doses.

These are times where the scientific knowledge is being updated on a daily basis and guidelines are changing every day in the light of new evidence. Under such circumstances the sound data available showing a benefit of high-dose steroids in severe COVID-19 pneumonia and the

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criteria where they should be instituted warrants further investigation in the form of adequately powered randomised control trials to answer this new but pressing question — is this the need of the hour?

Conflict of interest

None declared.

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Inhaled budesonide for mild COVID-19. Is there more to it than just airways?

To the Editor

As healthcare systems in many countries buckle under the immense pressure of rising COVID cases, a drug which can reduce emergency visits would be a huge boon. The results of the STOIC trial, therefore, are very uplifting [1]. Inhaled budesonide, a safe and simple intervention, seems to reduce hospital visits by almost 90% among mild COVID cases. None of the published, peer-reviewed trials have yet shown tangible benefits for this endpoint. In fact, seldom do therapeutic strategies show an effect size of this magnitude [2].

Therefore, it is only prudent to examine the data closely — is the effect of budesonide limited to reduction in emergency visits, or does it alter pathobiology of disease progression. Although the study excluded patients with recent use of inhaled or systemic glucocorticoids, there was a 15% prevalence of current or past asthma in both groups. Viral infections are known triggers of asthma, as acknowledged by the authors, which may present as worsening breathlessness leading to emergency visit. It is possible that it is only reversing the airway hyperreactivity in those already at risk, and not altering COVID pathophysiology. It would be interesting to know if the difference in outcomes is being disproportionately driven by this subset.

Patients in the treatment arm showed faster improvement in systemic symptoms, and lower antipyretic requirement. However, the biological plausibility of this effect is unclear. Systemic effects of 800 μg of inhaled budesonide are minimal, and it would be unusual to expect reduction in systemic inflammation. Unfortunately, the study did not collect data on inflammatory markers to explore this aspect. Moreover, the difference in respiratory symptom scores is not significant, while the difference in systemic symptom scores is. Also, the faster clinical recovery in the budesonide group plateaued after day-14, and the perceived difference in clinical recovery remained the same until day-28. Possibly there may be a bias in self-reporting due to the non-placebo-controlled nature of the study. Above all, the decision to terminate the trial early despite such a small number of events (3 in the treatment group *vs* 11 in the control group) raises strong concerns of chance association.

The situation of a COVID physician is no better than that of Coleridge's Mariner [3] — surrounded by a sea of over 100,000 studies, 100 clinical trials, and few dozen treatment options — yet only one or two drugs actually changing clinical outcomes [4]. In this situation, a 90% reduction in emergency visits is by itself an unparalleled feat. Such magnitude of effect is not seen with any other treatment, and the work of the authors is laudable. However, understanding exactly what drives this phenomenon is of utmost importance.

Conflict of interest

None declared.

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Airway management in personal protective equipment conditions

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To the Editor

Airway management is one of the key skills that medical personnel should master, especially by emergency medical service teams. As shown by many studies, the effectiveness of endotracheal intubation in emergency medicine conditions is insufficient, ranging from 57.6% to 89.9% [1, 2]. However, in the situation of the current SARS-CoV-2 pandemic, medical personnel should treat each patient in pre-hospital conditions as a potentially infected patient, therefore they should perform medical procedures wearing personal protective equipment (PPE) for aerosol generating procedures (AGPs) [3, 4].

It is problematic that PPE-AGP, by limiting movement and visibility, may reduce the effectiveness of individual medical procedures and extend their time [5]. Maslanaka et al. in his meta-analysis he showed that anaesthesiologists wearing PPE-AGP could intubate patients more efficiently with the AirTraq videolaryngoscope compared to the Macintosh laryngoscope (85.6% vs 68.4%; p = 0.006) [6]. However, because of the lack of commonly available videolaryngoscopes in prehospital care conditions, alternative methods of securing the airways to direct laryngoscopy, including new types of laryngoscopes (i.e. Vie Scope®, or the use of supraglottic ventilation devices), are worth considering [7].

Ladny *et al*. stated in his study that blind intubation is highly effective when using the iGel mask and the laryngeal mask, as a guide for the endotracheal tube [8]. Therefore, it is worth considering this method of intubation in the conditions of using PPE-AGP because it does not require such specialized skills as direct laryngoscopy from the operator. Nevertheless, it is necessary to conduct a study confirming the usefulness of this method of endotracheal intubation in the aspect of patients with suspected SARS-CoV-2.

In summary, thanks to the development of medical technology, there is a wide range of respiratory protection methods alternative to direct laryngoscopy, which medical personnel should use when securing a patient with suspected or confirmed SARS-CoV-2.

Conflict of interest

None declared.

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