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LETTERS

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Fibrinogen-to-albumin ratio predicts mortality in COVID-19 patients admitted to the intensive care unit

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is an inflammatory disease, and serum albumin and fibrinogen are two important factors in systemic inflammation. We aimed to investigate the relationship between the fibrinogen-to-albumin ratio (FAR) and in-hospital mortality in COVID-19 patients admitted to the intensive care unit (ICU).

Material and methods: Patients diagnosed with COVID-19 admitted to the Adiyaman Training and Research Hospital from August to November 2020 were enrolled in this retrospective cohort study. They were divided into 2 groups based on in-hospital mortality: a survivor group (n = 188) and a non-survivor group (n = 198). FAR was calculated by dividing the fibrinogen value by the albumin value. Mortality outcomes were followed up until December 15, 2020.

Results: The average age of the patients was 71.2 ± 12.9 years, and 54% were male. On multivariate logistic analysis, diabetes mellitus (OR: 1.806; 95% CI: 1.142–2.856; p = 0.011), troponin I levels (OR: 1.776; 95% CI: 1.031–3.061; p = 0.038), and FAR (OR: 1.004; 95% CI: 1.004–1.007; p = 0.010) at ICU admission were independent predictors of in-hospital mortality in patients with COVID-19.

Conclusions: The FAR at admission was associated with mortality in patients infected with SARS-CoV-2 in the ICU.

Key words: coronavirus disease 2019, intensive care unit, fibrinogen-to-albumin ratio, mortality

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Introduction

Severe respiratory distress syndrome caused by coronavirus-2 (SARS-CoV-2) has affected the whole world in terms of health, social, educational, and economic aspects. The main cause of morbidity and mortality in patients with COVID-19 is viral pneumonia leading to acute respiratory distress syndrome [1]. In COVID-19 patients, D-dimer, troponin, procalcitonin, ferritin, and fibrinogen levels progressively increase in parallel with disease severity, while lymphocyte counts and albumin levels gradually decrease. A thromboembolic state, thrombo-inflammation, and coagulopathy have been suggested to play pivotal roles in the severity of clinical deterioriation in COVID-19 patients [2].

Fibrinogen is a positive acute phase reactant secreted from the liver, and it plays an active role in both the coagulation cascade and inflammation. Its synthesis increases in both acute and chronic inflammation as well as cardiovascular diseases and malignancy. Fibrinogen stimulates the production of proinflammatory cytokines such as interleukins-1β, IL-6 and tumor necrosis factor alpha [3]. In clot formation, fibrinogen is converted to fibrin by the enzyme thrombin; it also increases blood viscosity and stimulates thrombocyte aggregation.

Albumin, a major plasma protein, is a negative acute phase reactant, and its plasma level decreases in inflammatory diseases. Low albumin levels in hospitalized patients at the time of admission are associated with increased short- and

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long-term mortality rates [4]. Previous studies have shown significant associations of hypoalbuminemia with increased cardiovascular morbidity and mortality [5, 6].

Recent studies have also shown that the fibrinogen-to-albumin ratio (FAR) is associated with poor clinical outcomes in patients with cardiovascular diseases characterized by inflammation and thrombosis, and in those with malignancies [7, 8]. In addition, the FAR is an independent risk factor predicting disease severity in COVID-19 [9]. A meta-analysis investigating the mortality of patients with COVID-19 admitted to the intensive care unit (ICU) has been published. It included 52 studies published up to 30 September 2020; mortality rates varied from 10.6% to 61.9% depending on the geographical region [10]. It is important to predict the mortality of patients with COVID-19 requiring ICU treatment. Therefore, this study investigated the potential association between the FAR and in-hospital mortality in patients with SARS-CoV-2 pneumonia requiring intensive care.

Material and methods

Study population

We retrospectively analyzed the data of patients with COVID-19 treated in the Adiyaman University Education and Research Hospital ICU between 1 August and 30 November, 2020. Patients attending the hospital who presented with cough, dyspnea, myalgia, malaise, weight loss, sore throat, headache, fever, loss of appetite, diarrhea, nausea, vomiting, rhinitis, and/or loss of smell received the polymerase chain reaction (PCR) test for SARS-CoV-2 using nasopharyngeal swab specimens. Those with positive PCR results and with severe SARS-CoV-2 pneumonia were included in the study. Patients with a negative PCR result, lack of appropriate laboratory test parameters, terminal malignancy, or who were < 18 years of age were excluded.

The diagnosis of SARS-CoV-2 pneumonia was made according to the World Health Organization interim guidelines. Patients with COVID-19 who had dyspnea, respiratory rate > 30/min, tachycardia > 100/min, blood oxygen saturation level < 90% despite 5 L/min oxygen treatment, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of < 300 mm Hg, infiltrates in > 50% of the lung fields on X-rays, need for mechanical ventilation, development of acute organ dysfunction, sepsis, septic shock, immunosuppression, acute bleeding diathesis, arrhythmia, or increased troponin level were admitted to the ICU [11, 12].

Demographic characteristics, laboratory parameters, comorbidities (cardiovascular diseases, cerebrovascular diseases, hypertension, diabetes mellitus [DM], chronic obstructive lung disease, chronic kidney disease, or prior malignancy), epidemiologic features, and treatment protocols of patients were collected from the electronic medical records of our hospital. The endpoints of the study were discharge from the ICU and/or in-hospital mortality. Patients were divided into two groups according to in-hospital mortality: survivors and non-survivors. The patients discharged from the hospital were followed-up with until 15 December 2020 to determine mortality.

Collection of blood samples and biochemical analysis

Blood samples were collected for hematological and biochemical testing within 24 h after admission to the ICU. Complete white blood cell counts, including neutrophil and lymphocyte counts, were measured using an automated hematologic analyzer (CELL-DYN Ruby, Abbott Diagnostics, Abbott Park, IL, USA) and are expressed as × 1,000 cells/mm^3. The hemoglobin level and platelet count were also measured. Glucose, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, albumin, sodium, potassium, calcium, ferritin, and C-reactive protein (CRP) levels were analyzed by the Architect c8000 Chemistry System (Abbott Diagnostics) using commercial kits (Abbott Diagnostics).

Troponin I and D-dimer levels were analyzed using an immunoassay analyzer (Radiometer AQT90 FLEX, Radiometer Medical ApS, Brønshøj, Denmark). The activated partial thromboplastin time (aPTT), prothrombin time, international standardized ratio, and plasma fibrinogen concentration were measured using an automatic coagulation analyzer (STA Compact, Diagnostica Stago, Parsippany, NJ, USA). FAR was calculated using the SPSS statistical program by dividing the fibrinogen concentration by the albumin concentration. Myocardial injury was diagnosed if the serum concentration of troponin I was > 99th percentile of the upper reference limit (> 0.023 ng/mL), as measured by our hospital laboratory.

The study procedures complied with the Declaration of Helsinki. The Ministry of Health and Adiyaman University Ethics Committee on Human Research approved the study protocol.

Table 1. Demographic features and comorbidities of the study population (n=386)

	Survivors (n = 188)	Non-survivors (n = 198)	P-value
Male, n (%)	94 (50)	115 (58)	0.111[a]
Age [years]	70.7 ± 13.8	71.7 ± 13.8	0.439[b]
Smoking, n (%)	72 (38)	85 (42)	0.355[a]
Heart failure, n (%)	21 (11)	30 (15)	0.240[a]
Hypertension, n (%)	101 (53)	122 (62)	0.117[a]
Coronary artery disease, n (%)	84 (44)	85 (43)	0.546[a]
Cerebrovascular disease, n (%)	20 (11)	19 (8)	0.388[a]
Diabetes mellitus, n (%)	58 (31)	75 (46)	0.003[a]
Chronic lung disease, n (%)*	61 (32)	59 (30)	0.574[a]
Malignancy, n (%)	12 (6)	10 (5)	0.572[a]
Chronic kidney disease, n (%)	14 (7)	31 (16)	0.012[a]
Length of intensive care unit stay [days]	4 (2.3–7.7)	8 (3–14)	< 0.001[c]

[a]Depending on the Expected count, Pearson Chi-Square or Fisher Exact test was used. Descriptive statistics were presented as a number (%).
[b]Student's unpaired t-test was used. Descriptive statistics were presented as mean ± standard deviation.
[c]Mann–Whitney U test was used. Descriptive statistics were presented as median [IQR].
IQR — Interquartile range.
*Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or chronic bronchitis

Statistical analysis

Data were examined using SPSS software 17.0 for Windows (Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the presence of a normal distribution of continuous variables. Variables with a normal distribution are expressed as means ± standard deviation, whereas those with a non-normal distribution are expressed as medians with interquartile ranges. Categorical variables are expressed as percentages. Group differences were assessed using the Student's unpaired *t*-test or the Mann–Whitney U test. Differences in categorical variables were assessed using the Pearson chi-square and Fisher exact tests, depending on the sample size. Pearson's and Spearman's tests were used for correlation analyses. Forward variable selection was applied to the binary logistic regression analysis to eliminate statistically non-significant predictors. The Hosmer-Lemeshow test was used to evaluate model fit. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent variable. A p-value < 0.05 was considered significant.

Results

The data of 838 COVID-19 patients treated in the ICU were analyzed retrospectively. Those with a negative PCR test (n = 320), a lack of appropriate laboratory parameters (n = 122), or terminal malignancy (n = 10) were excluded from the study. After exclusion, 386 patients (209 [54%] males, aged 71.2 ± 12.9 years) were included in this retrospective cohort study. The in-hospital mortality rate was 51.3%.

The demographic characteristics and comorbid conditions are shown in Table 1. The study groups included surviving (n = 188) and non-surviving (n = 198) COVID-19 patients. There were no significant differences between the groups in terms of age or sex. The rate of DM (p = 0.003), chronic kidney disease (p = 0.012), and duration of hospital stay (p < 0.001) were higher in the non-survivor group compared with the survivors.

The laboratory parameters and treatments are shown in Table 2 according to the study groups. White blood cell and neutrophil counts were higher, while the lymphocyte count was lower in the non-survivor group when compared with the survivors; however, these differences were not statistically significant. The FAR, neutrophil-to-lymphocyte ratio, prothrombin time, international standardized ratio, levels of CRP, glucose, creatine, urea, aspartate aminotransferase, lactate dehydrogenase, fibrinogen, procalcitonin, ferritin, D-dimer, and troponin I were higher in the non-surviving group when compared with surviving COVID-19 patients (all, p < 0.05). In contrast, the platelet count (p = 0.047) and albumin level (p = 0.004) were higher in the survivor

Table 2. Laboratory findings and treatments of patients with SARS-CoV-2 pneumonia on admission to the intensive care unit (n = 386)

	Survivors (n = 188)	Non-survivors (n = 198)	P-value
Haemoglobin, [g/dL]	12.1 ± 2.1	12.1 ± 2.3	0.569[b]
Platelet count (× $10_3/\mu$L)	233 (172–303)	207 (158–273)	0.047[c]
White blood cell count (× $10_3/\mu$L)	9.5 (6.3–14)	10 (7.1–14)	0.089[c]
Neutrophil count (× $10_3/\mu$L)	7.5 (4.7–11.6)	8.3 (5.6–11.7)	0.072[c]
Lymphocyte count (× $10_3/\mu$L)	1.0 (0.6–1.4)	0.9 (0.7–1.4)	0.725[c]
NLR	7.1 (4.5–12)	8.6 (6.1–12.4)	0.014[c]
Glucose [mg/dL]	141 (106–195)	166 (117–234)	0.009[c]
Serum creatinine [mg/dL]	0.8 (1.1–0.7)	1.1 (0.8–1.8)	< 0.001[c]
Urea [mg/dL]	46 (36–70)	63 (43–106)	< 0.001[c]
Alanine aminotransferase [U/L]	24 (16–37)	24 (17–42)	0.498[c]
Aspartate aminotransferase [U/L]	35 (23–54)	43 (27–65)	0.005[c]
Lactate dehydrogenase [U/L]	408 (324–483)	532 (418–678)	< 0.001[c]
Albumin [g/dL]	2.8 ± 0.5	2.6 ± 0.5	0.004[b]
Fibrinogen [g/L]	543.3 ± 164.8	595.6 ± 164.6	0.002[b]
FAR	206.8 ± 83.4	244.2 ± 98.1	< 0.001[b]
Serum potassium [mmol/L]	4.5 ± 0.7	4.6 ± 0.9	0.059[b]
Serum sodium [mmol/L]	136.1 ± 10.1	136.9 ± 7.7	0.446[b]
CRP [mg/dL]	9 (5–15)	14 (8–20)	< 0.001[c]
Ferritin [ng/mL]	389 (234–604)	456 (286–729)	0.021[c]
Procalcitonin [ug/L]	0.21 (0.12–0.69)	0.64 (0.21–1.62)	< 0.001[c]
D-dimer [μg/L]	1340 (784–2100)	1485 (911–3027)	0.017[c]
Troponin I [μg/L]	0.01(0.01–0.03)	0.01(0.01–0.22)	< 0.001[c]
Activated partial thromboplastin time [s]	32 (28–36)	33 (28–38)	0.543[a]
Prothrombin time [s]	16 (14–18)	17 (15–19)	0.008[c]
International standardized ratio	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.036[c]
Mechanical ventilation, n (%)	15 (8)	165 (83)	< 0.001[a]
Treatments, n (%)			
Antiviral agents	178 (95)	184 (93)	0.476[a]
Antibacterial agents	187 (99)	195 (98)	0.328[a]
Glucocorticoids	182 (97)	190 (96)	0.656[a]
Anticoagulants	180 (96)	188 (95)	0.711[a]
Antiplatelets	105 (56)	130 (66)	0.048[a]
Convalescent plasma	85 (45)	95 (52)	0.586[a]

[a]Depending on the Expected count, Pearson Chi-Square or Fisher Exact test was used. Descriptive statistics were presented as a number (%).
[b]Student's unpaired t-test was used. Descriptive statistics were presented as mean ± standard deviation.
[c]Mann–Whitney U test was used. Descriptive statistics were presented as median [IQR].
CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; IQR — interquartile range; NLR — neutrophil-to-lymphocyte ratio

group. The use of antiplatelet medications was greater in the non-survivor group.

The correlation analyses between the FAR and laboratory parameters is shown in Table 3. The FAR was positively correlated with the levels of CRP (r = 0.447; p < 0.001), procalcitonin (r = 0.195; p < 0.001) and troponin I (r = 0.204; p < 0.001) (Figure 1). Logistic regression analysis was performed to determine the independent predictors of in-hospital mortality. The analysis demonstrated that DM (OR: 1.806; 95% CI: 1.142–2.856; p = 0.011), troponin I level (OR:

1.776; 95% CI: 1.031–3.061; p = 0.038), and FAR (OR: 1.004; 95% CI: 1.004–1.007; p = 0.010) at ICU admission were independent predictors of in-hospital mortality in patients with severe COVID-19 (Table 4).

Discussion

We evaluated the association between in-hospital mortality and the FAR, calculated based on the laboratory parameters obtained from blood samples collected within 24 h of ICU admission. The FAR was higher in the non-survivor group and was an independent predictor of in-hospital mortality. Similar to other studies investigating the prognostic risk factors for COVID-19, our results showed that DM and an increased troponin I level were also independent predictors of in-hospital mortality.

Fibrinogen, also known as Factor I, is a glycopeptide composed of three pairs of polypeptides covalently linked by disulfide bonds. Fibrinogen plays a major role in platelet aggregation via enzymatic conversion to fibrin and is also the main determinant of plasma viscosity and erythrocyte aggregation [13]. Several studies and meta-analyses have investigated the association between the fibrinogen level and cardiovascular diseases [14, 15]. Fibrinogen was found to be an independent risk factor for cardiovascular disease in these studies.

COVID-19 is characterized by respiratory failure, endothelial dysfunction, and activation of the coagulation pathway [16]. Patients with severe COVID-19 are susceptible to coagulation as a result of increased levels of coagulation factors

Table 3. Correlation between the FAR and laboratory parameters

	R	P-value
CRP	0.447	< 0.001
Lactate dehydrogenase	0.052	0.277
Procalcitonin	0.195	< 0.001
Troponin I	0.204	< 0.001
NLR	0.098	0.054

CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; NLR — neutrophil-to-lymphocyte ratio

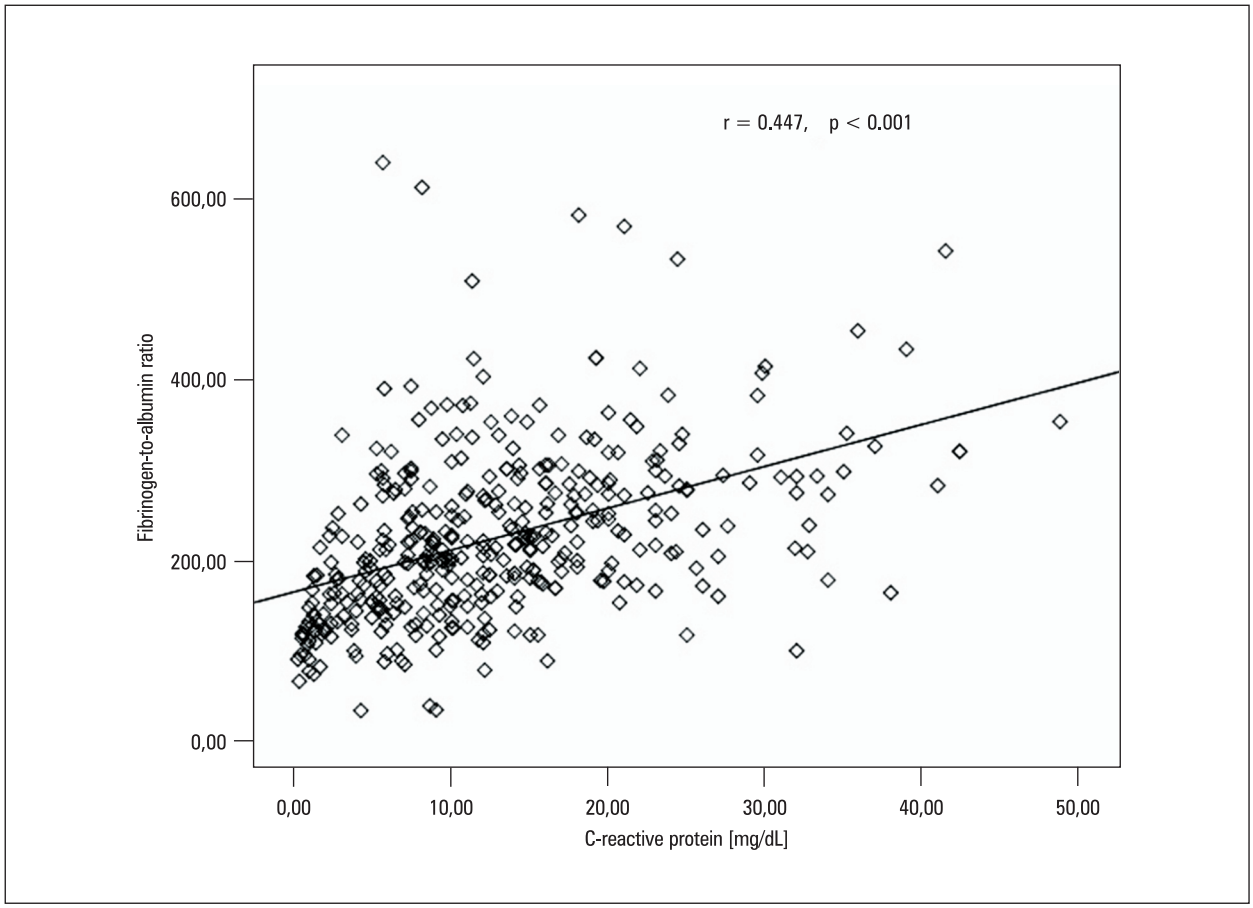

Figure 1. Scatter plot image of the correlation between fibrinogen-to-albumin ratio and C-reactive protein in patients with COVID-19 (n = 386)

Table 4. Multivariate logistic regression analyses of in-hospital mortality

	Odds ratio	95% CI	P-value
NLR	0.986	0.960–1.012	0.293
FAR	1.004	1.001–1.007	0.010
Age [years]	0.999	0.982–1.017	0.943
Sex, male	1.311	0.799–1.000	0.285
Diabetes mellitus	1.806	1.142–2.856	0.011
Hypertension	1.282	0.808–2.035	0.292
Procalcitonin [μg/L]	1.087	0.982–1.202	0.740
Smoking	1.017	0.623–1.660	0.946
D-dimer [μg/L]	1.000	1.000–1.000	0.968
Chronic kidney disease	1.364	0.644–2.889	0.448
Troponin I [μg/L]	1.776	1.031–3.061	0.038
Platelet counts ($\times$103/μL)	0.998	0.996–1.000	0.093

CI — confidence interval; CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; NLR — neutrophil-to-lymphocyte ratio

including fibrinogen, tissue factor, and Factor 7, a decrease in tissue plasminogen activator activity, and inhibition of the fibrinolytic pathway due to hypoxia, endothelial dysfunction, and hyperinflammation [17]. This leads to major venous thromboembolic events and arterial thrombosis [18] and is associated with a poor prognosis [19]. Thromboembolic events and in-situ thrombosis seem to contribute to multisystem injury, multiorgan failure, and mortality in patients with SARS-CoV-2 infection [20]. Increased D-dimer and fibrinogen levels together with prolongation of the aPTT promote coagulopathy in COVID-19 patients [21]. Increased levels of D-dimer, aPTT, and fibrinogen were associated with a poor prognosis in hospitalized patients with COVID-19 [22]. In our study, we observed that fibrinogen and D-dimer levels were higher in the non-survivor group when compared with the survivor group.

Albumin has anticoagulant and antiplatelet activities, probably due to its antioxidant effect [23]. Albumin increases fibrinolysis and inhibites erythrocyte aggregation. In addition, albumin neutralizes fibrinogen binding to endothelial cells, thus antagonizing several prothrombotic effects of fibrinogen [24]. Also, endothelial dysfunction and blood viscosity are increased in hypoalbuminemia [25]. During inflammatory states, the coagulation cascade favors thrombus formation due to decreased synthesis and increased catabolism of albumin. Lower albumin levels were observed in patients with severe COVID-19 compared with non-severe COVID-19 in a meta-analysis [26]. A serum albumin level < 3.5 g/dL is associated with a higher mortality rate in COVID-19 patients [27]. In our study, the serum albumin level was < 3.5 g/dL in both groups but was significantly lower in the non-survivor group. In a study of 299 COVID-19 patients, Huang et al. [28] showed a lower albumin level in the non-survivor group compared with the survivors, and hypoalbuminemia was a predictor of mortality regardless of age and comorbidities. Violi et al. [29] suggested that hypoalbuminemia may be related to hypercoagulability in patients with severe SARS-CoV-2 infection and found lower serum albumin levels in patients with ischemic events compared with thrombotic event-free patients with COVID-19.

The FAR has been introduced as a new prognostic marker based on inflammation. The association between FAR and mortality has been investigated because inflammation has an important role in the pathogenesis of both malignancy and cardiovascular disease. FAR was shown to be associated with a poor prognosis in these diseases [7, 8]. There are limited data in the literature on the associations among the FAR, disease progression, and mortality in COVID-19 patients. Bi et al. [30] investigated the associations among the FAR, platelet count, and disease severity in 91 patients with non-severe COVID-19 and 21 patients with severe COVID-19. They suggested that the FAR and platelet count were independent predictors of the development of severe illness in SARS-CoV-2 infection. To date, no studies have investigated the association between the FAR and mortality in COVID-19 patients. In our study, we have proven that the FAR is an independent

predictor of mortality in patients with severe COVID-19 in the ICU. The significant association between elevated fibrinogen/low albumin levels and mortality in COVID-19 patients found in our study supports the role of the FAR in the pathophysiology of the disease and the intensity of the thromboembolic and thrombotic state. FAR may be a useful and cost-effective parameter to predict in-hospital mortality in patients with severe SARS-CoV-2 infection.

Study limitations

As this was a retrospective, observational, and single-center study, our findings may not be generalizable. There were no ischemic/embolic events recorded in our study population. Fibrinogen and albumin levels were measured within 24 h of hospitalization, and serial measurements were not performed. All patients were administered low-molecular-weight heparin as an anticoagulant. Unfortunately, we were not able to measure plasma antifactor Xa activity, which is deemed to be the most accurate marker for monitoring therapeutic dosing of low-molecular-weight heparin.

Conclusions

We showed that the FAR, a novel inflammation-based prognostic parameter, was higher in non-surviving patients when compared with surviving COVID-19 patients. In addition, the FAR was associated with mortality in patients infected with SARS-CoV-2 in the ICU. An increased FAR (as an indicator of the inflammatory and thrombotic burden) might allow for early identification of COVID-19 patients at severe risk, which could assist in immediate optimization of the medical management of this highly susceptible group.

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Conflicts of interest

The authors declare no potential conflict of interest.

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Organizing pneumonia-like pattern in COVID-19

Abstract

Introduction: Organizing pneumonia (OP) is a radio-histologic pattern that forms in response to lung damage in patients with focal or diffuse lung injury. OP is frequently observed subsequent to viral-induced lung damage and is associated with a diverse range of clinical outcomes.

Material and methods: We included 210 patients (mean age: 55.8 ± 16.5 years old; 61% male) with mild Coronavirus disease 2019 (COVID-19) who underwent chest computed tomography (CT) from 25 February to 22 April, 2020. The patients were divided into two groups based on the presence (n = 103) or absence of typical OP-like pattern (n =107) on initial chest CT. The extent of lung involvement and final outcome was compared across the two groups. Serial changes in imaging were also evaluated in 36 patients in the OP-group with a second CT scan.

Results: Duration from symptom onset to presentation was significantly higher in the OP group (7.07 ± 3.71 versus 6.13 ± 4.96 days, p = 0.008). A higher COVID-19-related mortality rate was observed among patients with OP-like pattern (17.5% vs 3.7%, p = 0.001).There was no significant difference in the overall involvement of the lungs (p = 0.358), but lower lobes were significantly more affected in the OP group (p < 0.001). Of the 36 patients with follow-up imaging (mean duration of follow-up = 8.3 ± 2.1 days), progression of infiltration was seen in more than 61% of patients while lesions had resolved in only 22.2% of cases.

Conclusions: Our observation indicates that physicians should carefully monitor for the presence of OP-like pattern on initial CT as it is associated with a poor outcome. Furthermore, we recommend interval CT to evaluate the progression of infiltrations in these patients.

Key words: COVID-19, computed tomography, organizing pneumonia, respiratory, lung

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Introduction

Organizing pneumonia (OP) is a radio-histologic pattern which forms in response to lung damage in patients with focal or diffuse lung injury [1]. As it has previously been documented in H1N1 influenza, SARS-CoV and MERS-CoV, viral pneumonia is one of the many etiologies of secondary OP [2–4]. A diverse entity of clinical outcomes is seen in patients with OP-like pattern, ranging from complete clearance of lesions without any sequela to severe and progressive conditions such as pulmonary fibrosis [5]. Here, we briefly report the imaging findings and prognosis of Coronavirus disease 2019 (COVID-19) in patients with and without OP-like pattern on initial computed tomography (CT). Also, the serial changes of imaging findings are reported in a subset of patients with OP-like pattern.

Materials and methods

We retrospectively enrolled 210 adult patients (> 18 years old) with PCR-confirmed diagnosis of COVID-19 who underwent CT in a single institution from 25 February to 22 April,

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2020. All subjects had mild disease at presentation and did not require ventilation support. Demographic and clinical data and final outcome was collected. All patients had undergone at least one non-contrast CT with reconstructions of the volume at 3 mm to 5 mm slice thickness. OP pattern was defined as: 1) peripheral, bilateral, lower lung predominant multifocal consolidation or even a frequent appearance in all lungs zones and/or 2) peribronchovascular consolidation, which could extend to the subpleural regions in the lower lobes associated with patchy ground-glass opacities (GGO) [6]. Based on the presence or absence of typical OP-like pattern on the initial CT, the patients were divided into two groups: OP group (n = 103) and non-OP group (n = 107). CT images were reviewed by two radiologists blinded to the patients' final outcome. Imaging findings were first interpreted independently based on the Fleischner society nomenclature [7]. Final decision was reached by consensus. To assess the extent of lobar involvement, a score was given based on the percentage of infiltration: 0 (none), 1 (1–5%), 2 (6–25%), 3 (26–49%), 4 (50–75%), and 5 (> 75%). Total lung score was obtained by summing the individual scores of each specific lobe. Temporal changes of imaging on follow-up CT were defined as follows: 1) disease resolution: complete or near-complete resolution of radiologic opacities; 2) disease progression: increased extent of lung infiltration; 3) no change.

Normality tests were used to assess distribution. Categorical variables are reported as frequency (percentages) and continuous variables are expressed as mean (standard deviation (SD)). Continuous data were compared between the groups by using t-test and categorical variables were compared using Chi-square or Fisher's exact test. Statistical tests were performed by SPSS v.23 (IBM Inc., Chicago, IL, USA). P-value < 0.05 was considered statistically significant.

The ethical review board of our institution approved the study (ethics code:IR.SBMU.MSP.REC.1399.083).

Results

The mean age of patients was 55.85 ± 16.52 years old (range: 26–97); 61% were male. Death had occurred in 22/210 patients (10.5%) and the rest were discharged; the COVID-19-related mortality rate was significantly higher in the OP group compared with the non-OP group (17.5% vs 3.7%, p = 0.001). The mean presentation time for the entire cohort was 6.6 ± 4.3 days after symptom onset. This duration was significantly higher in the OP group (p=0.008). Non-adjusted mortality rate was approximately 5.5 times higher in the OP group compared with the non-OP group (Table 1). Peripheral and bilateral lesion distribution was the predominant finding in both groups. The extent of right middle lobe (RML), right lower lobe (RLL) and left lower lobe involvement was significantly different between the two groups (p = 0.001, p < 0.001, p < 0.001, respectively); however, total lung involvement did not differ across the two groups. In both groups, the least amount of involvement was seen in the RML while the RLL and the right upper lobe had the most involvement in the OP and non-OP groups, respectively (Table 1).

Table 2 shows in detail the imaging findings of patients with OP. Sixty-nine percent of patients demonstrated involvement of more than three lobes; higher number of involved lobes was not related to worse prognosis (p = 0.394). Subpleural band-like consolidation (72.8%), GGO (62.3%) and peripheral consolidation (39.8%) were the predominant patterns. Bronchial dilatation (29.1%), peribronchovascular opacities (25.2%) and air space nodules (23.3%) were also common; however, halo sign, bronchiectasis, crazy paving and honeycomb sign were infrequent. In a subset of 36 patients in the OP group who had follow-up CT (mean duration of 8.3 ± 2.1 days; range: 4–50), progression of infiltrations, mostly seen as lower-lobe GGO, was found in more than 61% of patients (Figure 1) and in 22.2% of patients, lesions had obviously resolved (Figure 2).

Discussion

We observed that the mean interval from symptom onset to admission in patients presenting with radiologic OP-like pattern was approximately a week (7.1 ± 3.7 days), and this duration was significantly higher compared with the non-OP group. More importantly, we found that in patients who manifest OP-like pattern at initial imaging, the mortality rate was significantly higher than others, suggesting a possible worse prognosis for these cases. Identifying imaging patterns that reflect more advanced stage of COVID-19 is helpful for selecting the most appropriate therapy and avoiding acute-phase treatments that most probably do not bring benefit to patients [8]. Our study showed that subpleural band-like consolidation, GGO and peripheral consolidation were the most common imaging findings of patients with OP-like pattern. GGO was mostly seen in

Table 1. Comparison of demographic, clinical and radiologic findings across organizing pneumonia (OP) and non-OP groups

	OP group (n = 103)	Non-OP group (n = 107)	P-value
Age, years	61.94 ± 15.98 (29–97)	49.98 ± 15.17 (26–92)	< 0.001
Sex			
Male	63 (61.2)	65 (60.7)	0.532
Female	40 (38.8)	42 (39.3)	
Symptom onset to presentation, days	7.07 ± 3.71 (1–20)	6.13 ± 4.96 (1–30)	0.008
Disease outcome			
Discharged	85 (82.5)	103 (96.3)	0.001
Death	18 (17.5)	4 (3.7)	
Positive smoking history*	3 (2.9)	5 (4.7)	0.382
Comorbidities			
Cardiovascular disease	14 (13.6)	16 (15)	0.845
Hypertension	19 (18.4)	13 (12.1)	0.250
Diabetes	25 (24.3)	20 (18.7)	0.327
Respiratory disease	3 (2.9)	7 (6.5)	0.333
Renal disease	2 (1.9)	2 (1.9)	0.969
Liver disease	2 (1.9)	2 (1.9)	0.969
Malignancy	3 (2.9)	6 (5.6)	0.268
Obesity	5 (4.8)	13 (12.1)	0.058
Other	2 (1.9)	7 (6.5)	0.054
Any comorbidity	47 (45.6)	48 (44.8)	0.911
Lobar score			
Right upper lobe	2.17 ± 0.99 (0–5)	2.06 ± 1.03 (0–4)	0.524
Right middle lobe	1.77 ± 0.98 (0–4)	1.31 ± 1.02 (0–4)	0.001
Right lower lobe	2.89 ± 1.02 (0–5)	1.48 ± 1.05 (0–4)	< 0.001
Left upper lobe	2.17 ± 1.03 (0–5)	1.90 ± 1.03 (0–4)	0.54
Left lower lobe	2.67 ± 1.05 (0–5)	1.76 ± 1.07 (0–4)	< 0.001
Total score	11.72 ± 3.67 (4–22)	10.17 ± 3.16 (3–20)	0.358
Pattern of involvement			
Predominant ground-glass opacification	44 (42.7)	64 (59.8)	0.003
Predominant consolidation	33 (32.1)	34 (31.7)	
Mixed pattern	26 (25.2)	9 (8.4)	
Lesion distribution			
Axial			< 0.001
Central	5 (4.9)	7 (6.5)	
Peripheral	94 (91.3)	53 (49.5)	
Diffuse	4 (3.9)	47 (43.9)	
Bilateral	100 (97.1%)	97 (90.6%)	0.872

Continuous data is represented as mean ± SD (range) and categorical data is reported as frequency (percentage); *Positive smoking history was defined as former or current smoker with ≥ 20 pack/year history of smoking

the upper lobes and was not a common finding of the lower lobes. In fact, lower-lobe GGO was seen in less than 5% of subjects with OP-like pattern. When comparing with the non-OP group, mixed pattern was more frequently observed in patients with OP-like pattern. A previous study investigating temporal CT findings of COVID-19 reported that mixed pattern becomes more frequent at later stages, usually during day 12–17 of the disease course. They also noted that mixed pattern probably suggests the presence of secondary OP [9].

A notable finding of our study was that in more than 90% of patients with OP-like pattern, lesions were distributed peripherally, while in the non-OP group, less than half of cases demonstrated predominant peripheral lesions. This observation is consistent with that of previous studies, reporting peripheral or peribronchial infiltrations as a characteristic finding of OP [10]. Also, single-lobe involvement was seen in about 10% of patients with OP-like pattern, which is relatively similar to the results of a similar study (6.9%) [11].

In general, OP is associated with a relatively good prognosis. In most cases, the damage is mild and the lung undergoes repair without any permanent sequela; however, relapse rates

Table 2. Imaging findings in patients with organizing pneumonia-like pattern

	OP group (n = 103)
Involvement pattern	
Ground-glass opacification	64 (62.3)
Peripheral consolidation	41 (39.8)
Subpleural band-like consolidation	75 (72.8)
Honeycombing	1(0.9)
Crazy paving	1(0.9)
Interstitial fibrosing pneumonitis	15 (14.5)
Traction bronchiectasis	1 (0.9)
Bronchial dilatation	30 (29.1)
Air space nodule	24 (23.3)
Perilobular pattern	3 (2.9)
Halo sign	—
Reversedhalo sign	18 (17.5)
Reticulation	14 (13.6)
Peribronchovascular opacification	26 (25.2)
Number of involved lobes	
1	11 (10.6)
2	21 (20.3)
3	39 (37.9)
4	18 (17.5)
5	14 (13.6)
Findings on follow-up CT imaging (n = 36)	
Lesion resolution	8 (22.2)
Progression of lung infiltration	22 (61.1)
No change	6 (16.6)

Data are represented as frequency (percentage)

can be seen in 13% to 58% of patients [10, 12, 13]. In a recent study on 77 patients with mild COVID-19, OP-pattern was found to be predictive of short-term evolution to severe disease [14]. In our study, after a mean duration of eight days from presentation, progression of lung infiltrations was seen in 61.1% of patients and in less than one-fourth, lesions resolution had occurred. A recent study showed that 60% of cases with COVID-19 displayed improvement on follow-up CT while 40% presented with exacerbation of lesions [11]. Another study reported complete radiological resolution to be 53% at three-week post-discharge [15]. Reports from previous viral pandemics indicate that few months to several years might be needed for pulmonary imaging abnormalities to resolve [16, 17].

Our study was associated with some limitations. First, we did not adjust the mortality rate for other parameters that could possibly affect survival such as the presence of comorbidities or disease severity; thus, the difference in mortality rate between the two groups should be interpreted with caution. Also, we included a small sample size that might bias the results.

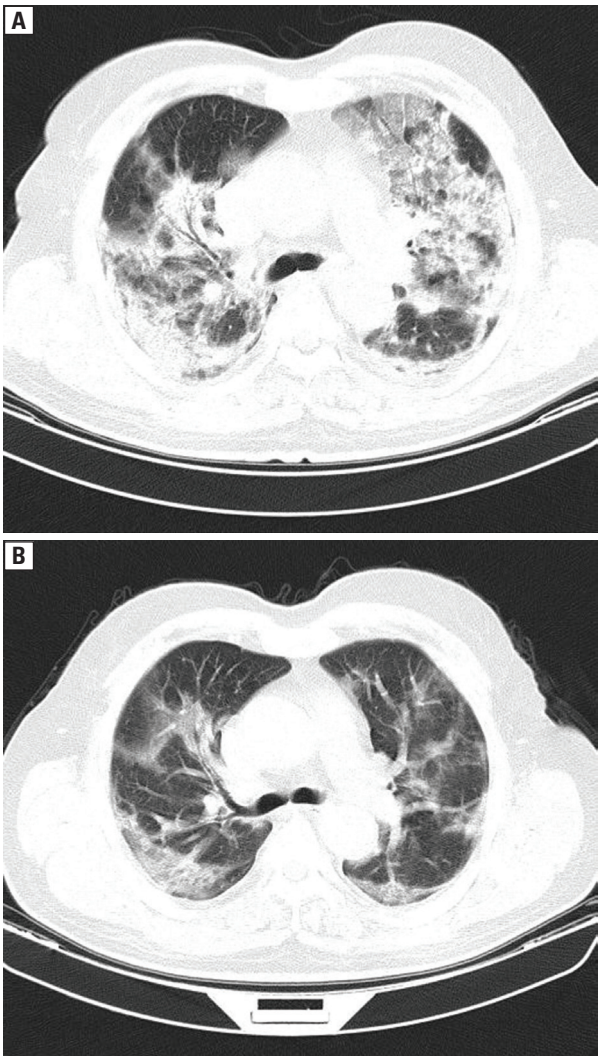

Figure 1. A. Early imaging (at admission) of a 73-year-old man without a positive history for any comorbidity, presenting about 7 days after the onset of respiratory symptoms. Non-enhanced chest CT shows sub-pleural mixed pattern of infiltration. **B.** Follow-up CT scan performed after 8 days shows extensive consolidation and bronchial dilation. The patient recovered after 10 days from admission and was discharged in good clinical condition

Clinical implications and future directions

In the appropriate clinical setting, radiologists should be aware to consider COVID-19 as a differential diagnosis of OP. This is particularly important as we observed a higher mortality rate among patients presenting with OP-like pattern on their initial CT. Also, progression of infiltrations was observed in more than half of these patients on follow-up. Thus, we recommend interval imaging to monitor for progression of pulmonary involvement. Also, increasing recognition of OP diagnosis in patients with COVID-19 will

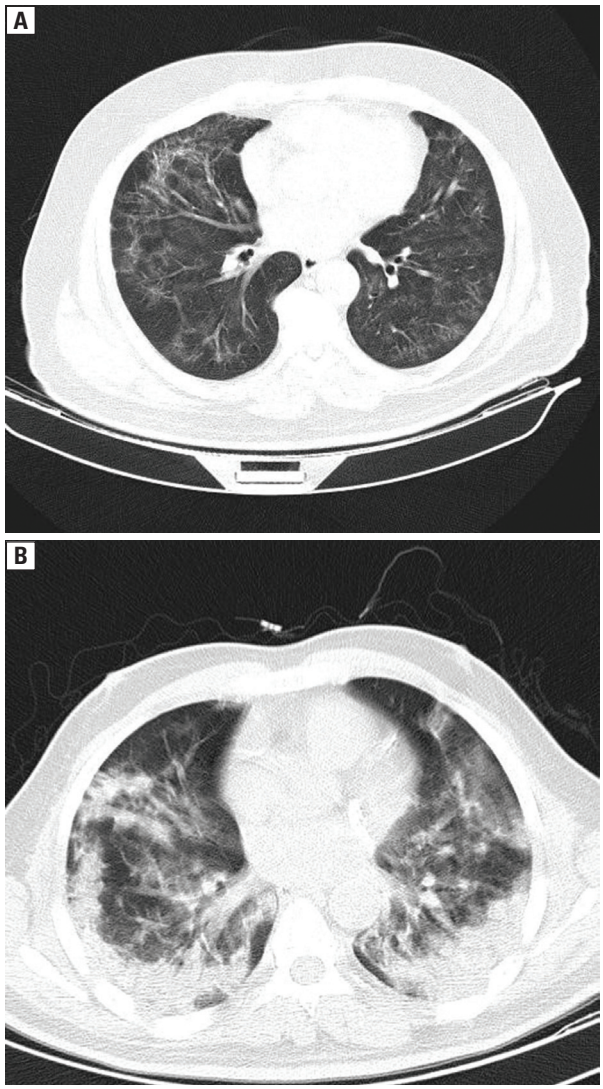

Figure 2. A. Subpleural band-like consolidation in the lung base of a 54-year-old man presenting with acute onset of respiratory symptoms. **B.** Follow-up CT scan performed 50 days later showed ground-glass opacification and innumerable small linear opacities that, by summation, resembled a net-like reticulation pattern appearance

lead to more appropriate and effective treatment approaches, subsequently reducing the need for ventilation support and improving survival.

Conflicts of interest

None declared.

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Nebulisation therapy in patients with cystic fibrosis — consensus of the Polish Cystic Fibrosis Society

Abstract

Introduction: Nebulisation therapy plays a key role in the treatment of cystic fibrosis (CF). Its effectiveness depends on obtaining a high concentration of drugs in the respiratory tract. Particle deposition is determined by many factors resulting, inter alia, from the essence of the lung disease (mucus, structural changes such as bronchiectasis, fibrous changes, cirrhosis) and the quality of the aerosol and breathing techniques during the procedure.

Aims: A large variety of available drugs that can be used in the form of aerosols (bronchodilators, mucolytics, antibiotics), a wide range of devices for their delivery, and a different approach to the practical aspect related to the use of inhalation, makes it necessary to systematize knowledge in order to optimize nebulisation therapy. The paper presents an overview of inhaled drugs used in cystic fibrosis and their administration devices.

Results: The principles of inhalation antibiotic therapy, which constitute the basis for the treatment of primary and chronic respiratory tract infections of *Pseudomonas aeruginosa* etiology, are discussed in detail. A very important issue was raised related to the proper selection of devices and their proper operation. In the context of the key role of nebulisation therapy in cystic fibrosis, a huge problem is the limited availability of inhaled antibiotics in Poland.

Conclusions: The possibility of choosing an antibiotic and using alternating therapy increases the effectiveness of inhalation treatment, which results in slowing down the progress of bronchopulmonary disease and extending the life of patients.

Key words: cystic fibrosis, chest physiotherapy, nebulisers system, drug deposition, aerosol

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Introduction

Progress in medicine at the turn of the last four decades has led to a significant improvement in the treatment and care of patients with cystic fibrosis [1, 2]. The quality and length of life is determined by the course of bronchopulmonary disease, and respiratory failure is the most common cause of death. The basic genetic defect underlying the pathogenesis of cystic fibrosis leads to impaired mucociliary clearance of the airways, formation of mucus plugs, and secondary infections with pathogens such as *Staphylococcus* aureus and *Pseudomonas aeruginosa* and others. Chronic infection accompanied by neutrophilic inflammation, recurrent exacerbations of bronchopulmonary disease, cause gradual impairment of lung function and progression of permanent changes such as bronchiectasis, cirrhoidal and fibrous lesions. Chronic treatment of lung disease and treatment of exacerbations are the basic measures to slow

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Table 1. Mechanisms of drug deposition in the respiratory tract

Type of deposition	Mass median diameter	Mechanism description	Respiratory tract	Remarks
Inertia	> 5 μm	Depends on the inspiratory flow velocity through the airways. Settlement of particles occurs as a result of their collision with the airway wall	Main deposition mechanism in the upper respiratory tract	With a high inspiratory flow, the likelihood of particles smaller than 5 μm being deposited in the upper respiratory tract increases
Sedimentation	1–5 μm	Under the influence of gravity, the particles settle, the number of which is directly proportional to the time the air is held at the top of the inhalation	Lobar and segment bronchi	A few seconds' breath hold at the apex of inspiration allows more particles to be deposited in segmental bronchi
Diffusion	< 1 μm	Particle deposition due to Brownian motion	Peripheral airway	Increase in inspiratory volume with reduced inspiratory flow significantly increases drug deposition in peripheral bronchi

down the progression of the disease. In this context, bronchial tree physiotherapy including inhalation therapy, bronchial drainage and education of the patient and family are the main elements of both European [2, 3] and American [4] guidelines. Comprehensive physiotherapy should be implemented in the treatment of every patient with cystic fibrosis from the moment of diagnosis and modified at every stage of life, taking into account age, clinical condition and the possibility of cooperation.

Drug deposition in the lungs and the effectiveness of nebulisation therapy

The effectiveness of nebulisation therapy, both in the central and peripheral airways, is influenced by many factors. The most important of them are:

- related to the laws of physics,
- related to the quality of the aerosol,
- patient-dependent [5, 6].

Factors influencing drug deposition related to the laws of physics

Drug deposition depends on 3 main mechanisms:

- **inertia** — this is the body's ability to maintain its state of motion due to the force of inertia; a mechanism typical of particles with a diameter greater than 5 μm and their deposition in the upper respiratory tract;
- **sedimentation** — this is the falling of particles due to gravity; concerns particles 1–5 μm in diameter and their settlement in the bronchial tree;
- **diffusion**, typical for particles < 1 μm in diameter, deposited under the influence of Brownian motion (Table 1, Figure 1).

Factors influencing drug deposition related to aerosol quality

The most important factors in determining the quality of an aerosol are drug particle shape, size, density, as well as electric charge and hygroscopicity. Usually, the following parameters are taken into account:

- mass median diameter — MMD;
- median aerodynamic diameter of particles — MAD;
- mass median aerodynamic diameter — MMAD, describing the particle size distribution in the aerosol; its value means that 50% of the aerosol particles will have a smaller or equal diameter than the specified value. It is a more accurate indicator of aerosol quality than MAD;
- fine particle fraction of the aerosol — FPF, describing the particle size distribution; it determines the percentage of particles ≤ 5 μm in diameter in the aerosol as a measure of the spread of the drug in the lower respiratory tract.

Patient-dependent determinants of drug deposition and distribution include

- the diameter of the central airways (small children have a narrower airways and higher inspiratory flow compared to adults, resulting in deposition mainly in the central and lobar bronchi). In this context, it is extremely important to correctly select a nebuliser for the

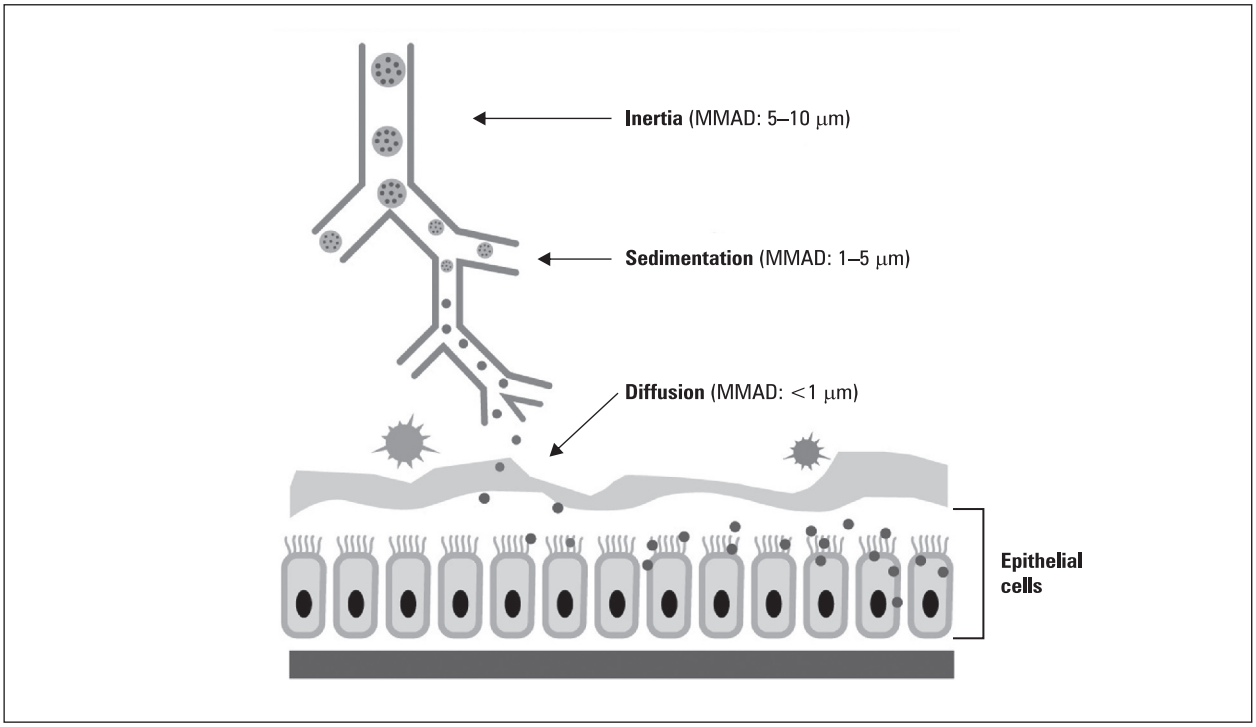

Figure 1. Mechanisms of the deposition of aerosol particles in individual parts of the respiratory tract
MMAD — (mass median aerodynamic diameter) median of the mass distribution of aerosol particles in relation to the aerodynamic diameter [5]

youngest children, which will produce the highest-class aerosol with the lowest MMD/MMAD values;

- breathing pattern, which depends on age and physical fitness and the severity of the disease. The ability to perform specific breathing techniques dependent on cooperation with the patient plays an important role; high inspiratory flow creates more turbulence in the central airways, which leads to more drug depositing in the central bronchi; in turn, reducing the inspiratory flow while increasing the inspiratory volume will result in less turbulence and increase the likelihood of molecules reaching the peripheral airways. Guidelines for breathing maneuvers are different depending on the device.
  During nebulisation, it is recommended that the patient takes slow, deep breaths during inhalation with a pause of 3 seconds at the peak of the inspiration, so that a large number of the smallest particles have a chance of reaching the peripheral airways.
- the presence of structural abnormalities of the airways and/or mucus, disturbing the airflow, reduces drug deposition at sites of airway obstruction;
- homogeneity of lung ventilation, that is, the ability of the lungs to expand evenly. Good drug deposition depends on proper lung ventilation. Structural abnormalities of the lungs disturbing ventilation, e.g. fibrous changes in patients with cystic fibrosis have a negative effect on drug distribution. As a result, there is a preferential airflow to healthier regions of the lung and deposition of drug particles mainly there (Figure 2).

Devices for inhalation

Inhalation devices used by patients with cystic fibrosis can be divided into 3 categories:

1. Nebuliser Systems:
   a. pneumatic, compatible with Jet nebulisers,
   b. ultrasonic,
   c. mesh (MESH type) — vibrating membrane;
2. pressurized meter-dose inhalers (pMDI), including breath-activated pMDI (BA-pMDI) or in combination with a valved holding chamber (VHC);
3. dry powder inhalers (DPI).

Nebuliser Systems

Pneumatic nebulisers

The force that breaks down a liquid medicine into very fine particles is compressed air. The

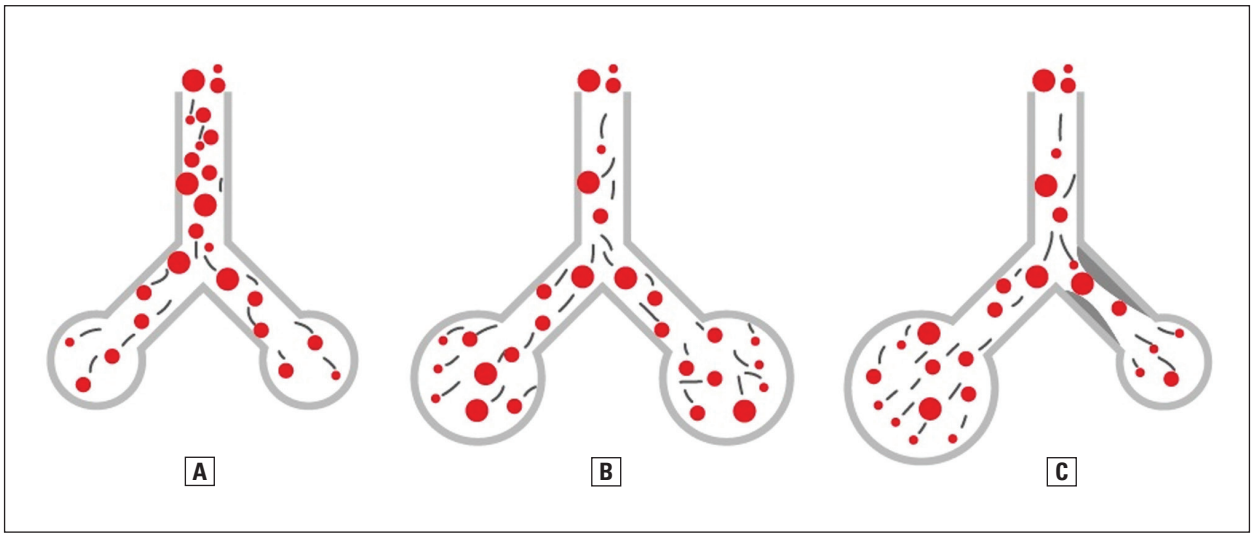

Figure 2. Scheme of deposition of aerosol particles of different sizes (1, 3 and 5 μm) in the bronchial tree of a healthy person (A, B) and a patient with lung disease (C). A. Homogeneous distribution of the drug in the lung segments of a healthy person while breathing calmly. Deposition is greater in the central airways compared to the peripheral airways and lung parenchyma; B. The same person takes a deep breath, more of the drug reaches the peripheral airways and the flesh, the drug is evenly distributed in both lobes; C. Lung of a patient with lung disease and single-lobe lesions: during a quick and deep inhalation in the affected lobe, there is increased airway resistance and decreased compliance compared to the healthy part of the lung. As a result, there is a preferential airflow to a healthier airfoil; ultimately, the healthier lobe receives more drug than the diseased lobe [6]

quality of the aerosol is determined by the air pressure expanding at the outlet of the nebuliser nozzle (0.7–2 bar), called the operating pressure. Higher pressure will break the drug into large, irregular particles, less pressure than 0.7 bar will not break the drug down. The operating pressure depends on the pressure created by the compressor and the diameter of the nozzle outlet passage in the nebuliser.

Ultrasonic nebulisers

Ultrasound is the force that breaks down liquid medicine into particles. The oscillator's vibration frequency is 1–2 MHz. The particles produced in ultrasonic devices vary in size and shape.

MESH or vibrating membrane nebulisers

The best drug deposition in the peripheral bronchus is achieved with particles with an ideal sphere shape. MESH nebuliser systems have a perforated membrane (mesh) through which drug particles pass, obtaining a perfect ball shape. The force breaking down the drug is ultrasound with a vibration frequency of approximately 117 kHz. MESH nebuliser systems allow you to shorten the inhalation time while obtaining the appropriate drug concentration in the lungs.

Characteristics of a proper nebuliser system

- good quality of the aerosol,
- low residual capacity,
- high efficiency (volume/time),
- allows the use of a variable inspiratory volume,
- good quality and shape of the mouthpiece,
- can be used in positions other than sitting. It applies to patients with inadequate ventilation of the lungs, for which the so-called positioning to use gravity should be applied to obtain better drug deposition in diseased areas,
- comfortable to hold in the hand,
- noise volume < 60 dB.

Nebuliser efficiency and aerosol quality

The efficiency of a nebuliser is determined by the amount of drug sprayed per unit time, most often given in mL/min or mg/min. The high efficiency of the nebuliser often means a shorter inhalation time but a poorer aerosol quality (MMD/MMAD > 5 μm). This dependence raises a lot of controversy due to the apparent contradiction in assessing the quality of the nebuliser system. There are different priorities, different for clinicians and patients. Clinicians want a very good quality aerosol (MMD/MMAD < 3 μm), which is a condition for obtaining a high concentration of the drug in the lungs. In turn, patients and their caregivers care about the shortest possible inhalation time. Work has been underway for many years to reconcile these two factors. MESH nebuliser systems, thanks to the dense aerosol

Table 2. Characteristics of nebulisers used in patients with cystic fibrosis — based on [7–11]. Aerosol parameters were determined based on: [1]the mass median diameter (MMD) or [2]the mass median aerodynamic diameter (MMAD)

Nebuliser	Total output rate	Aerosol parameters MMD[1]/MMAD[2]	Percentage share of particles smaller than 5 μm
PARI LC SPRINT BABY* (red insert)	150 mg/min	2.5 μm[1]	82%
PARI LC SPRINT STAR** (red insert)	296 mg/min	2.2 μm[1]	86%
PARI LC SPRINT Junior** (yellow insert)	370 mg/min	2.9 μm[1]	76%
PARI LC SPRINT*** (blue insert)	600 mg/min	3.5 μm[1]	67%
PARI LC SPRINT STAR*** (red insert)	450 mg/min	2.2 μm[1]	89%
PARI LC PLUS***	440 mg/min	3.6 μm[1]	67%
AeroEclipse XL BAN	no data	4.3 μm at 3.5 L/min 3.7 μm at 5.0 L/min[2]	58% at 3.5 L/min 67% at 5.0 L/min
SideStream	300 mg/min	3.17 μm[2]	77%
eFlow Rapid	610 mg/min	4.1 μm[1]	69%
InnoSpire Go	0.26 mL/min	3.99 μm[2]	52.3%

PARI LC SPRINT/LC PLUS: Measured with 0.9% NaCl in Malvern Master Sizer, 23 °C, 50% rel. humidity, inspiratory flow 6 L/min for babies*, 12 L/min for children** and 20 L/min for adults***; compressor pressure 1,6 bar with LC SPRINTs, 1.2 bar with LC PLUS

due to high amount of particles produced, allow to reconcile good aerosol quality with a shorter inhalation time. In the case of Jet nebuliser systems, an important role is played by educating patients and their families, making them aware that a short inhalation time is important, but for the health of their child it is more important to obtain the appropriate concentration of the drug in the lungs.

When choosing the right inhalation device for a cystic fibrosis patient, the following should be considered:

- the form of the drug,
- characteristics of the nebuliser and the aerosol,
- the patient's age,
- the possibility for the patient to inhale synchronized with the device,
- the severity of your lung disease, including the occurrence of complications (e.g. haemoptysis, pneumothorax),
- device availability,
- patient's acceptance [7].

Mostly Jet and MESH nebuliser systems find application in cystic fibrosis. They vary in efficiency, aerosol quality and drug delivery to the lungs. In both cases, liquid solutions of the drug are used. The characteristics and techniques of using nebulisers are presented in Tables 2 and 3.

Selection of individual pressure and powder inhalers

Most inhaled medications for people with cystic fibrosis are administered through nebulisers. However, due to the ease and convenience in everyday use of pMDI and DPI inhalers, it is recommended to use them instead of nebulisers whenever possible and in accordance with the manufacturer's instructions. The choice of pMDI or DPI should depend on the patient's age and ability to perform a specific respiratory maneuver (Table 4). pMDI should be used with an valved holding chamber (VHC), and for children under 3 years of age VHC with mask should be attached. Patients from the age of 5 can use DPI.

Principles of inhalation medication administration

It is very important to select the nebuliser and compressor correctly, in accordance with the recommendations of the attending physician and the manufacturer. Any inhalation medication should only be administered with an appropriate device. Most cystic fibrosis inhaled medications are licensed for use with pneumatic nebulisers. However, recently new antibiotics have been introduced for use with vibrating membrane nebulisers or DPI (Table 5). Their use

Table 3. Advantages and disadvantages of different types of nebulisers [12]

Type of nebuliser	Advantages	Disadvantages
Jet nebulisers with a corrugated tubing (choice depending on MMD/MMAD and FPF)	Easy to use Low drug waste The nebuliser insert can be replaced depending on the size of the drug particles* Effective in delivering drugs, which cannot be delivered by pMDI and DPI	Drug losses due to ineffective nebulisation
Breath-actuated and Breath--enhanced jet nebulisers	Drug is delivered by inhalation only Easy to use Low drug waste More efficient than a continuous nebulizer Effective at delivering drugs that cannot be delivered by pMDI and DPI	Requires that sufficient inspiratory flow is achieved to initiate drug delivery The drug delivery takes longer
Ultrasonic nebulisers	Easy to use	More expensive than pneumatic nebulisers. Large residual volume Inability to spray viscous solutions in the form of an aerosol Damage to the structure of heat-sensitive drugs
Mesh (type MESH) nebulisers	Fast, quiet, portable. It has an independent power source Optimization of particles' sizefor specific drugs More efficient than other nebulisers Easy to use	More expensive Cleaning more difficult. The dose of the drug should be adjusted when changing from the Jet nebuliser Not compatible with viscous liquids or those that crystallize during drying (do not give salt with hyaluronic acid)**

* applies to PARI nebulisers
**antibiotics are highly viscous formulation, nevertheless very efficient to be nebulised with eFlow *rapid*

Table 4. Selection of inhaler and interface depending on the patient's age based on [13]

Age	0–3 years	3–5 years	6–12 years	≥ 13 years
Inhaler type	Nebuliser* or pMDI with VHC	Nebuliser, pMDI with VHC	Nebuliser, pMDI with VHC, DPI, breath activated pMDI or breath-activated nebuliser	All types
Interface	Mask	Mask or mouthpiece with nose clip	Mouthpiece with nose clip	Mouthpiece with nose clip

*****breath-activated nebulisers are not recommended

significantly shortens the inhalation time, with comparable effectiveness, and improves compliance with recommendations [8, 9]. However, it should be remembered that new inhaled medications are registered with the device intended for their administration. By administering older drugs with the use of modern nebulisers, e.g. mesh instead of pneumatic, the pharmacokinetics of the drug changes. The dose may need to be adjusted to avoid side effects, especially for younger children. In some cases that is not necessary when switching from PARI jet nebs to eFlow *rapid*. A general overview of inhaled drugs and devices dedicated to their administration is presented in Table 6.

Inhaled antibiotics

Inhaled antibiotic therapy is the basic procedure for the eradication and treatment *Pseudomonas aeruginosa* chronic respiratory infections, which are the main cause of bronchopulmonary disease progression and death in patients with cystic fibrosis. Its use has an advantage over systemic therapy, as a relatively high concentration of the drug is delivered directly to the lungs, thus improving the pharmacokinetic and pharmacodynamic properties, while reducing the risk of toxicity. Correct administration of antibiotics such as colistin, tobramycin, aztreonam or levofloxacin is essential, both in terms of device selection and administration schedule (Table 7). The alternating

Table 5. Devices for the inhalation of drugs in patients with cystic fibrosis [14]

Drug	Nebuliser	DPI*	pMDI**
Hipertonic saline	+	–	–
Mannitol	–	+	–
Dornase alfa	+	–	–
Bronchodilators	+	+	+
Inhaled corticosteroids	+	+	+
Tobramycin	+	+	–
Colistin	+	+	–
Aztreonam	+	–	–
Liposomal amphotericin	+	–	–
Liposomal amikacin	+	–	–
Ciprofloxacin	–	+	–
Vankomycin	–	+	–
Levofloxacin	+	–	–

*DPI — dry powder inhaler; **pMDI — pressurized, metered-dose inhaler

cycles of antibiotics from different groups are increasingly recommended as a strategy to improve treatment outcomes, especially in patients with advanced lung disease [20]. In Poland, the limited access to inhaled antibiotics is a huge problem: only the preparation of colistin (Colistin TZF) is reimbursed, while tobramycin is available as part of a drug program, that excludes colistin interchangeability. The restrictive eligibility criteria for the drug program significantly limit the availability of highly concentrated tobramycin preparations for inhalation.

Practical aspect of inhalation treatments

To optimize the effectiveness of treatment, it is very important to follow the principles and procedures of physiotherapy, which include:

- compliance with the procedures for combining inhalation and drainage treatments,
- use of appropriate breathing and positioning techniques,
- use in inhalations of increased expiratory pressure (PEP — positive expiratory pressure),
- correct operation of the inhaler,
- continuous education of patients and their families.
- cleaning and disinfection of inhalers.

Procedures for combining inhalation and drainage treatments

- **Bronchodilators** — usually 10–15 minutes before physiotherapy; it is recommended to use them before inhalation with hypertonic saline or an antibiotic to prevent bronchospasm.
- **Hypertonic saline solutions** — immediately before physiotherapy, but after administration of a bronchodilator. It can also be administered during airway clearance in combination with PEP or with oscillating positive expiratory pressure OPEP (OPEP). This saves the patient's time, but while it improves the deposition in the peripheral airways, the total lung deposition is reduced, so an increase in volume of the drug is often suggested, e.g. up to 5–6 mL. It should also be kept in mind that the drainage performed in this way is much less effective, and therefore it may be recommended for daily physiotherapy only in patients with a very bad motivation.
- **Dornase alfa (rhDNase)** — usually nebulisation is performed after drainage and after at least 1.5–2 hours another drainage is performed. In some cases, however, the drainage time may be set individually. Based on a Cochrane review, it was found that dornase alfa can be administered before or after bronchial drainage, individually, depending on the patient [15]. It can be administered exceptionally in the evening, before going to bed. This decision should be made by the attending physician. At night, the patient's parents or guardians should monitor for excessive coughing. It should be emphasized that administering rhDNase in the evening is an exceptional situation and should not be a routine practice.
- **Inhaled glucocorticosteroids** — usually used after physiotherapy.
- **Inhaled antibiotics** — both dry powder inhalers and nebuliser solutions should be used after physiotherapy. Appropriate nebuliser systems should be used for antibiotics, depending on the manufacturer's recommendations (Table 8).

It should be remembered that the patient should rinse the oral cavity after both the use of steroids and after inhalation of dornase alfa, hypertonic saline solution and an antibiotic.

Breathing and positioning techniques

The use of breathing techniques that increase the deposition of the drug in the lungs depends on the age, severity of the disease and the patient's motivation. They can be used in cooperating patients with a very good motivation. Patients who are weakly motivated or who cannot cooperate yet, such as preschool children, are better advised

Table 6. Inhaled drugs used in patients with cystic fibrosis and nebulisers recommended by manufacturers

Drug	Trade name	Dosage	Nebuliser	Expiratory filter	Time from ACT	Comments
Inhaled antibiotics						
Liposomal amikacin	Arikayce	590mg/8.4 mL QD	Lamira Nebuliser System	yes	after ACT	alternating cycles of 28 days
Aztreonam lysine	Cayston	75 mg TID	Altera nebuliser with eFlow controller unit	yes	after ACT	alternating cycles of 28 days
Colistimethate sodium	Colistin TZF	1–2 mln IU BID/TID max 6 mln IU/day	PARI LC STAR, eFlow rapid, PARI LC SPRINT, PARI LC PLUS*	yes	after ACT	chronic therapy
Colistin nebuliser solution	Promixin	1–2 mln IU BID/TID max 6 mln IU/day	PARI LC SPRINT, I-neb AAD-System; eFlow rapid	n/a	after ACT	chronic therapy
Lewofloxacin	Quinsair	240 mg BID	Zirela nebuliser with eFlow controller unit	yes	after ACT	alternating cycles of 28 days
Tobramycin	Bramitob	300 mg/4mL BID	PARI LC PLUS or PARI LC SPRINT/ /PARI BOY Pro	yes	after ACT	alternating cycles of 28 days
	Tobi	300 mg/5 mL BID	PARI LC PLUS	yes	after ACT	alternating cycles of 28 days
	Vantobra	170 mg/1.7 mL BID	Tolero nebuliser with eFlow controller unit	yes	after ACT	alternating cycles of 28 days
	Tobramycin Via Pharma	300 mg/5 mL BID	PARI LC PLUS, PARI LC SPRINT STAR	yes	after ACT	alternating cycles of 28 days
	Tobramycyna SUN	300 mg/5 mL BID	PARI LC PLUS, PARI LC SPRINT STAR	yes	after ACT	alternating cycles of 28 days
	Tobi Podhaler	112 mg (4 kaps) BID	podhaler DPI	n/a**	after ACT	alternating cycles of 28 days
Anti-fungal drugs						
Amphotericina B liposomal	Ambisome	50 mg/week	I-neb, PARI LC SPRINT STAR	n/a**	after ACT	
Mucolytics						
Dornase alfa	Pulmozyme	2.5 mg QD	Pari LC PLUS, eFlow rapid	no	usually after ACT and not earlier than > 1.5–2 hours before the next ACT	
Hypertonic saline		3–7%	Nebuliser Jet, eFlow rapid, I-neb	no	immediately before or during the ACT	
Mannitol***	Bronchitol	400 mg (10 kaps) BID	DPI	no	after ACT	High risk of bronchospasm

ACT — airway clearance technique (based on [8–11, 16–19]); QD — once a day; BID — twice a day; TID — three times a day
* no manufacturer indications regarding the type of nebulisers, the recommendations are based on the experience of Polish experts
** n/a (not applicable)
*** third line drug in patients not responding to treatment with dornase alfa and hypertonic saline

Table 7. Antibiotics used in nebulisation solution in *Pseudomonas aeruginosa* respiratory tract infection in patients with cystic fibrosis — based on [20]

Antibiotics	Antibiotic group	Mechanism of action	Trade name	Nebulisation time	Dose	Frequency
Tobramycin	Aminoglycosides	Inhibition of protein synthesis	Tobramycin	15 min	300 mg/5 mL	BID
			Tobi	15 min	300 mg/5 mL	BID
			Bramitob	15 min	300 mg/4 mL	BID
			Vantobra	4 min	170 mg/1.7 mL	BID
			Tobramycin Via Pharma	15 min	300 mg/5 mL	BID
			Tobramycyna SUN	15min	300 mg/5 mL	BID
Aztreonam lysine	Monobactams	Inhibition of bacterial wall protein synthesis	Cayston	2–3 min	75 mg/1 mL	TID
Levofloxacin	Fluoroquinolones	Effect on DNA gyrase and topoisomerase IV	Quinsair	5 min	240 mg/2.4 mL	BID
Sodium colistimethate	Polimyxin	Disturbance in the structure of bacterial cell membrane	Promixin	3 min	80 mg/3 mL	BID/TID
			Colistin TZF	15–30 min	1 mln IU (80 mg)*	BID/TID

BID — twice a day; TID — three times a day
* 1 vial contains 1 million IU (80 mg) of lyophilisate for solution for injection, infusion and inhalation

Table 8. Recommendations for cleaning and disinfection of nebulisers used by patients with cystic fibrosis at home and during hospital stay [21]

Recommendations for the hygiene of nebulisers	
At home	**In the hospital**
1. Wash your hands thoroughly with soap and water and use a hand disinfectant gel before cleaning the nebuliser	
	Medical personnel should wear gloves and, after taking them off, follow recommendation 1
2. Disconnect the nebuliser from the compressor or controller and disassemble it	
3. Washing: wash the nebuliser parts in a solution of warm water and dishwashing liquid according to the manufacturer's recommendations	
4. Location: do not wash the nebuliser parts directly in the kitchen or bathroom sink or in the dishwasher. The nebuliser parts should be washed in a dedicated plastic, glass or metal bowl in the patient's kitchen	4. Location: nebuliser parts should be washed in a disposable bowl, metal bowl or wash basin (but not directly in the sink) in the patient room
5. Rinsing: use distilled water for the final rinse, if any disinfection is not possible	
6. Wastewater treatment: dirty water should be poured down the toilet, its lid should be closed before flushing	6. Disposal of sewage: the metal bowl with dirty water should be taken to the departmental lock and poured out there, the metal bowl should be sterilized in an autoclave
7. Wash your hands thoroughly with soap and water and use hand disinfectant gel	
8. Disinfection: the washed and rinsed nebulisers should then be disinfected after each use in an electric steam steriliser or scaled in boiling water	8. Disinfection: washed and rinsed nebulisers should be disinfected immediately after each use in an electric steam steriliser or reusable nebulisers can be autoclaved as recommended by the manufacturer
9. Drying: nebulisers should be thoroughly dried	
10. Storage: leave the disinfected nebuliser parts in a closed box until next use (within 24 hours)	

to breathe calmly, in a natural breathing rhythm appropriate for each patient. A sitting position should be used during inhalation. However, in some patients, drug deposition may improve positioning in positions other than sitting. By using gravity, a better effect of sedimentation and deposition of drug particles in areas with a significant degree of disturbance of ventilation can be obtained. The physiotherapist decides whether to use certain positions.

Use of elevated expiratory pressure (PEP) during inhalation

Some devices operating in the PEP system can be connected to Jet nebulisers. However, there are no clear recommendations regarding the use of PEP for inhalation. Study results concerning differences of aerosol deposition in the lungs when inhaled with or without PEP are inconclusive. Studies show that when PEP is used, significantly less aerosol is deposited in the lungs than when inhaled without PEP [23]. At the same time, better aerosol deposition and more proportional aerosol distribution in the peripheral bronchi during inhalation with PEP than without PEP was observed [23, 24]. The condition for the use of PEP is good cooperation with the patient and knowledge of breathing techniques that reduce drug losses during exhalation with resistance.

Correct use of the inhalation device

Proper handling of the inhalation device allows for its trouble-free operation for many years and the production of good-quality aerosols. Attention should be paid to the correct cleaning of the jet-nebuliser or the perforated membrane in the MESH nebuliser system, replacement of the air filter in the compressor and the systematic replacement of used nebulisers and compressors with new ones.

Continuous education of patients and their families

The effectiveness of inhalation therapy depends on the inhalation technique and adherence to recommendations. Patients and their parents / guardians should receive repeated training in physiotherapy. In case of lack of the expected results of treatment, the method of performing inhalation and drainage procedures should always be checked and re-education should be performed.

Cleaning and disinfection of nebulisers

Proper daily use of inhalation devices is aimed at ensuring optimal drug delivery and the prevention and control of infections [21, 22, 25]. Currently, there is a great need for education in this area, especially adults. The following are guidelines for cleaning and disinfecting nebulisers in both home and hospital settings (Table 8).

1. Always wash and disinfect new parts of the nebuliser before first use.
2. During a hospital stay as well as at home, wash and steam the parts of the nebuliser after each use.
3. The nebuliser should be washed and disinfected again immediately before use if it has not been used for more than 24 hours.
4. After boiling or steaming in a steam disinfector, the parts of the nebuliser should be immediately removed from the water or the steamer, and dried quickly and thoroughly. A sterilizer with a drying function can be used. Do not leave the nebuliser parts to dry on the dryer or on the edge of the wash basin or sink.
5. After cleaning the nebuliser, hands should be washed thoroughly with soap and water and hand disinfectant gel should be used.

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Conflicts of interest

None declared.

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Rasmussen's aneurysm: a rare and potentially fatal cause of hemoptysis

Abstract

Rasmussen's aneurysm is a rare and fatal cause of hemoptysis secondary to infection with pulmonary tuberculosis. The most commonly involved vessels include the bronchial arteries, but rarely can involve the pulmonary artery.

We report the case of a 62-year-old female from the Philippines with undiagnosed pulmonary tuberculosis who presented with massive hemoptysis. After hemodynamic stabilization, Rasmussen's aneurysm was diagnosed by computed tomography of the chest with angiography, confirmed with invasive angiography. She was treated definitively with glue embolization of the affected artery.

Key words: hemoptysis, tuberculosis, critical care, angiography

Adv Respir Med. 2021; 89: 581–584

Introduction

Tuberculosis (TB), caused by the bacterium *Mycoplasma tuberculosis*, is an infectious disease with significant global burden, with approximately 25% of the world's population estimated to be infected [1]. Multidrug resistant strains have become an increasing problem complicating treatment. In the United States, however, the incidence rate of TB has been consistently declining for at least the past fifty years. In 2019, the United States' TB rate declined to its lowest rate yet, at 2.7 cases per 100,000 persons [2]. A large portion of these cases are attributed to reactivation of latent TB infection. Because of its low incidence overall in the United States, and effective screening programs in high-risk populations, significant complications are rarely seen. We present a case of a patient with a previously undiagnosed TB infection who suffered massive hemoptysis due to invasive cavitation of the pulmonary parenchyma with involvement of an adjacent branch of the pulmonary artery, a phenomenon known as the Rasmussen's aneurysm.

Case presentation

A 62-year-old woman from the Philippines presented to the hospital with a complaint of dyspnea and hemoptysis. The patient initially began to have dyspnea at rest for several months. One month prior to presentation, she developed a productive cough. The patient was diagnosed by her primary care provider with "acute bronchitis" and was first given a course of levofloxacin, then three courses of amoxicillin. Despite this, she continued to have worsening cough with blood noted in the sputum, prompting her to come to the emergency department. Her prior medical history included hypertension and a history of breast cancer on tamoxifen therapy. She also had a history of multiple positive purified protein derivative (PPD) tests for TB in the past, but with no formal diagnosis or treatment of latent TB.

On initial physical examination, the patient was dyspneic but able to speak full sentences. Her oxygen saturation was 95% on room air. Pulmonary exam was remarkable for bilateral rhonchi to lung auscultation. The rest of physical exam was

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unremarkable. While the patient was waiting in the emergency department, she experienced an episode of massive hemoptysis, became hypoxic, and then bradycardic without pulse. Advanced cardiac life support was initiated, and she received four rounds of cardiopulmonary resuscitation with return of spontaneous circulation. Subsequently she was intubated, resuscitated with fluids, and then started on a norepinephrine drip for shock. Initial laboratory workup revealed a hemoglobin level of 8.8 g/dL (baseline was 14 g/dL), white blood cell count of 19,600/mm^3, and lactate of 8.8 mmol/L. The patient was taken emergently for computed tomographic pulmonary angiography (CTPA) which showed an active pulmonary arterial bleed in the left lower lobe, with an associated 4.5 cm blood filled mass-like cavitary lesion in the left upper lobe in proximity with mentioned bleeding artery (Figures 1, 2). Invasive pulmonary angiography was performed confirming a large pseudoaneurysm arising from the proximal left lower lobe pulmonary artery with active bleeding into a cavitary lesion (Figure 3).

The patient underwent emergent glue embolization with coils placed in the remnant proximal left lower lobar pulmonary artery (Figure 4). Sputum and bronchoalveolar lavage (BAL) specimens were sent for acid-fast bacilli (AFB) direct and concentrated smears. These were positive for *Mycobacterium tuberculosis* complex without any drug resistance genes. The patient was started on a liver sparing anti-tuberculosis regimen as she showed evidence of acute hepatic injury, likely due to shock. The regimen included rifampin, ethambutol, and levofloxacin. She remained sedated and intubated for five days following the embolization. There were no further episodes of hemoptysis and her hemoglobin remained stable.

Unfortunately, the patient was diagnosed with a severe anoxic brain injury as a result of her initial cardiac arrest. Her family requested a change in her goals of care to comfort care. Her anti-tuberculosis regimen was maintained until her passing for infection control purposes.

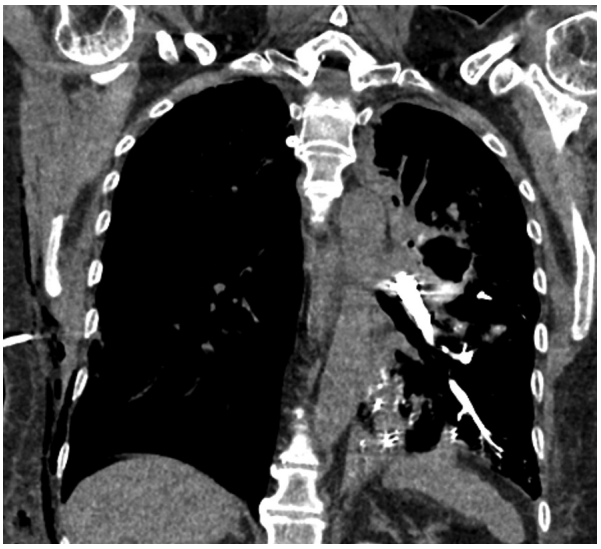

Figure 1. Coronal CT of the chest showing the mediastinal window of a left upper lobe cavitation in direct contact with the left lower branch of the pulmonary artery

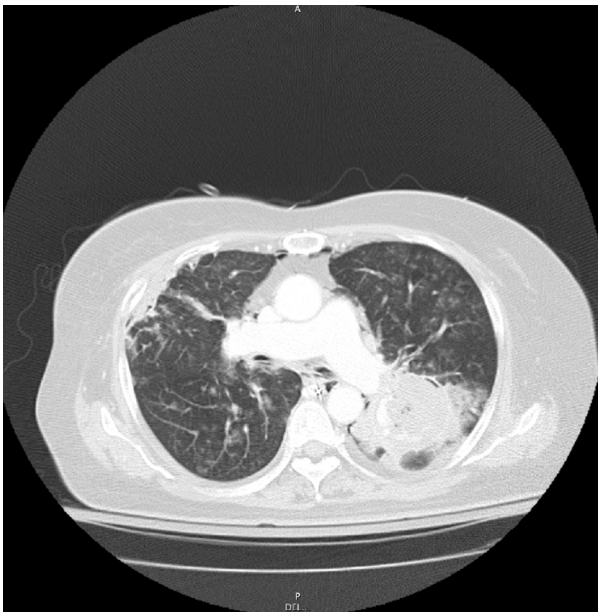

Figure 2. Transverse CT of the chest showing the lung window of a left upper lobe cavitation in direct contact with the left lower branch of the pulmonary artery

Discussion

The differential diagnosis of life-threatening hemoptysis such as in this patient includes bronchiectasis (particularly in cystic fibrosis), fungal infections, tuberculosis, malignancy, and vascular disorders including the vasculitides [3, 4]. Based on our patient's previously positive PPD tests, imaging studies, and the fact that the patient lived in an endemic country for most of her life, there was a high suspicion that the hemoptysis was secondary to TB infection. Pulmonary TB presents with a variety of symptoms, which are usually insidious in onset and progression. Symptoms include low-grade fever, night sweats, cough, weight loss and mild hemoptysis that usually persist for weeks before patients seek healthcare. Rarely, patients can present with massive hemoptysis, which has a mortality rate up to

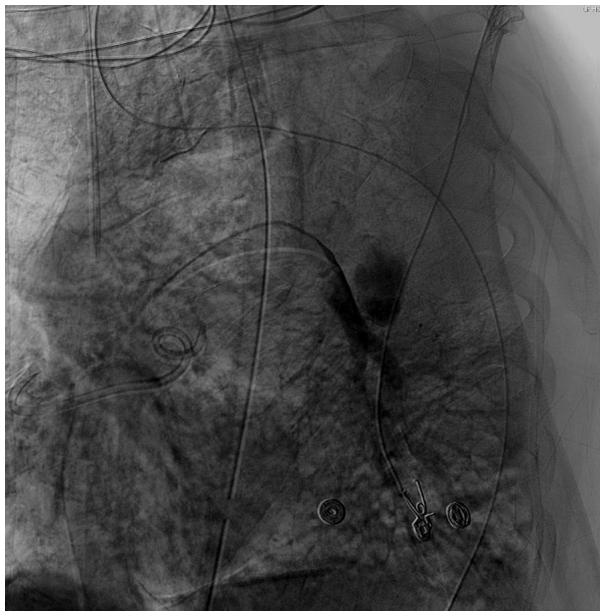

Figure 3. Angiography of the left upper lobe of the lung demonstrating active bleeding into the cavitary lesion

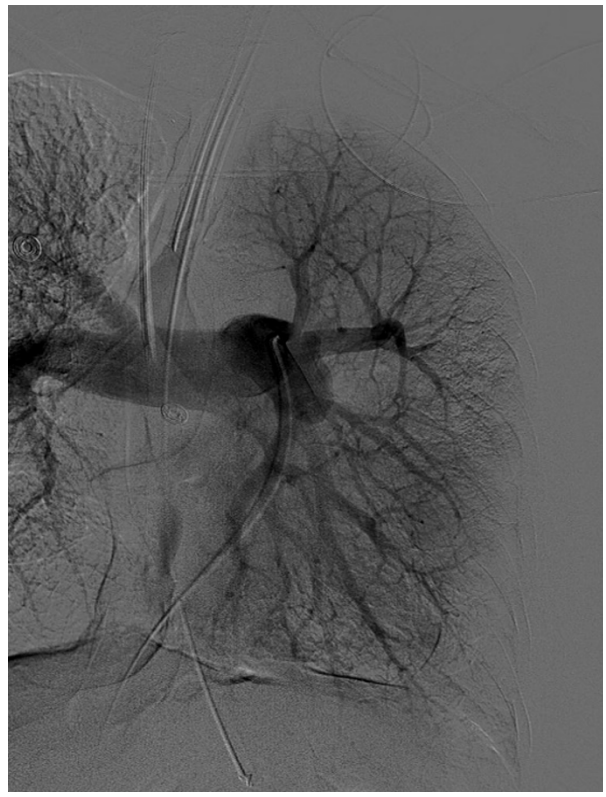

Figure 4. Post-embolization angiography of the left upper lobe of the lung demonstrating resolution of the bleeding pulmonary artery

50%. Massive hemoptysis in tuberculosis can be caused by a phenomenon known as the Rasmussen's aneurysm, as was the case with our patient. Rasmussen's aneurysm is a potential complication of chronic cavitary pulmonary disease, due to the invasion into the pulmonary vasculature. In a post-mortem analysis of patients with chronic cavitary tuberculosis, it has been estimated that up to 4% of patients had pathology consistent with Rasmussen's aneurysm [4]. Of those with massive hemoptysis secondary to a Rasmussen's aneurysm, the most commonly involved vessels are the bronchial arteries. In less than 10% of cases, the main pulmonary artery may be involved.

Rasmussen's aneurysm is a pseudo-aneurysmal dilatation of a branch of pulmonary artery adjacent to a tuberculous cavity that can rupture and cause massive hemoptysis. As a tuberculous cavity begins to extend into the pulmonary artery, granulation tissue begins to invade and replace the adjacent pulmonary arterial wall (specifically the tunica adventitia and tunica media). Fibrin replacement of the vessel wall leads to thinning, and eventually herniates into the lumen of the vessel creating a pseudoaneurysm [5]. This pathology is reported to be associated with 5% of all tuberculous cavitary lesions [6]. The advent of contrast-enhanced CT has enabled a noninvasive, first-line method of localizing the site of arterial bleeding in the setting of massive hemoptysis, as seen in our case [7]. In our patient, both fiberoptic bronchoscopy and CTPA helped to identify the site of bleeding from a pulmonary artery pseudoaneurysm, leading to prompt intervention.

After resuscitation and stabilization of the patient, endovascular management techniques like trans-arterial catheter embolization are the preferred management strategy. Embolization techniques can include glue embolization, coil packaging, gel foam, detachable balloons, or stent grafts [6]. In Rasmussen's aneurysm, glue embolization is the preferred technique due to the fragility of the artery [8].

Conclusions

Rasmussen's aneurysm is a rare complication of pulmonary TB that can cause life-threatening hemoptysis, particularly in non-endemic countries. In patients presenting with massive hemoptysis, it is important to include in the differential diagnosis, and treat rapidly with embolization. Glue embolization is the preferred trans-catheter technique due to the fragility of the involved vasculature.

Conflict of interest

None declared.

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Clinical improvement in Job syndrome following administration of co-trimoxazole, omalizumab and inhaled tobramycin

Abstract

Established treatment regimens for the autosomal dominant hyperimmunoglobulin E syndrome, denominated Job syndrome, are lacking. Thus, Job syndrome still exerts a dramatic impact on patients' quality of life. Our aim was to present safety and effectiveness of a regimen including co-trimoxazole, omalizumab and inhaled tobramycin in Job syndrome. A 26-year-old woman diagnosed with Job syndrome since infancy through sequencing revealing G342D mutation in STAT3 gene was initiated in the above mentioned treatment regimen; she was followed for 6 months, and to date, none recurrent pulmonary or skin infection was noticed. Furthermore, a considerable improvement in skin lesions was observed. A combination of anti-IgE and longitudinal use of inhaled antibiotics seems well-founded in Job syndrome.

Key words: Job syndrome, recurrent infections, omalizumab, inhaled antibiotics

Adv Respir Med. 2021; 89: 585–588

Introduction

A 26-year-old woman, never smoker, presented to our department with cough, yellow sputum and localized left chest pain. Chest radiograph revealed consolidation in the left lower lobe and a fluid-filled cavity in the middle lobe. She denied the presence of fever, night sweats or weight loss. She had a medical history of Job syndrome diagnosed during infancy based on compatible genetic (G342D mutation in STAT3 gene) and clinical (recurrent lower respiratory and skin infections in need of repeated hospitalizations with several courses of empirical antimicrobial agents) findings.

Material and methods

Physical examination findings

Physical examination revealed the following vital signs: blood pressure of 110/70 mm Hg; heart rate, 85 beats/min; temperature, 36,8°C and oxygen saturation, 97% on room air. Lung auscultation revealed crackles mainly on left side while heart and abdomen examination results were unremarkable. There were no palpable lymph nodes. Clubbing was present, as well as extensive skin lesions on the upper limbs and hyperextensibility of finger joints.

Diagnostic studies

The complete blood and metabolic panel revealed elevated white blood cells (WBC) (16,1 K/μL) with neutrophilic predominance on admission (62%) and eosinophilic predominance on discharge (40%) and elevated c-reactive protein (22,33 mg/dL). Urinalysis and electrocardiogram were normal. Chest computed tomography (CT) showed cystic bronchiectatic lesions in the right upper lobe combined with a fluid-filled cavity within the middle lobe and consolidation in the left lower lobe (Figure 1). The patient underwent conventional bronchoscopy with the presence of purulent bronchial secretions bilaterally and hemorrhagic mucosa in the middle lobe. Culture of washing for common pathogens was

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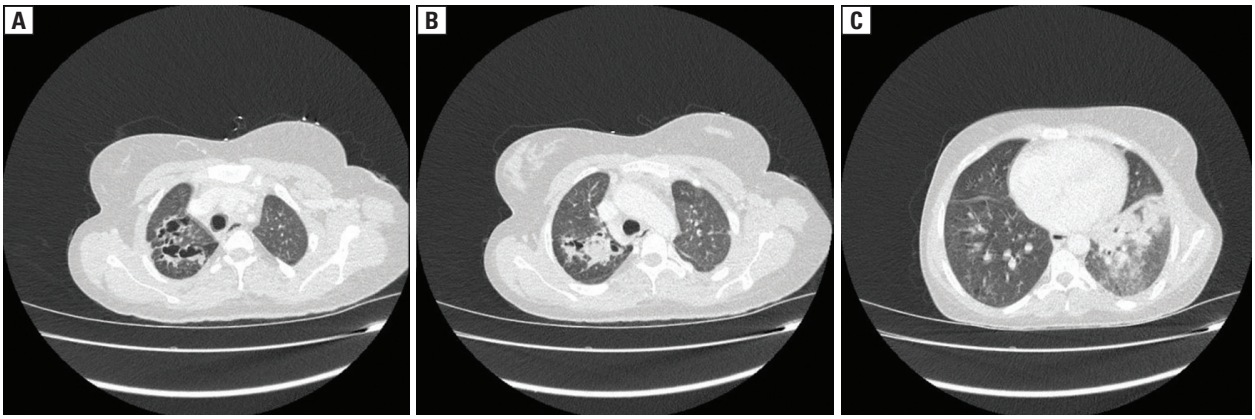

Figure 1. Chest computed tomography showed cystic bronchiectasis in the right upper lobe (**A**), a fluid-filled cavity in the middle lobe (**B**) and consolidation in the left lower lobe (**C**)

positive for Methicillin-resistant *Staphylococcus aureus* (MRSA) infection and negative for mycobacterium infection. Cytological examination of washing was negative for malignancy. Pulmonary function tests showed bronchodilator reversibility (PRE: forced expiratory volume in 1 second [FEV_1] / forced vital capacity [FVC]: 83%, FEV_1 of 1.65 L [59% of predicted] and FVC of 2 L [63% of predicted] — POST: FEV_1/FVC: 87%, FEV_1 of 1.8 L [68% of predicted] and FVC of 2.06 L [66% of predicted]). Skin prick test was positive for mixed fungus, *Tilia tomentosa* and *Candida*. Moxifloxacin and linezolid were administered for ten days based on antibiogram. An improvement on chest radiogram performed four weeks later was obvious. This was the sixth hospitalization for our patient within the previous year attributed to pneumonia following multiple hospitalizations since infancy due to recurrent lower respiratory or skin infections.

Clinical course

The patient was admitted with recurrent pneumonia in setting of diagnosed Job syndrome since infancy. Genetic confirmation of the disease had been conducted through sequencing revealing G342D mutation in STAT3 gene. Recent laboratory examination had revealed remarkably elevated serum IgE levels >30 000 IU/mL and eosinophilia (31% WBC count: 9.27 K/μL). During her last hospitalization, the patient was treated with antimicrobial therapy based on antibiogram, as part of symptomatic management of recurrent respiratory infections observed throughout the clinical course of syndrome. Considering multiple hospitalizations and extensive post-infectious structural abnormalities of lung parenchyma, multidisciplinary approach yielded a therapeutic regimen including biological anti-IgE agent and longitudinal antibiotics on a chemoprophylactic basis as the optimal strategy. In particular, the patient was commenced on co-trimoxazole, omalizumab and inhaled tobramycin. Established evidence has shown that co-trimoxazole is a safe and effective substitution to penicillins and has anti-MRSA coverage [1]. Furthermore, omalizumab, a monoclonal anti-IgE, has been shown closely related to a decline in serum IgE with symptomatic improvement especially in atopic conditions [2–4]. Eventually, inhaled antibiotics have emerged as a new option for specific groups of patients, including patients with bronchiectasis, combining high drug concentrations directly to the site of infection and concomitantly minimizing systemic absorption and potential side effects. Co-trimoxazole was administered orally in prophylactic dosage three times a week, omalizumab in dosage adjusted by the patient's weight and baseline IgE once a month subcutaneously and inhaled tobramycin 300 mg twice a day. The woman was followed for 6 months, with no recurrent respiratory or skin infections. Furthermore, a considerable improvement of skin lesions was observed (Figure 2). To the extent of our knowledge, this is the first time that combination of anti-IgE and longitudinal use of inhaled antibiotics is proposed in Job syndrome.

Discussion

Hyperimmunoglobulin E syndrome is a rare primary immunodeficiency disorder characterized by eczema, skin abscesses, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, candidiasis, eosinophilia, and elevated serum levels of IgE [5]. It was

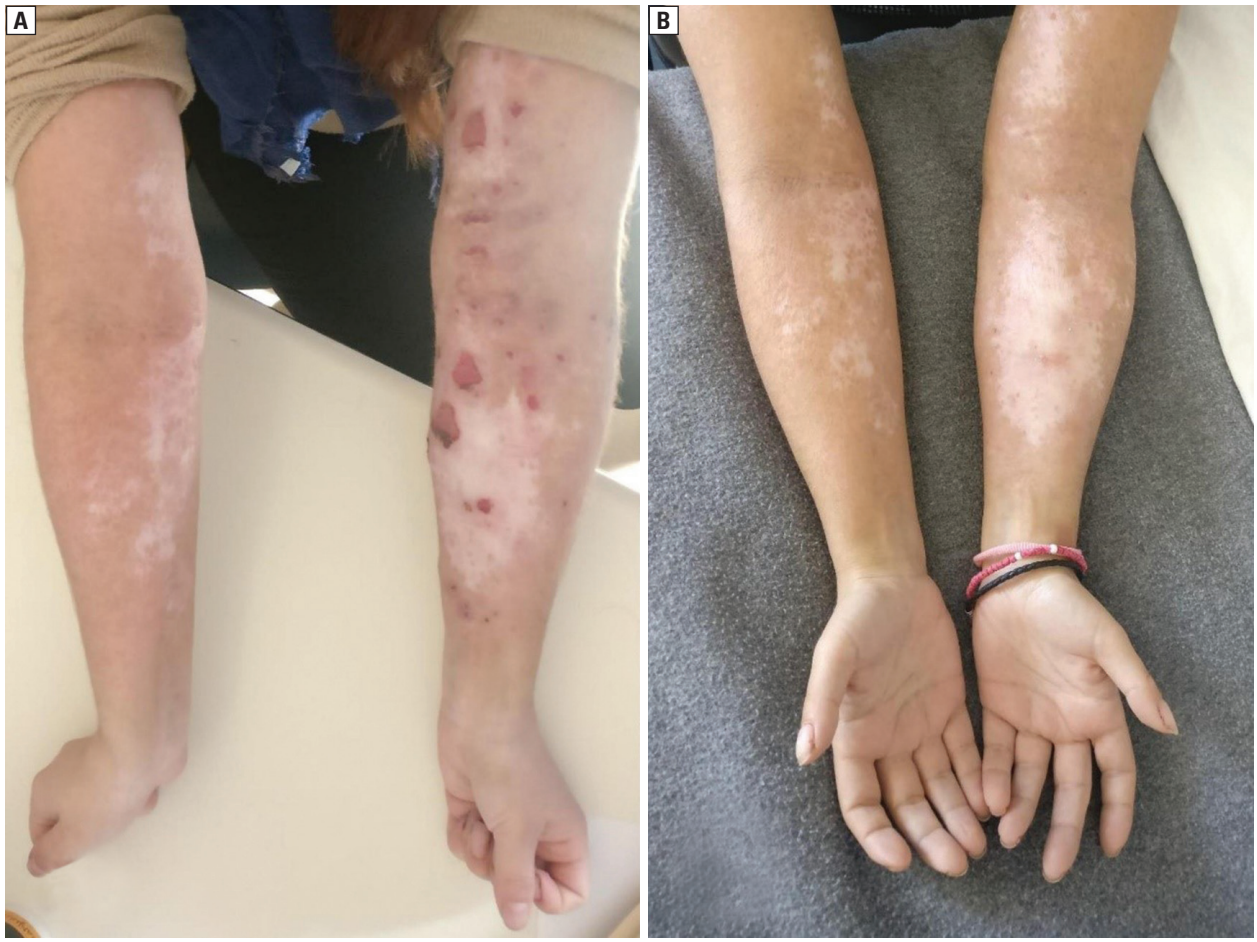

Figure 2. Improvement of skin lesions following administration of omalizumab for 6 months

first described as "Job syndrome" by David *et al*. in 1966 in two patients with eczema, recurrent pulmonary infections and cold lung abscesses and was later associated by Buckley *et al*. in 1972 with increased serum immunoglobulin E levels [6]. Job syndrome is classified as the autosomal dominant hyper-IgE syndrome, in which patients have abnormalities in different systems, including the immune system, connective tissue, skeletal and vascular structures [7]. It is attributed to a mutation in the STAT3 gene in more than two-thirds of cases (70%) with the etiology of the rest cases remaining unclear [8]. Clinical signs of immunological features include recurrent skin and pulmonary bacterial or candidiasis infections. *Staphylococcus aureus* is the predominant pathogen resulting in follicular skin lesions or recurrent lung abscesses, bronchiectasis and pneumatoceles. *Streptococcus pneumoniae* and *Haemophilus* are observable less frequently, while *Aspergillus* and *Pseudomonas* are usual cause of chronic colonization of bronchiectasis. The main laboratory diagnostic feature is an increase in serum IgE levels of more than 2000 IU/mL. Eosinophilia is observed in more than 90% of the patients while WBC count can be normal, elevated or reduced in number [9]. The established treatment is the long-term, sometimes consecutive, use of antibiotics by adapting the administration of antimicrobial agents to opportunistic infections occurring in affected patients, and in selected cases, applying surgical procedures during abscess development. In order to overcome purely symptomatic treatment applied for the moment, biological treatment with monoclonal antibodies or combination of biologics and antibiotics could be an optimal strategy. Further studies towards this direction are greatly anticipated.

Conflict of interest

None to declare.

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Early experience of nintedanib in COVID-19 ARDS-related pulmonary fibrosis: a case series

Abstract

The current COVID-19 pandemic has spread like wildfire worldwide and has affected millions of people. The novel corona virus mainly affects the lungs leading to life threatening disease like acute respiratory distress syndrome (ARDS). The aftermath of the disease in form of pulmonary fibrosis is upcoming cause of further increase in morbidity and mortality. Nintedanib is an oral antifibrotics with proven role in idiopathic pulmonary fibrosis, however its use in COVID-19 related pulmonary fibrosis has not been studied. We report our early experience of use of nintedanib in COVID-19 related pulmonary fibrosis.

Key words: SARS-CoV-2, ARDS, pulmonary fibrosis, antifibrotics, nintedanib

Adv Respir Med. 2021; 89: 589–596

Introduction

The current SARS-CoV-2 pandemic has affected millions of people worldwide. It mainly affects the lung progressing to respiratory failure. Post COVID-19 ARDS related pulmonary fibrosis is an important entity which is posing a management dilemma to the clinicians. The pulmonary fibrosis begins early in the course of ARDS and is more common in patients with longer duration of ICU stay [1, 2]. The risk factors constitutes advanced age, male gender, underlying co-morbidities like diabetes and patients with severe COVID-19 disease [3–5]. The pathophysiology of pulmonary fibrosis in COVID-19 patients includes dysregulated immune mechanisms which causes generalized epithelial and endothelial injury and finally an aberrant healing process leading to pulmonary fibrosis [1, 6, 7]. Nintedanib is currently used widely in management of idiopathic pulmonary fibrosis and prevents the decline in lung function [8–10]. Here we present our early experience of use of nintedanib in COVID-19 related pulmonary fibrosis.

Case series

This is a case series of four patients carried admitted at our tertiary care hospital in western Maharashtra from April 2020 to October 2020. All four patients were confirmed COVID-19 cases by nasopharyngeal swab RT-PCR test.

Case 1

A 62-years-old female with no known co-morbidities, reported to emergency with history of fever and cough of five days and insidious onset breathlessness of one day duration. She was diagnosed as COVID-19 infection on her nasopharyngeal RT PCR test. She reported to the hospital on seventh day of symptoms and on arrival, she was tachypnoeic and her saturation was 78% on room air which improved to 90% with oxygen through non- rebreather mask (NRBM) at 15 litres/min. On evaluation, she had mild anaemia (Hb-12 gm/dL) with lymphopenia and high neutrophil/lymphocyte ratio (N/L-8). Her liver enzymes and renal function tests were within normal limits. Her chest radiograph showed

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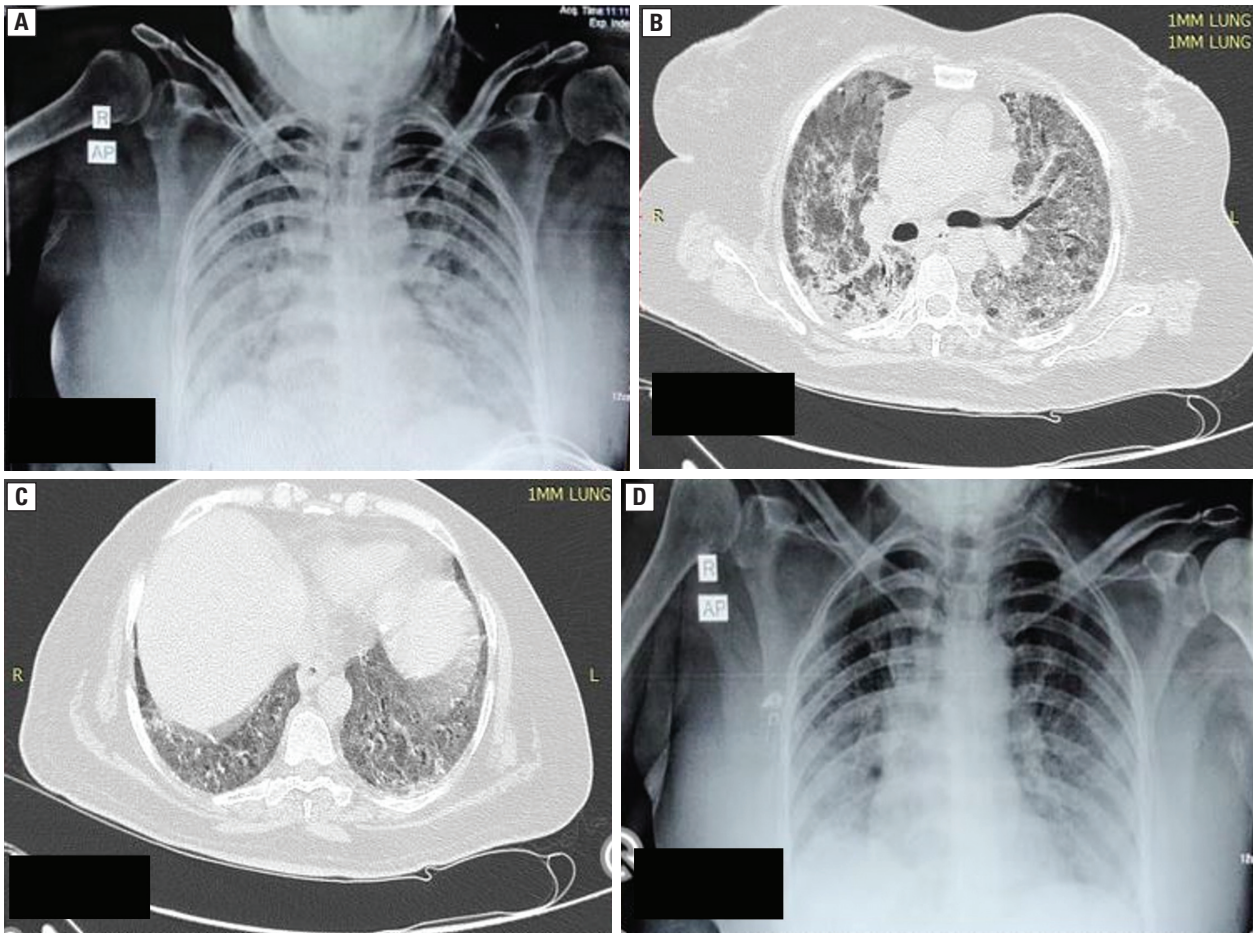

Figure 1A. Chest skiagram showing bilateral airspace opacities in mid and lower zones; **B, C.** High resolution computed tomogram of chest showing pulmonary fibrosis in bilateral lower lobes; **D.** Chest skiagram showing improvement after 3 weeks of antifibrotics therapy

bibasal peripheral airspace opacities (Figure 1A). She was managed with injectable antibiotics, steroids (Inj dexamethasone 6 mg once daily for 10 days), therapeutic dose of low molecular weight heparin (LMWH) and oxygen therapy. However, she had progression of disease to acute respiratory distress syndrome (ARDS) and was not maintaining saturation on high flow oxygen, therefore was commenced on non-invasive ventilation (NIV) (settings: pressure support — 4 cm H_20, PEEP — 10–12 cm H_20, FiO_2 — on titration with target saturation 88–92%). Her arterial blood gas showed hypoxemia with low partial pressure of oxygen (pO_2) to fraction of inspired oxygen (FiO_2) — (pO_2/FiO_2) less than 100. She also showed features of hyperinflammation in form of raised LDH, ferritin, CRP and IL-6 (Table 1) for which she was administered 2 doses of tocilizumab (8 mL/kg), 24 hours apart. She was also given two doses of COVID convalescent plasma (CCP) (200 mg/dose), 24 hours apart. The patient showed significant response and was gradually weaned off NIV but she continued to have high oxygen requirement. Her chest roentgenogram showed dense fibrotic opacities in bilateral lower zones. She underwent a high resolution computed tomography (HRCT) of chest which showed severe involvement of bilateral lung with fibrosis in bilateral lower zones which was more on the right side (Figure 1B, C). She was diagnosed as post COVID-19 ARDS pulmonary fibrosis and was commenced on oral tablet nintedanib (150 mg twice daily). She showed significant response and was gradually weaned off high flow nasal oxygen after 3 weeks and was discharged on minimal domiciliary oxygen supplementation. The follow-up chest roentgenogram showed significant clearing of fibrotic opacities (Figure 1D).

Case 2

A 36-years old male with no known co-morbidities, initially reported with history of fever and cough of three days duration and history of breathlessness of one day duration. On arrival, he was tachypnoeic (respiratory rate — 32/min) and hypoxic at room air (82% at room air and

Table 1. Detailed laboratory parameters of patients

		Patient 1		Patient 2		Patient 3		Patient 4	
Date	**Normal values**	**11/07**	**06/08**	**04/08**	**11/08**	**22/7**	**27/7**	**22/10/2020**	**04/12/2020**
Hb [g/dL]	13.5–17.5 [Men] 12–15.5 [Women]	13.3	11.4	15.6	15.4	13.3	14.2	14.3	14.2
TLC[/cmm]	4000–11000	11700	4100	15800	9500	3100	5100	4400	9000
Neutrophil/lymphocyte ratio	0.78–3.53	90/05	64/20	92/04	86/09	78/19	85/13	72/21	63/27
Plt[/cmm]	150,000–400,000	265000	157000	216000	294000	127000	129000	95000	256000
CPK/CKMB	21–232/5–25	197/98	223/68	51/24	46	774/42	247/48	300/50	68/24
PT/INR/PTTK	11–12.5/0.8–1.1/ /30–45 seconds	14/1.0/42.5	22.1/1.82/40	27.7/2.05/41	30/2.0/44	14.7/1.05/46	17.2/1.34/29	18/2/5/28	14/1.08/24
UREA [mg/dL]	10–30	31	11	34	59	57	65	35	14
CREATININE [mg/dl]	0.7–1.3	0.8	0.2	1.1	0.7	1.4	1.1	0.7	0.7
ALT/AST [IU/L]	15-37/16–63	72/31	58/53	29/59	67/42	109/35	42/37	77/72	91/85
LDH [IU/L]	85–227	993	636	237	345	724	927	245	314
Procalcitonin [μg/L]	< 0.05	3.93	< 0.05	< 0.05	< .022	0.90	0.03	< 0.05	< 0.05
D.DIMER [g/L]	< 0.50	1.96	5	8.0	.50	4.1	> 20	5.2	2
S. Ferritin [pg/mL]	24–336 [men] 11–307 [women]	710	650	900	804	597	984	727	450
CRP [mg/L]	< 10 mg/L	40	Neg	38	Positive	48	24	6.3	16
IL6 [pg/mL]	5–15	24	15	20	12	18	19	35.4	2.4
TG [mg/dL]	< 150	334	152	51	93	69	150	230	200

g/dL — grams per decilitre; TLC — total leukocyte count; /cmm — per cubic milimeter; Plt — platelets; CPK — creatinine phosphokinase; MB — creatinine kinase; PT — prothrombin time; INR — international normalised ratio; PTTK — partial thromboplastin time activated with kaolin [hemostasis]; mg/dL — miligrams per decilitre; ALT — alanine transaminase; AST — aspartate transaminase; IU/L — international unit per liter; LDH — lactate dehydrogenase; CRP — C-reactive protein; IL-6 — interleukin 6, TG — triglycerides

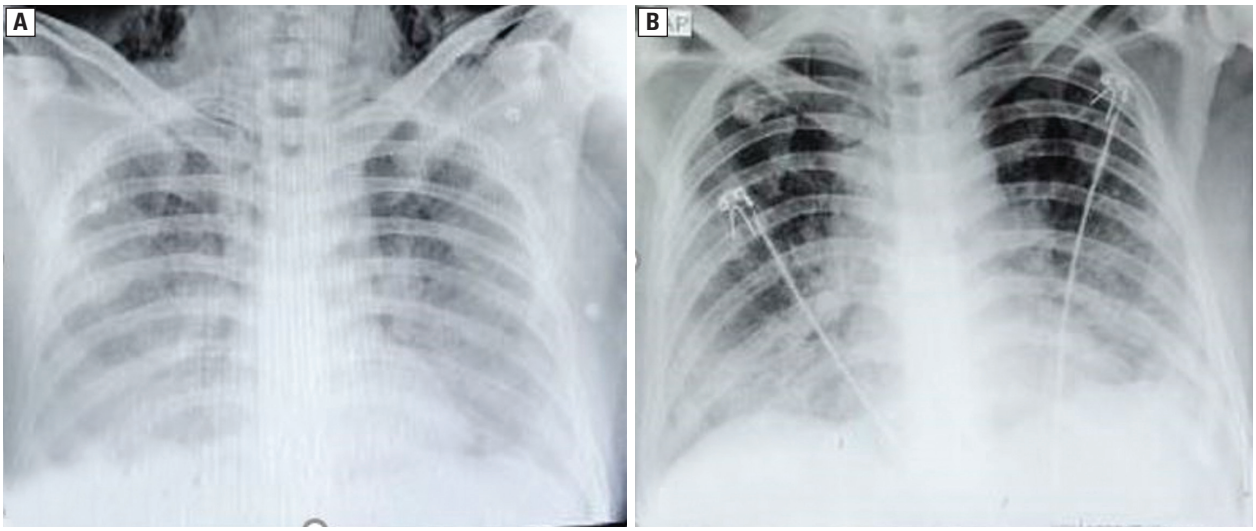

Figure 2A. Chest skiagram showing bilateral airspace opacities involving all the lobes; **B.** Chest skiagram showing radiological improvement after 3 weeks of nintedanib

Table 2. Arterial blood gas details of COVID-19 patients pre and post (4 weeks) nintedanib

	Patient 1		Patient 2		Patient 3		Patient 4	
	Day 1	Day 10	Day 1	Day 8	Day 1	Day 6	22/10/2020	04/12/2020
pH (7.35–7.45)	7.3	7.38	7.42	7.45	7.36	7.42	7.39	7.45
pCO_2 (mmHg) (35–45)	38	38	32	38	40	38	36	38
pO_2 mmHg (80–100)	40	55	50	58	40	56	52	58
HCO_3 (mEq/L) (22–26)	18	23	23	25	20	24	22	25

94% with oxygen through NRBM). On evaluation, he had lymphopenia (total leukocyte count-3100/Cumm)withhighneutrophil/leukocyteratio (> 3.8). He also had raised markers of hyperinflammation (LDH, ferritin, D-dimer and interleukin 6 levels) (Table 1). His chest roentgenogram showed severe COVID pneumonia with bilateral air space opacities and consolidation in mid and lower zones (Figure 2A). His arterial blood gas showed features of type-1 respiratory failure with ARDS (pH — 7.42, pO_2 — 45, pCO_2 — 28, HCO_3 — 24). He was managed as a case of severe COVID-19 pneumonia with injectable antibiotics, parenteral steroids (Inj dexamethasone 6 mg once daily for 10 days), therapeutic dose of LMWH and oxygen therapy through NRBM@ 15 litre/min. However, his respiratory parameters worsened requiring non-invasive ventilation (settings: Pressure support — 2–4 cm H_20, PEEP — 10–12 cm H_20, FiO_2 — on titration with target saturation 88–92%). He showed favourable response but continued to have high oxygen demand. He was diagnosed as having COVID-19 related pulmonary fibrosis and started on nintedanib (150 mg twice daily) and he showed significant response with improvement in oxygenation after four weeks (Figure 2B, Table 2).

Case 3

72-year-old male, non-smoker, known case of type-II diabetes mellitus and primary hypertension reported with history of fever, cough and generalised malaise of three days and history of increased breathlessness of one day duration. On arrival he was tachypnoeic (respiratory rate — 35/min) and hypoxic at room air (saturation at room air — 80%). On evaluation, he had normal complete blood count, liver and kidney function tests but had raised serum markers of hyperinflammation. He was managed with parenteral steroids (Inj dexamethasone 6 mg once daily for 10 days), IV antibiotics, subcutaneous LMWH and oxygen therapy through NRBM@ 15 litres/min. Hid ABG showed features of type-1 respiratory failure and ARDS (pO_2/FiO_2 < 100). He was also given two doses of injection tocilizumab for cyto-

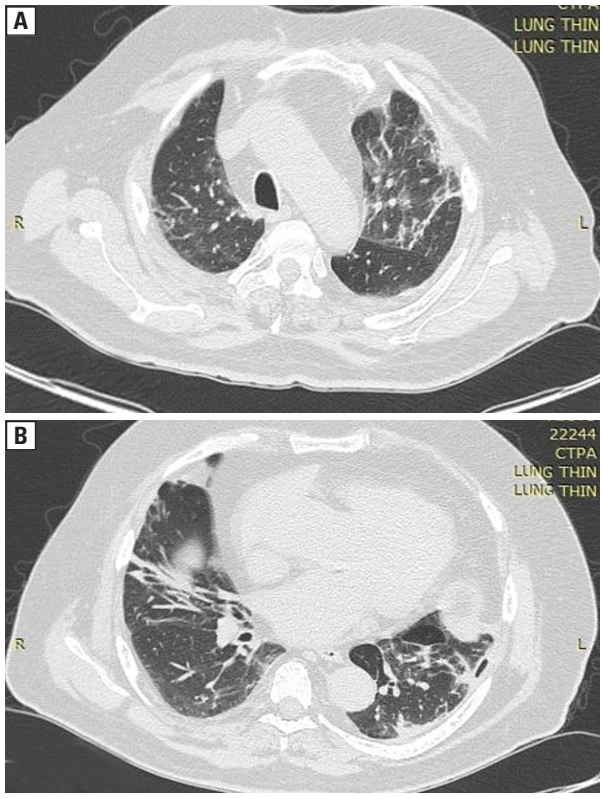

Figure 3A, B. High resolution computed tomography of chest showing fibrotic opacities in bilateral upper lobes (left > right)

kine storm syndrome. However, even after three weeks of intensive management, he continued to have high oxygen requirement. His HRCT of chest showed moderate involvement of bilateral lung with post COVID-19 changes in form of dense fibrosis in bilateral upper lobe (Figure 3A, B). He was started on oral nintedanib and he showed significant improvement and was weaned off oxygen after four weeks.

Case 4

52-year-old male, known case of type-II diabetes mellitus on oral hypoglycaemic agents, presented with history of fever with chills and dry cough of four days duration. he reported to emergency department on sixth day of symptoms, with history of increased breathlessness. On arrival he was hypoxic (saturation at room air — 82% and 92% with oxygen through NRBM@ 15 litres/min). On examination, he was febrile and maintaining saturation at room air (94%). On evaluation, he had normal complete blood count, liver and renal parameters. However, he had raised parameters of hyperinflammation (Table 1). His arterial blood gas showed features of type-1 respiratory failure with ARDS (pH — 7.39, pO_2 — 36, pCO_2 — 52, HCO_3 — 22). His chest skiagram showed bilateral diffuse peripheral airspace opacities and HRCT of chest showed peripheral ground glass opacities with an apico-basal gradient. He was managed with inj dexamethasone (6 mg once daily for 14 days), antibiotics, intermediate dose of LMWH (Inj LMWH 40 mg Subcutaneous route twice daily) and NIV (settings: pressure support — 2–4 cm H_20, PEEP — 10–12 cm H_20, FiO_2 — on titration with target saturation 88–92%). He showed good response initially but later there were features of disease progression in form of dyspnoea and increased oxygen requirement for which he was started on NIV (settings: pressure support — 2–4 cm H_20, PEEP — 10–12 cm H_20, FiO_2 — 100% initially later on titration with target saturation 88–92%). He was managed with increased dose of steroids (Inj dexamethasone 6 mg twice daily and therapeutic dose of LMWH. He showed improvement and his steroids were tapered off but he continued to have oxygen requirements. Computed tomography pulmonary angiography (CTPA) was done which did not reveal any evidence of pulmonary embolism but showed features of severe involvement of bilateral lung and interlobular and interseptal thickening with traction bronchiectasis (Figure 4A, B). He was started on antifibrotics (nintedanib tablet 150 mg twice daily). He has completed four weeks of antifibrotics and has shown significant response and is presently maintaining saturation at room air (Figure 4C, D).

DISCUSSION

The current SARS-CoV-2 pandemic has spread like wildfire and has affected millions of people around the world. COVID-19 primarily affects lungs and has a varied presentation including organising pneumonia to severe lung injury inform of acute respiratory distress syndrome [China, and has subsequently spread worldwide. Risk factors for the clinical outcomes of COVID-19 pneumonia have not yet been well delineated. Objective To describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS]. Post COVID-19 pulmonary fibrosis is an upcoming important entity causing increased mortality and morbidity in these patients [2–4].

The risk factors for developing post COVID-19 fibrosis includes old age, severe illness, prolonged ICU stay, requiring mechanical ventilation and those who had significant history of smoking and alcohol consumption [5]. In our

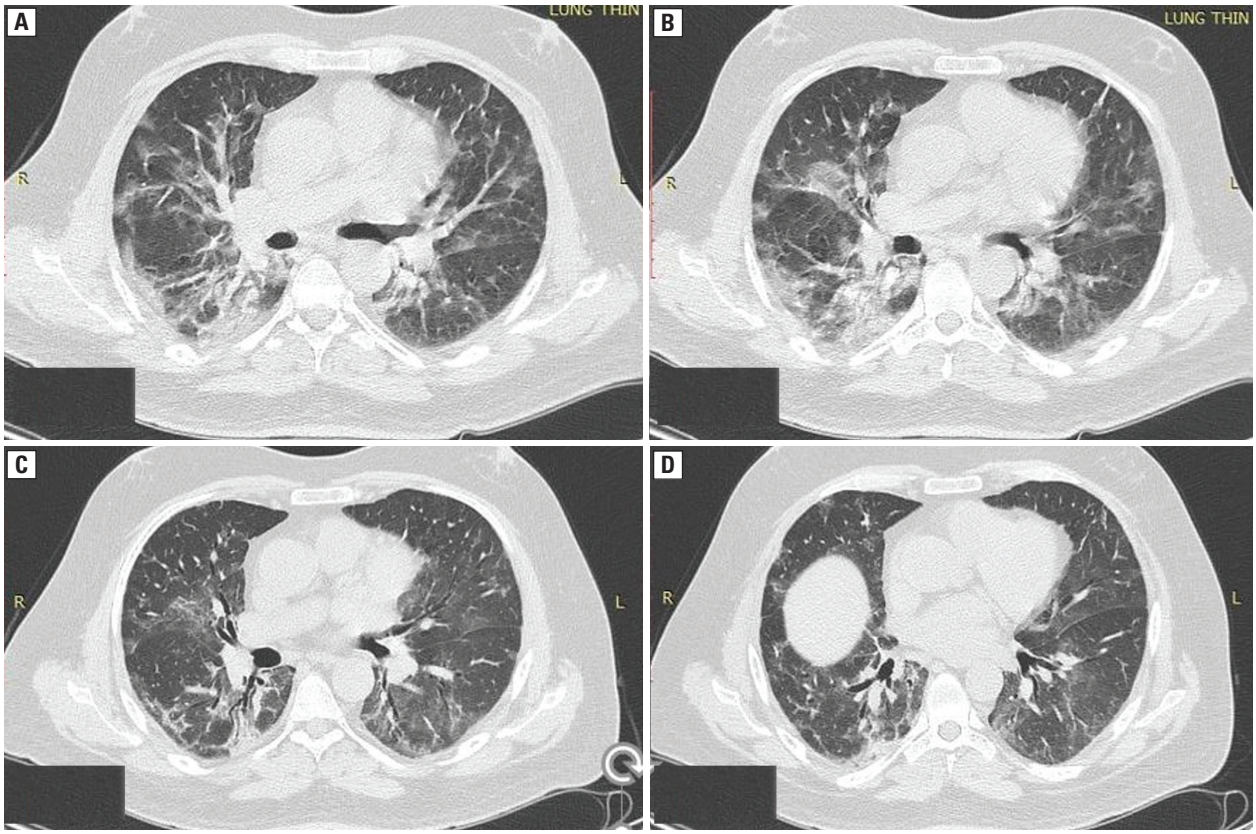

Figure 4A, B. High resolution computed tomography of chest showing bilateral consolidation with traction bronchiectasis; **C, D.** High resolution computed tomography of chest showing clearing of fibrotic opacities after 4 weeks of nintedanib

study, two of the patients had diabetes while the others had no comorbidities and the development of pulmonary fibrosis was the cause of prolonged hospital stay and difficult weaning.

The pathophysiology of pulmonary fibrosis includes variable mechanism like direct endothelial injury, alveolar epithelial damage, cytokine mediated damage, dysregulated release of matrix metalloproteinases and uncontrolled fibroproliferation. The severe form of ARDS is marked by higher release of cytokines and inflammatory markers which predisposes to higher incidence of pulmonary fibrosis. These factors stimulate the hyperproliferation of type-II vesicular endothelial cells which causes release of fibroblasts and their maturation into myofibroblasts, leading to excessive extracellular matrix accumulation and ultimately fibrosis and alveolar dysfunction [6–8]. This correlates with the duration of disease and is generally seen more in patients with a disease duration more than 3 weeks [7].

All our patients presented with moderate to severe COVID pneumonia and were optimally managed with steroids, LMWH and oxygen therapy. The patients during the course of admission showed progression to ARDS and three patients required non-invasive ventilator support. They showed good response but even after maximal therapy continued to have high oxygen requirement and were difficult to wean off the oxygen support leading to prolonged hospital stay. HRCT chest can confirm the presence of fibrosis in form of reticulations, interlobular and interseptal thickening, traction bronchiectasis, honeycombing and volume loss on the involved side [7, 8]. On functional evaluation, they usually have restriction on spirometry with decreased diffusion capacity of lungs for carbon monoxide (DLCO) and reduced total lung capacity (TLC) [7, 9]. These patients can also have reduced exercise tolerance which can be demonstrated on a 6 minute walk test (6MWT).

The patients of moderate to severe COVID-19 pneumonia with prolonged intensive care unit stay should be suspected of having pulmonary fibrosis. However other causes of increased oxygen requirements like pulmonary thromboembolism should be ruled out by doing a base line CTPA and these patients should preferably should have a negative or reduced C-reactive protein levels and other hyperinflammatory markers which otherwise will benefit more in

combination with other modalities like prolonging the duration of steroids [2]. All our patients had shown good response with steroids and CTPA done in the patient did not show any features of pulmonary thromboembolism but they continued to have high oxygen requirement which indicated clinical diagnosis of post COVID fibrosis which was confirmed on radiology.

There is great uncertainty in management of COVID-19 pulmonary fibrosis mainly due to non-availability of treatment modalities [2, 6]. Antifibrotics agents like pirfenidone and nintedanib have an established role in fibrotic diseases like idiopathic pulmonary fibrosis (IPF) and they can be used in post COVID-19 fibrosis by that analogy [10, 11]. They have been proven to reduce the rate of deterioration of forced vital capacity (FVC) in patients with IPF [12, 13]. These drugs do not ameliorate the SARS-CoV-2 immune dysregulation neither address the catastrophic pro-thrombotic state of this infection but can address the development of pulmonary fibrosis post COVID-19 pneumonia. Nintedanib is a tyrosine kinase inhibitor which has been extensively evaluated for its antifibrotics role in IPF [9, 11, 13]. It has displayed anti-angiogenesis properties through blockade of the vascular endothelial growth factor (VEGF) pathway. Nintedanib has shown significant antifibrotic role and has potential anti IL-1 and IL-6 activity which are one of the main culprits in cytokine storm and post COVID fibrosis [8–10]. The main side effect of nintedanib includes diarrhoea, nausea, reduced appetite and deranged liver function tests [9, 14]. We chose nintedanib for these patients as it has significant immunomodulatory, and anti- inflammatory and anti-thrombotic action in addition to it triple kinase inhibitor activity.

All our patients were started on oral tablet nintedanib and was well tolerated. The decision to start anti-fibrotic was taken as patients, after showing an initial response, failed to show significant clinical improvement, with negative inflammatory markers and continued to be oxygen dependant. HRCT showed evidence of pulmonary fibrosis and they were initiated on anti-fibrotics. All our patients had different extent of pulmonary involvement however they all had severe COVID pneumonia and post COVID pulmonary fibrosis which responded to nintedanib. The exclusion criteria for starting nintedanib includes deranged liver function tests, recent myocardial infarction or haemorrhagic stroke, active haemoptysis or gastrointestinal bleed and deranged coagulation profile. At present there is no biomarker to prompt the administration of anti-fibrotic and the presence of fibrosis on CT scan has been agreed as the best indicator to start therapy [15]. This is our initial experience of using nintedanib in post COVID-19 fibrotic lung disease; however it needs bigger randomized controlled trials to assess the safety and efficacy of this drug.

Conflict of interest

None.

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Sarcoidosis in coexistence with chronic granulomatous disease

Abstract

Granulomas formations are present in many lung diseases. Coexistence of one or more of these diseases is very rare. Diagnostics of such cases always poses a challenge. We present a case of coexistence of chronic granulomatous disease (CGD) and sarcoidosis.

Key words: chronic granulomatous disease, sarcoidosis, granulomas

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Introduction

Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency disorder. There are two inheritance patterns of CGD: an autosomal recessive manner and the X-linked manner. Mutations in the *CYBB*, *CYBA*, *NCF1*, *NCF2* and *NCF4* genes are responsible for inappropriate function of structural or regulatory subunits of phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [1]. These genetic defects are presented with an impaired respiratory burst in phagocytes (neutrophils, mononuclear cells, macrophages, and eosinophils). Absence or minimal (low) respiratory burst activity, that is crucial for generating superoxide, the precursor of hydrogen peroxide and other reactive oxygen intermediates (ROI), leads to recurrent bacterial and fungal infections [1, 2]. Every organ or tissue may be affected, but the skin, lungs, lymph nodes, liver and bones are the most frequent sites of infection. Granulomas formations in multiple organs are the second characteristic feature of CGD [1, 3].

Granulomas are areas of macrophages which are transformed into epithelial-like cells called histiocytes or epithelioid cells, admixed with other inflammatory cells such as lymphocytes and plasma cells [4–6]. Etiology of granulomas divides them into two histologic subtypes: foreign-body giant cell granulomas and immune granulomas [6]. The last group further splits into necrotizing and non-necrotizing granulomas.

Granulomatous disorders are numerous and include infections, vasculitis, immunological upsets, leukocyte oxidase defects, hypersensitivity, exposure to chemicals, and neoplasia [5]. The most common noninfectious condition where granulomas are found is sarcoidosis [5, 7, 8]

The following report describes a rare case of coexistence of both CGD and sarcoidosis.

Case report

A 28-year-old non-smoking man known to be suffering from CGD was admitted to our hospital in order to investigate persistent, unproductive cough and shortness of breath. In childhood he had been hospitalized multiple times in pediatric departments, presenting recurrent fever, lymphadenopathy, infections of the lower respiratory tract and liver abscesses. Initial laboratory tests had revealed microcytic anemia, anisocytosis, leukocytosis, very high marker of inflammation, hypergammaglobulinemia. CGD had been properly diagnosed at the age of 13 in immunology

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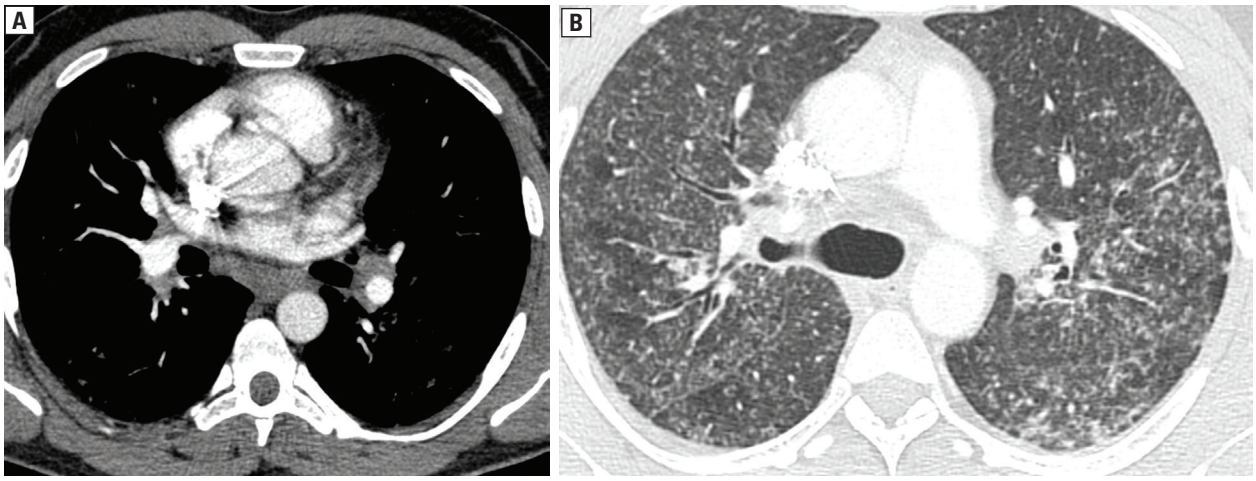

Figure 1A. Contrast enhanced computed tomography (CT) scan, mediastinal window, at the level of hila, depicts hilar and subcarinal lymph nodes enlargement; **B.** High-resolution CT (HRCT) scan at the level of trachea demonstrates multiple small nodules in upper lobes in peribronchiolar location, mainly subpleural and perifissural

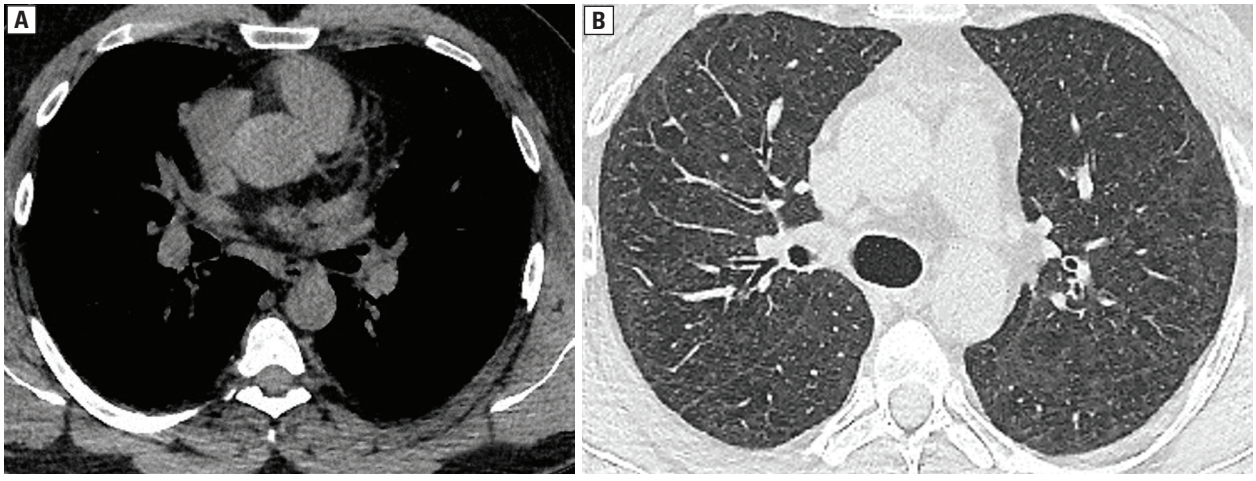

Figure 2A. Contrast non-enhanced CT scan, mediastinal window, depicts regression of mediastinal and hilar adenopathy; **B.** HRCT scan shows partial regression of nodules

department and received prescribed antibacterial (trimethoprim/sufamethoxazole 5 mg/kg/day) and antifungal prophylaxis (firstly itraconazole 5 mg/kg/day then posaconazole 600 mg daily) longitudinally. At the time of admission the patient complained about left shoulder joint pain accompanied with erythema nodosum in the past. On physical examination, there were no abnormalities. Chest X-ray showed bilateral hilar lymphadenopathy with nodular opacities distributed especially in middle zone, that was absent in his previous radiograms (Figures 1A, B). Chest computed tomography (CT) showed bilateral hilar and mediastinal lymphadenopathy as well as widespread nodules present especially along interlobular septa and subpleurally. Fiberoptic bronchoscopy showed normal bronchial tree. Endobronchial ultrasound-guided lymph node biopsy and bronchoscopic lung cryobiopsy were performed. Histological examination revealed non-necrotising granulomata consistent with sarcoidosis. The culture of endobronchial samples was negative for M. tuberculosis, other bacteria and fungi. Pulmonary function tests revealed a restrictive pattern (TLC 76% pred, FVC 59% pred, FEV_1 62% pred.) with no significant post-bronchodilator improvement and reduced transfer factor for carbon monoxide (TL_{CO}) to 48% pred. The 6 min. walk distance (6MWD) was 590 m, with oxygen desaturation from 97% to 84%.

In February 2016, due to lung functional impairment caused by sarcoidosis, prednisone treatment at 0.5 mg/kg/day was started. This treatment

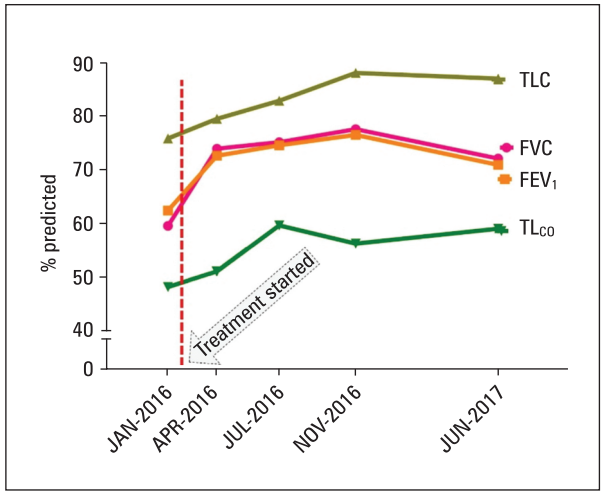

Figure 3. Lung function indices expressed as % of predicted before and during the treatment TLC — total lung capacity; FEV_1 — forced expiratory volume at first second; FVC — forced vital capacity; TL_{CO} — single breath carbon monoxide transfer factor of the lung

was effective and already after 2 months, clinical, radiographic (Figures 2A, B) and functional improvement (Figure 3) were observed.

Based on clinical, radiological and histopathological findings with exclusion of the other reasons of such test results and very good response to corticosteroids treatment, the diagnosis of sarcoidosis was confirmed.

Discussion

There have only been few cases reported where sarcoidosis and CGD coexisted [8]. The incidence of CGD is about 1 per 200 000 live births whereas sarcoidosis affects 1 to 50 per 100 000 individuals and is the most common cause of lung granulomas unrelated to infection [8]. The real number of cases with coexistence of both diseases is unknown. Due to lack of defined criteria of sarcoidosis it is very often a diagnosis of exclusion. Granulomas however accompany a wide variety of other diseases. These disorders are commonly divided into two groups with infectious and noninfectious background. The first group refers to mycobacterial tuberculosis and non — tuberculous mycobacterial infections as well as fungal or parasite infections [4, 8]. Noninfectious causes of lung granulomas include numerous conditions which comprise, aside from sarcoidosis, other interstitial lung diseases, antinuclear antibody associated diseases, immunodeficiency disorders, lymphoproliferative disorders, connective tissue diseases and granulomas related to foreign bodies [8]. Considering some of these conditions may coexist, as is often the case, the differential diagnosis can be challenging. Maintaining an acute clinical awareness of this coexistence minimizes the risk of misdiagnosis or delayed diagnosis and leads to early and appropriate treatment allowing a reduction of long term complications.

Conflict of interest

None declared.

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Hiding in plain sight — relapsing polychondritis disguised as uncontrolled asthma

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A 55-year-old man was evaluated at the emergency department because of increasing shortness of breath and cough. His medical history included pulmonary embolism and asthma for 9 years which was uncontrolled despite montelukast, omalizumab and inhaled fluticasone, vilanterol and beclomethasone. Recent treatment with methylprednisolone and amoxicillin and clavulanic acid did not sufficiently alleviate his symptoms.

On presentation the patient appeared mildly ill. Blood pressure was 137/84 mm Hg, pulse 104/min, temperature 37.7°C and oxygen saturation 95% while breathing ambient air. On auscultation inspiratory wheezing was heard. Clinical examination was otherwise normal including external inspection of nose and ears. Blood analysis showed elevated inflammatory markers (C-reactive protein [CRP] 129.1 mg/L) with a normal white blood cell count. His last spirometry from one month prior showed severe obstruction (forced expiratory volume in one second to forced vital capacity [FEV_1/FVC] 43% and FEV_1 1.57 L or 35% predicted) with no reversibility after inhalation of salbutamol.

Contrast-enhanced computed tomography (CT) of the chest demonstrated remarkable thickening and calcification of the tracheobronchial walls with sparing of the posterior tracheal wall (Figure 1A and 1B). Bronchoscopy revealed tracheobronchomalacia (TBM) and thickened tracheal mucosa with a cobblestone appearance (Figure 1C and 1D). Tracheal biopsies showed non-specific chronic inflammation without granulomas. Congo red staining was negative. On additional fluorodeoxyglucose (FDG)-positron emission tomography (PET) hypercaptation of the nasal and costal cartilage and the thickened tracheal and bronchial walls (Figure 1E and F) was seen. Further elaborate auto-immune screening was negative. A diagnosis of relapsing polychondritis was made.

Relapsing polychondritis is a rare auto-immune disorder characterized by recurrent episodes of cartilaginous inflammation throughout the body, especially in the ears, nose, eyes, respiratory tract and joints. Annual incidence ranges from 0.71 to 3,5 cases per million persons [1, 2]. Men and women are equally affected with symptom onset usually between the fifth and seventh decade.

The most common and striking feature is auricular chondritis, present in 43% of patients at disease onset and in 89% throughout disease course [2]. Typically, pain, tenderness and an erythematous appearance of the ear with sparing of the ear lobes is present. Involvement of the respiratory tract, however, is often underrecognized and underreported, although laryngotracheal disease occurs in 55% of patients [3]. The most common symptoms are dyspnea, cough, stridor and hoarsesness [4]. Often symptoms are mistaken for other conditions and diagnosis is delayed. CT shows TBM and/or tracheobronchial wall thickening, with sparing of the posterior wall and with or without calcifications, in more than 50% [4]. Other possible respiratory tract complications include subglottic and tracheal/tracheobronchial stenoses.

Diagnosis is based on a high level of suspicion and diagnostic criteria, such as the McAdam and Modified Damiana criteria [5, 6]. Need for biopsy of affected cartilage depends on these criteria and is not routinely recommended. Since laryngotracheal involvement is associated with a poor prognosis, prompt appropriate treatment with high dose corticosteroids and cyclophosphamide is recommended [7]. Our patient was started on corticosteroids and cyclophosphamide orally with a slow but steady improvement of symptoms and continues to do well. The most recent FEV_1 was 52% predicted.

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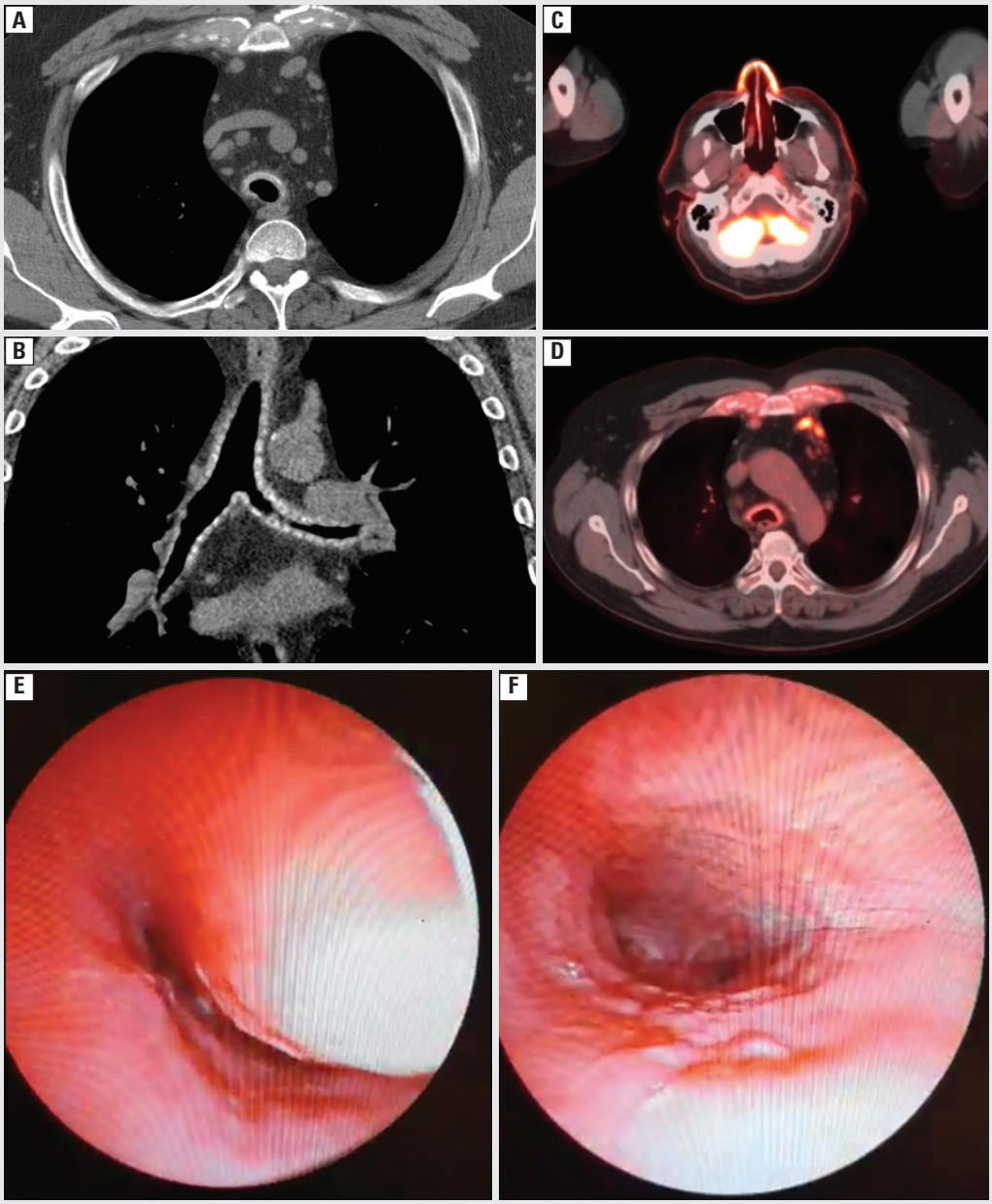

Figure 1. Chest computed tomography showing thickening and calcification of tracheal (**A**) and bronchial cartilage (**B**). Positron emission tomographyshowing fluorodeoxyglucose (FDG) captation of the nasal cartilage (**C**) and FDG captation of costal and tracheal cartilage (**D**). Bronchoscopy revealing tracheobronchomalacia (**E**) and thickened tracheal mucosa with cobblestone appearance (**F**)

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A challenging case of tuberculous peritonitis

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A 24-year-old female was admitted to the hospital for recurring irregularities of menstruation and a nine day history of abdominal tenderness. Physical exam revealed an abnormal build-up of fluid in the abdomen. Lab results within normal range. Normal chest X-ray. Abdominal ultrasound displayed ascites and nodular peritoneal thickening (Figure 1). Abdominal paracentesis exposed an exudative effusion, lymphocyte-rich inflammatory cells, no malignant cells and an adenosine deaminase level of 59 U/L. QuantiFERON-TB Gold test negative and also HIV-negative. Cancer antigen 125 level of 98.70, carcinoembryonic antigen level of 0.46, carcinoma antigen 15-3 level of 19.87, alpha-fetoprotein level of 1.99, cancer antigen 19-9 level of 0.99. Magnetic resonance imaging of the abdomen disclosed ascites and bilateral nodular opacities in the peritoneum. Ultrasound-guided tru-cut biopsy from nodular opacities expressed tuberculoid granulomas [1, 2]. According to our national guidelines, received a standard anti-TB regimen [3]. After six months, good clinical response. Tuberculous peritonitis is a rare condition which may simulate malignancy. TB ascites is an exudative pleural effusion as in the presence of a malignant tumour. Both illnesses have plenty correlations regarding lab results, imaging features and symptoms. Tuberculous peritonitis is accountable for approximately 1% of all tuberculosis cases [4]. In peritoneal carcinomatosis, CA125 level is elevated [5]. Early diagnosis of extrapulmonary tuberculosis responds well to the specific treatment and also prevents surgery.

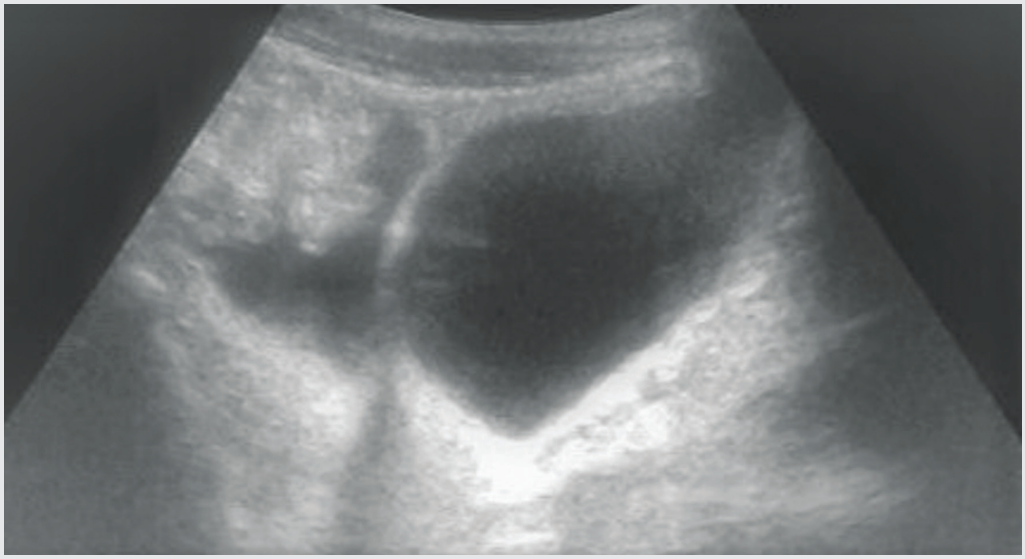

Figure 1. Abdominal ultrasound reported ascites in pelvis

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Massive pleural effusion: an uncommon but important cause to consider

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A 44 years old female presented with complaints of diffuse right sided chest pain, progressively increasing shortness of breath (mMRC grade 3), fever, loss of weight and anorexia for last 2 months. She had history of dysphagia to solids, intermittent vomiting and regurgitation during feeding for which she was taking symptomatic treatment from local practitioner. Her vitals were heart rate 88/min, blood pressure 116/78 mmHg, respiratory rate 21/min and saturation of 95% on room air. Chest examination showed findings suggestive of pleural effusion which was confirmed on chest X-ray. CECT chest was planned in view of massive right sided pleural effusion with air loculations on chest X ray. Oral contrast on table was administered in view of esophageal wall thickening on NCCT chest. CT-scan with oral contrast showed fistulous track from right lateral aspect of thoracic esophagus extending to right pleural cavity suggesting esophageal-pleural fistula (Figure 1). Upper GI endoscopy showed ulcerative proliferative growth in the thoracic esophagus with suspicious fistulous opening showing pus drainage. Biopsy revealed squamous cell carcinoma of esophagus. Intercostal tube drainage was done for right sided massive effusion which drained about 2.5 liters of purulent material. Pleural fluid examination showed amylase — 3141 U/L, protein — 4.6gm/dL, sugar — 174 mg/dl, LDH-120U/L and gram negative bacilli on gram staining. Feeding jejunostomy was performed and empirical broad spectrum antibiotics were started. Follow-up chest X-ray showed significantly reduced pleural effusion with partial lung expansion. Patient was transferred to department of gastrointestinal surgery for further definitive surgical management.

Esophageal-pleural fistula presenting as massive pleural effusion is rarely encountered. The diagnosis of EPF is difficult as symptoms and signs related to EPF are non-specific and can mimic many other diseases. Hence a meticulous history taking and high degree of clinical suspicion is must to diagnose EPF. History of

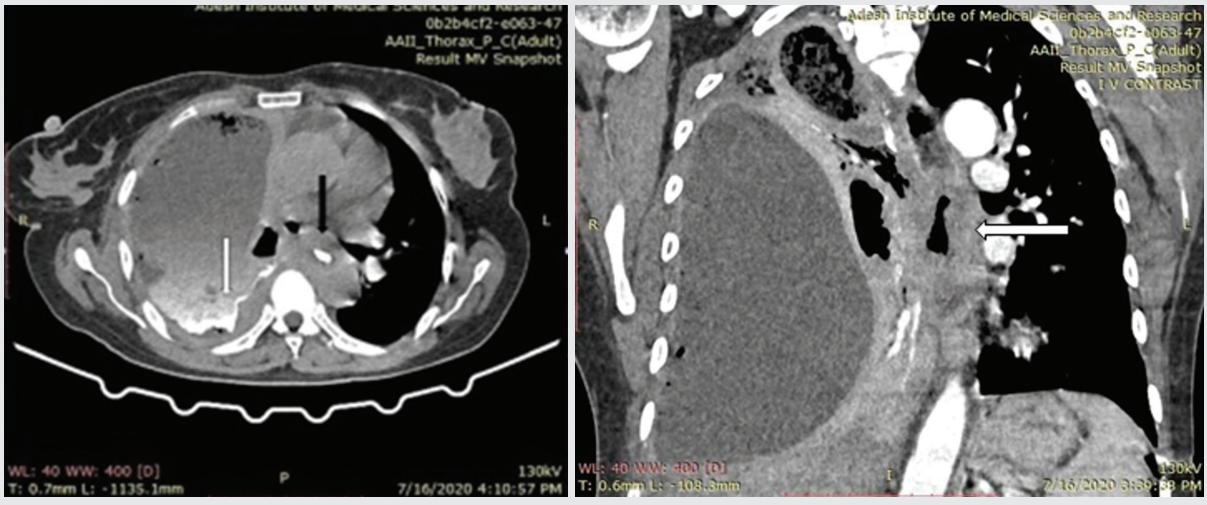

Figure 1. Axial and coronal CECT images show right sided hydro-pneumothorax. Oral contrast filled fistulous track seen from mid esophagus to right pleural cavity (shown as white arrow in axial CT). Circumferential eccentric wall thickening of esophagus is seen (shown as black arrow in axial CT and white arrow in coronal CT)

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dysphagia, odynophagia, a known esophageal malignancy, esophageal ulcer or trauma and prior upper GI endoscopy or esophageal instrumentation can help to raise the clinical suspicion [1, 2]. Various imaging modalities that aid in diagnosis include chest radiograph, ultrasound, barium swallow, contrast-enhanced CT, and MRI with each modality having its own advantages; however CECT chest is very useful modality and should be performed early whenever there is clinical suspicion. CT chest can show focal esophageal wall thickening as in our case, thinning or ballooning of esophagus at the site of perforation, mediastinitis and can help to delineate the fistulous track after giving oral contrast which is the pathognomonic sign of esophageal—pleural fistula. CT chest can delineate pleural lesions from parenchymal and help to exclude other alternate differential diagnosis [3, 4]. Upper GI endoscopy helps to confirm the etiology of EPF and hence helps in the further definitive management for EPF. The management options include conservative therapy like empyema drainage, management of mediastinitis, tube feeding, feeding jejunostomy or gastrostomy; stenting or definitive surgical repair for EPF and endoscopic management like stenting, suturing, fibrin glue or clips. Early treatment helps to prevent further devastating complications [5]. EPF should be considered as one of differentials for unilateral massive pleural effusion.

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COPD patient with a classical radiological sign

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A 55 years old smoker was admitted with chief complaints of progressive dyspnea, dry cough, fever, loss of appetite and loss of weight. On examination, patient was febrile and his physical examination showed reduced breath sounds and crepts in left axillary and mammary area in association with bilateral diffuse polyphonic rhonchi. Laboratory investigations showed hemoglobin 12.4g/dL, white blood cell count (≥ 13200/mm), increased proportion of neutrophils on differential analysis (77% neutrophils), blood urea 86 mg/dL and serum creatinine 1.8 mg/dL. Conventional chest radiograph was done and patient also underwent computed tomography (CT) chest. Flexible bronchoscopy guided bronchoalveolar lavage revealed growth of streptococcus pneumoniae.

Questions: Can u name the radiological sign demonstrated in CT chest? Can u explain its occurrence?

Answer: Swiss cheese sign COPD with superadded infection, pulmonary edema or hemorrhage Pulmonary lacerations with pneumatocele

Here we present an interesting case of a patient who presented in our outpatient department with acute exacerbation of COPD. Patient was initially suspected on lines of pulmonary tuberculosis as cause of exacerbation of COPD but later found to be case of bacterial infection giving typical appearance of 'Swiss Cheese Sign' in background of emphysema.

The COPD patients are prone for infective exacerbation and these infections can present as lung consolidation. The consolidation in background of emphysematous changes of COPD may look inhomogeneous and mimic multiple cavities because of underlying low attenuation areas. Hence in this situation, lung may appear

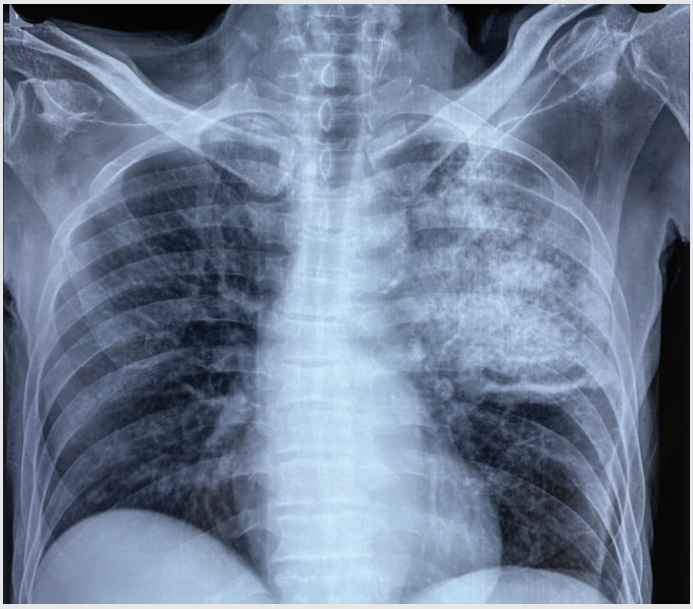

Figure 1. Chest X-ray posteroanterior view showing air space consolidation with central tiny air lucencies

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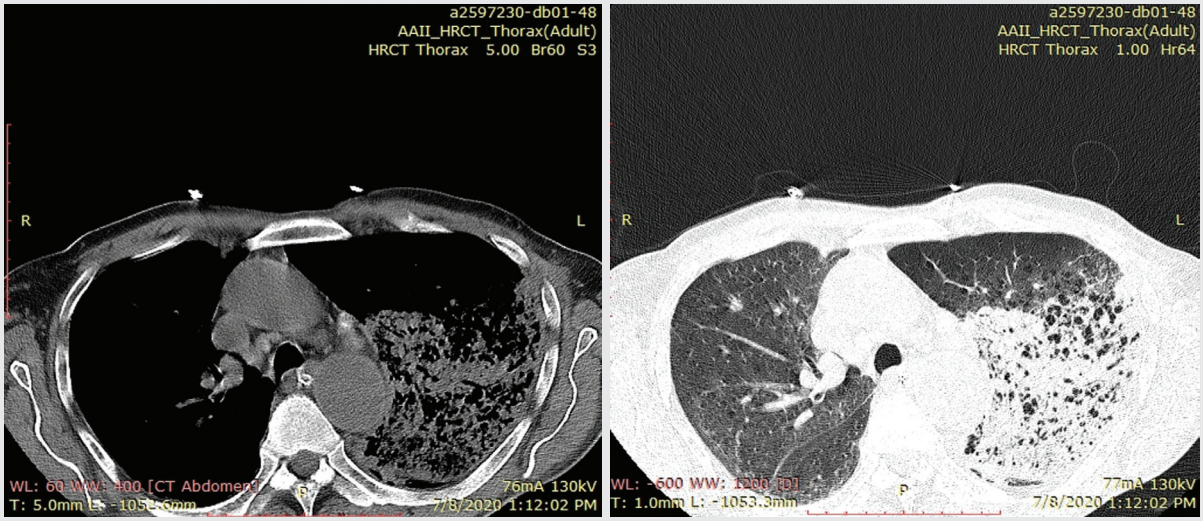

Figure 2. HRCT chest pulmonary and mediastinal window showing patch of consolidation in the background of emphysematous changes giving swiss cheese appearance

non-uniformly perforated forming 'Swiss Cheese appearance' (Swiss — style cheese that contain multiple holes) due to parenchymal consolidation [1, 2]. These cavity like holes within the pneumonic consolidation due to emphysema can mimic cavity forming consolidations like necrotising pneumonia, adenocarcinoma in situ and occasionally reticulo-nodular pattern giving appearance of interstitial lung diseases [1–3].

Other than pneumonia, pulmonary edema and hemorrhage in COPD patients have been described to have swiss cheese sign appearance. The sign has also been described for fluid containing pneumatoceles on CT chest secondary to pulmonary lacerations [4].

Hence it is crucial for a radiologist or pulmonologist to look for evidence of emphysema on radiology to correctly diagnose the unusual patterns of air space consolidation in the background of emphysema rather than cavitation or reticular-nodular pattern.

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A rare cause of ST segment elevation: avoiding critical errors in an emergency

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A 72-year-old female with a history of hypertension and chronic cough presented with worsening dyspnoea, left-sided chest pain, and vomiting that had been present for two days. In the emergency department, her vital signs were stable but room air oxygen saturation was 85%. An electrocardiogram (ECG) showed ST segment elevation in precordial leads (Figure 1A). A chest X-ray showed a left-sided opacity with an air-fluid level and a mediastinal shift to the opposite side (Figure 1B). Laboratory studies showed arterial blood gas (ABG) measurements of 7.47/27.5/52/19.9 on 4 litres/minute oxygen via nasal cannula, white blood cell count of 11.3 K/μL, a haemoglobin level of 15.3 g/dL, and a serum sodium level of 128mmol/L. The serum troponin level was < 0.01 ng/mL.

1. What is your provisional diagnosis?
2. What is the probable cause of ST segment elevation?

Physical examination showed bowel sounds along the left lower chest with absent air entry. Contrast-enhanced computed tomography of the chest showed a large diaphragmatic hernia causing a mediastinal shift to the other side (Figure 1C, D). Misdiagnosis of diaphragmatic hernia as hydropneumothorax is not uncommon in both acute and chronic settings and can commonly lead to incorrect chest tube placement [1]. Various findings that may suggest a diagnosis of diaphragmatic hernia rather than hydropneumothorax include hearing bowel sounds on chest auscultation, curling up of the nasogastric tube in the stomach, history of preceding/associated traumatic injuries, an elevated hemidiaphragm, irregular diaphragmatic contour, a gas bubble or air-fluid levels in the chest above the expected level of the diaphragm, compression atelectasis of the lower lobe, and intrathoracic intra-abdominal viscera with or without a focal constriction (collar sign) [2, 3]. An increase in intra-abdominal pressure can lead to protrusion of the abdominal content into the thoracic cavity. This is what we believe happened in our case as the history of chronic cough and vomiting may have caused increased intra-abdominal pressure in our patient.

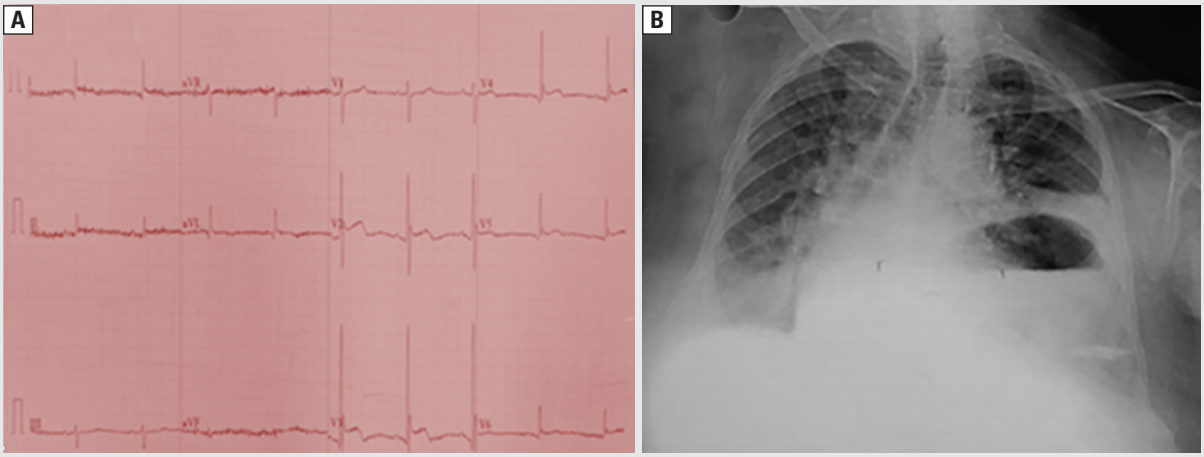

Figure 1A. Electrocardiography showing sinus bradycardia and ST elevation in leads V3, V4, and V5; **B**. Chest X-ray posteroanterior view showing an air-fluid level in the left hemithorax

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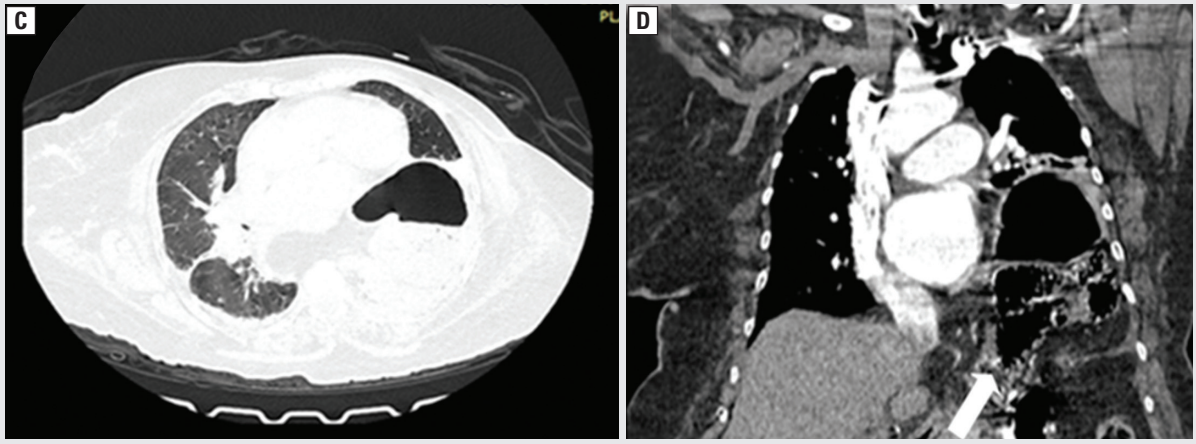

Figure 1C. Computed tomography (CT) pulmonary window axial section showing an air-fluid level in the left hemithorax; **D.** CT mediastinal window coronal section white arrow showing a defect in the left hemidiaphragm with herniation of the stomach and bowel loops into the left hemithorax, and a mediastinal shift towards the right side

ST segment elevation on the electrocardiogram in our case was attributed to a large diaphragmatic hernia causing a mediastinal shift. Serial troponin levels and a subsequent coronary angiogram were normal. Tension pneumothorax and hiatal hernias causing ST segment elevation have been reported in literature [4]. Possible mechanisms include cardiac rotation, pressure on the heart and coronary vessels leading to decreased coronary flow and ischemia, acute right ventricular strain, or dilation from hypoxia and decrease in preload due to increased intra-abdominal pressure [5]. One or more of the said mechanisms may be responsible for ST changes observed in our case.

Our experience in this case is particularly useful for emergency medicine physicians and cardiologists who must remember that diaphragmatic hernias can closely mimic hydropneumothorax and can cause ST segment changes on electrocardiograms. This case also emphasizes the utmost importance of physical examination in emergency medicine in order to avoid critical errors.

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A rare case of tuberculous pyopneumothorax

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A divorced 37-year-old male from an urban enviroment with a history of known childhood tuberculosis (TB) complained of having the following symptoms over the past 3 months: anorexia, fatigue, exertional dyspnea, left-sided chest pain, excess sweating during the night, a persistent mild elevation of body temperature above normal, productive cough, and a reduction of total body mass by 9 kilograms. Upon admission, physical examination revealed tachycardia and an oxygen saturation of 81% while breathing room air. Lung auscultation was abnormal. Routine tests conducted revealed the following: an oropharyngeal swab test for SARS-CoV-2 by RT-PCR assay was negative; hemoglobin — 10.6 g/dL; hematocrit — 38.9%; red blood cell count — 5.98 10^{12}/L; white blood cell count — 18.78 10^{9}/L; neutrophils — 5.12 10^{9}/L; lymphocytes — 42%; HIV test — negative. Chest X-ray revealed an air fluid level in the left hemithorax and a minimum deviation of the mediastinum to the right side (Figure 1). Chest CT showed a left hydropneumothorax. Ultrasound-guided thoracentesis was implemented and 2 liters of pleural effusion were removed (Figure 2). Both sputum and pleural fluid samples were analyzed, and the results confirmed an exudative lymphocytic effusion with an ADA level of 58 U/L [1]. Ziehl-Neelsen staining revealed acid-fast bacilli, and culture of pleural pus on Lowenstein-Jensen medium displayed colonies that were non-pigmented, dry, rough, raised, and irregular with a wrinkled surface. The patient received a broad-spectrum antibiotic, an oral corticosteroid, and anti-TB treatment (regimen I) according to Romanian Guidelines. On 6-month follow-up evaluation, the patient had a good clinical response and no sequelae of pleural thickening. The combination of pneumothorax and pulmonary emphysema is a rather unusual occurrence [2], but certain underlying circumstances like TB may boost the risk of pleural diseases [3, 4]. If treatment fails, preoperative evaluation can be unavoidable [5].

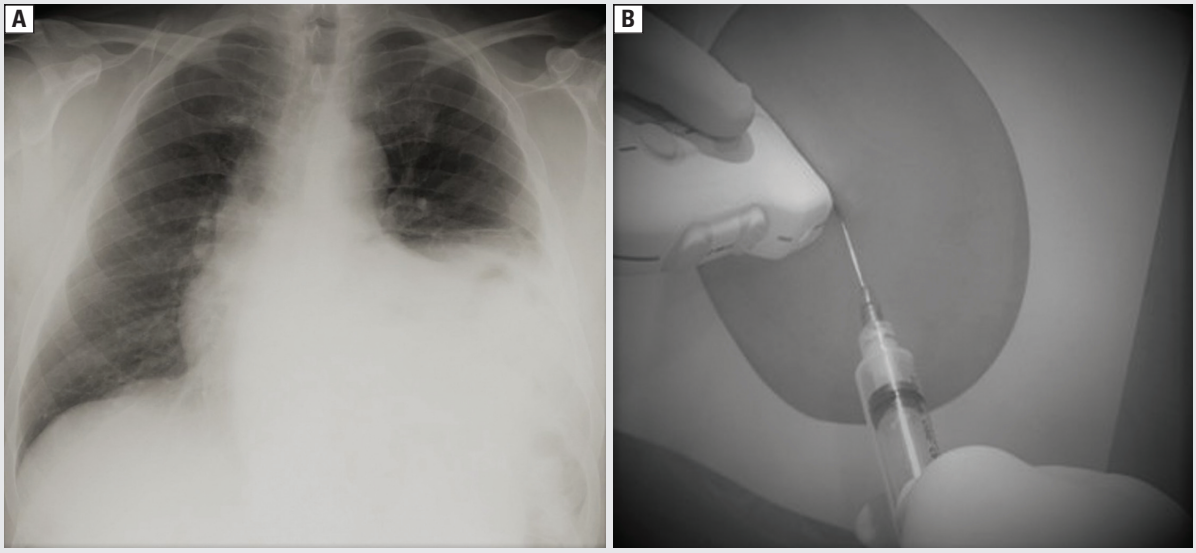

Figure 1. A. Chest X-ray; **B.** Ultrasound-guided thoracentesis

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COVID-19 — deliberating beyond steroids in 2021

To the Editor

COVID-19 has caused huge morbidity and mortality in the second peak in India in 2021. The healthcare system is stretched to its limits trying to manage the huge burden of patients in disproportionate limited health care facilities. Triaging [1] has helped manage mild cases at home, moderate at health care centres so that tertiary hospitals are able to treat the severe cases requiring oxygenation or ventilatory support. However, severe cases of COVID-19 pneumonia despite oxygenation, ventilatory support and steroids [2] have poor outcome, which triggered various trials evaluating immunosuppressive drugs to improve prognosis by controlling the hyperinflammatory state. The evidence of use of these drugs is limited and based on available literature till date, the use of these drugs has been summarised in Table 1 [3–9] Although tocilizumab is an off-label drug described in Indian national guidelines, there are no official guidelines for the use of the other drugs in India leading to variability in usage. It is imperative to use these drugs under a trial mode to generate further evidence and regularise the usage. The use of these drugs should be judicious and after carefully ruling out contraindications following the concept of *primum non-nocere* i.e., first do no harm.

Conflict of interest

None declared.

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Table 1. Evidence for Immunosuppressants drugs beyond steroids for COVID-19

Name	Mechanism	When to give	When not to give	Major Trial	Remarks	Dose	Outcome	ADR
Baricitinib	TKI- JAK 1/2	Illness of any duration with $SpO_2 \leq 94\%$ or Supplemental O^2 or Mechanical ventilation	Pregnancy/lactation	ACTT-2 [3]	Most efficacious in patient on O^2 and above, receiving Remdesivir for 10 days	4 mg once a day (2 mg in deranged renal functions) for 14 days	Reduced day of recovery (10 days vs. 18 days)	Infections— respiratory and H. Zoster, Transaminitis, Prothrombotic (FDA black box warning), Hypersensitivity
Tofacitinib	TKI- JAK 1/3	No criteria specified	Underlying malignancy, lymphoproliferative disorders and active tuberculosis are usual contraindications of the drug. None have been mentioned in the trial	Hayek et al (retrospective observational study) [4]	Any admitted patient- requiring dexamethasone	5 mg twice a day	Mortality benefit	Hyperglycaemia, risk of carcinoma and prothrombotic state. However, trial found increased bleeding in tofacitinib group attributed to anticoagulation
Bevacizumab	MAB- VEGF A	$SpO_2 \leq 93\%$ or RR ≥ 30 or P/F ratio 100–300 AND median duration- 10 days from symptom onset (maximum benefit)	Severe hepatic failure (CPS- C) Severe renal failure (GFR < 30/RRT) Uncontrolled HTN, Heart disease Coagulopathy/ active bleed Procoagulant state Major surger/trauma in 28 days Active HIV/hepatitis Pregnancy/lactation	Pang et al. [5]		Single dose 500 mg	Rapid improvement in fever and PF ratio Vs. Standard care (± steroids ± anticoagulants)	Hypertension, Haemorrhage, Cardiac failure, Posterior reversible encephalopathy syndrom, Thromboembolism, Infusion reaction
				Islam et al. [6]	Severe Covid- observational study- no control	Three groups (Tocilizumab, Bevacizumab, Both)	Survival benefit was found in patients receiving bevacizumab (92%)	
Itolizumab	MA-CD6 on T cell- Co-stimulation inhibition	$SpO_2 < 94\%$ or PF ratio < 200 With Ferritin > 400 or IL-6 > 4times ULN	Active/latent/inadequately treated TB Hep B/Hep C/HIV ANC < 1000 ALC < 500 Plt count < 50000	Saavedra et al. [7]	$SpO_2 < 94\%$ or PF ratio < 200 With Ferritin > 400 or IL6 > 4 times ULN	1.6 mg/kg infusion after 1 week- 0.8 mg/kg	Mortality benefit	Diarrhoe, infusion related reactions

→

Table 1. cont. Evidence for Immunosuppressants drugs beyond steroids for COVID-19

Name	Mechanism	When to give	When not to give	Major Trial	Remarks	Dose	Outcome	ADR
Tocilizumab	MAB -sIL-6 R	Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendatio, Low certainty of evidence)	Concern regarding interruption of treatment/ /relative contraindication GI symptoms suggestive of perforation Neutropenia/ /thrombocytopenia Transaminitis — 5 times ULN Active infection Active malignancy	IDSA [8] and MOHFW, India [9]		8 mg/kg single dose		Infection and GI perforation Avoid if baricitinib is used
		All criteria to be met. Severe disease Raised inflammatory markers. No response to steroids No active TB/ bacterial/fungal infection		MOHFW, India [9]		4–6 mg/kg		

ADR — adverse drug reaction; TKI — tyrosine kinase inhibitor; JAK —Janus kinase; FDA— Food and Drug Administration; MAB — monoclonal antibody; VEGF — Vascular endothelial growth factor; RR — respiratory rate; P/F — partial pressure of O_2/FIO_2; CPT — child Pugh score; GFR — glomerular filtration rate; RRT — renal replacement therapy; HTN — hypertension; HIV — human immunodeficiency virus; CD-6 — complement of differentiation; IL-6 — interleukin; ULN — upper limit of normal; TB — tuberculosis; Hep — hepatitis, ANC — absolute neutrophil count; ALC — absolute lymphocyte count; Plt — platelet; IDSA — Infectious Diseases Society of America; MOHFW — Ministry of Health and Family Welfare; GI — gastrointestinal

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ROX index in COVID-19 patients — is it the answer?

To the Editor

As the world stands witness to the havoc caused by the COVID-19 pandemic, the shortage of mechanical ventilators a common peril in the already stressed healthcare system around the globe. HFNC (high flow nasal cannula) is being used now in most ICU settings to prevent ventilator requirements in patients with type 1 respiratory failure. It allows high flows and fractions of inspired oxygen (FiO_2) at a more physiological level of temperature and humidity. The mechanism of HFNC includes small pliable nasal prongs which increase the comfort of the patient, humidification facilitates expectoration of secretions, washout of nasopharyngeal dead space that improves the efficiency of ventilation, high flow rates that help in reliable delivery of FiO_2, and a small continuous positive airway pressure effect. The prediction of the success of HFNC is recently been done by using the ROX index.

ROX index is defined as the ratio of pulse oximetry/fraction of inspired oxygen (SpO_2/FiO_2) to respiratory rate (RR). This index has been used in emergency [1] to predict intubation as well in patients with pneumonia who are having acute respiratory failure [2]. The studies on the ROX index have measured different time intervals post-initiation of HFNC and suggested either 6 hours or 12 hours value as the most sensitive predictor for the probability of intubation [2, 3]. Recently a new index modified ROX has been devised in a study. Modified ROX is defined as (respiratory rate oxygenation-heart rate) the ratio of ROX index over HR (beats/min) and multiplying by a factor of 100 [4]. This study showed that that modified ROX helped in the early identification of HFNC failure, as early as 1–2 hours.

WHY? — a scoring system such as ROX is required in an emergency or critical care setting to make it easier for the physician to decide on the institution of mechanical ventilation. It has been seen in multiple studies [5, 6] that late failure of NIV has lead to adverse outcomes and increased mortality, the reason being increased disease progression with increased respiratory rate. During NIV trial in severe respiratory disease, if high driving pressures are used for ventilation; lung injury occurs due to over-distension of the healthy lung. This phenomenon is known as self-inflicted lung injury. Patient-ventilator dyssynchrony also plays a major role in lung injury. There are not many studies comparing late HFNC failure (> 48 hours) with mortality. The study done by B. J. Kang et al. [7] showed late HFNC failure was associated with higher mortality when compared to early HFNC failure. The reason for the same being that delayed intubation can lead to further disease progression causing respiratory muscle fatigue and cardiac dysfunction which cumulatively lead to increased mortality in ICU. Hence from these findings, we can analyze the importance of an objective prediction score which will help in the early identification of HFNC failure so that mortality can be reduced.

Role of ROX in COVID-19

ROX index was being used earlier in acute respiratory failure in pneumonia. Since the arrival of COVID-19, it has gained newfound interest. L.A. Suliman et al. [8] in their study validated the diagnostic accuracy of ROX in COVID-19 pneumonia. ROX index has been used in the emergency department which is generally the first point of contact in tertiary care hospi-

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Table 1. ROX index and HFNC based trials

Study	Type of study	Number of patients (n)	Interventions & remarks
Goh, K.J et al. (2020)	Prospective observational	145	Introduced a new index ROX-HR. Helped in early prediction of HFNC failure, as early as 1–2 hours
Panadero C et al. (2020)	Retrospective observational	196	After initiating HFNC, a ROX index below 4.94 predicts the need for intubation in COVID-19 patients
Lee CU et al. (2020)	Retrospective observational	2862	ROX index < 10 is an independent prognostic factor for 28-day mortality in patients with sepsis or septic shock.
María Laura Vega et al. (2021)	Multi-centre retrospective observational analysis of prospectively collected data.	120	The ROX index at 12 hours of < 5.99 was associated with HFNC failure. This value was higher than the non-covid patients, possibly due to different pathophysiology of the disease per se.
Gianstefani A et al. (2021)	Prospective observational	554	They measured the ROX index in emergency setting. A ROX index value < 25.7 was associated with hospitalization whereas ROX index < 22.3 was associated with higher 30-day mortality

tals. It has been observed that a lower ROX score was associated with increased hospitalization and increased mortality. A ROX index value < 25.7 was associated with hospitalization whereas a ROX index < 22.3 was associated with higher 30-day mortality [1]. Hence ROX index makes the decision-making easier and also helps the clinician to prognosticate early regarding the probable course of illness.

The next question which remains unanswered is what is the earliest and most sensitive time point to predict the effectiveness of the HFNC therapy. Minh hu et al. [3] in a retrospective cohort study compared the ROX index in patients admitted with acute respiratory distress due to COVID-19. They studied the ROX index at 3-time points namely 6 hours, 12 hours, and 24 hours post-initiation of HFNC therapy. They inferred that the ROX index assessed at 6 hours post-HFNC initiation had higher predictability for HFNC failure as compared to other time points. The cut-off for determining success or failure was 5.55 in their study. In another study done by O. Rocca et al. on non-covid patients, the cut-off point was determined to be 4.88 whereas the best predictability regarding the success of HFNC was achieved at 12 hours post initiation which was different from the cut-off of the previous study. Carolina Panadero et al. [9] had retrospectively studied ARDS in COVID-19 patients requiring HFNC. They found that a ROX index < 4.94 measured between 2 to 6 hours after initiation of HFNC was associated with an increased rate of intubation and hence HFNC failure. This cut-off value was slightly higher than that recorded by Rocca et al. Maria Laura Vega et al. [10] as a further continuation of the study conducted by Carolina Panadero did a multi-center trial in COVID-19 patients not admitted to ICU. The patients generally had a moderate degree of respiratory failure. They set their cut-off of ROX index higher than O.Rocca et al at 5.99 which was much higher than the cut-off for non-covid patients (4.88). The different cut-offs for COVID-19 pneumonia as compared to other causes of acute respiratory failure are explained by the different pathophysiology of COVID-19 particularly the varied phenotypes. The most commonly associated phenotypes are the classical ARDS, lung injury plus high dead-space related to emboli/diffuse microthrombi, or normal lung with embolism [11]. Maria Laura Vega also found the ROX index measured at 12 hours co-related well with determining the success or failure of HFNC. They argued that 12 hours intervals didn't delay the institution of mechanical ventilation as this is the usual duration in patients having moderate ARDS, as was the case in their study. Table 1 represents various studies using the ROX index and their outcome.

Hence we can see from the above discussion that the cut-off is relatively higher for COVID-19 pneumonia for the ROX index. It is also clearly evident that an early time point for the assessment of ROX is needed in ICU patients compared to patients not admitted to ICU.

Other application of ROX index

Other than the application of ROX in hypoxaemic respiratory failure, recently it has found its

role in sepsis. A study done by Che Uk Lee et al. [12] found that the ROX index is the simple index for the prediction of mortality. They found that a ROX index of ≤ 10 in an emergency can be an independent predictor of mortality in patients with signs of sepsis. They also found that the prognostic performance of ROX was better than qSOFA in sepsis.

Future research

A well-designed RCT is needed to predict the optimal point of measuring the ROX index to improve outcome in COVID-19 patients. The actual cut-off for determining failure of HFNC by ROX index has not been determined. A well-planned RCT catering to this objective is also desirable.

Conflict of interest

None declared.

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Early experience of vascular endothelial growth factor (VEGF) inhibitor in COVID-19 ARDS

To the Editor

The current severe acute respiratory syndrome-corona-virus-2 (SARS-CoV-2) has spread like wildfire and engulfed the entire world in its wake. It has caused immense morbidity and mortality in our country. It causes severe inflammatory response which causes profound pulmonary vasculature endothelial damage and edema leading to generalised hypoxia [1]. This generalised hypoxia causes release of various cytokines including vascular endothelial growth factor (VEGF) through activation of the Prolyl hydroxylases (PHD)-hypoxia-inducible factor (HIF)-1 pathway, which upregulates VEGF expression through transcription activation. VEGF further aggravates the pulmonary edema by increasing the vascular permeability which increases the plasma extravasation [2, 3]. VEGF also has a role in increasing pulmonary inflammation. Though there have been commendable efforts worldwide but there are still no defined treatment modalities for treatment of COVID-19 patients. VEGF inhibitor is being used to treat severe Coronavirus disease 2019 (COVID-19) patients with ARDS with an aim to improve oxygenation, reduce inflammation and improve clinical outcome [1, 4]. Herein we report our experience of using VEGF inhibitor — Bevacizumab in three patients at a tertiary care hospital.

All the three patients had confirmed COVID-19 on throat swab reverse transcription-polymerase chain reaction. One of the patients had hypertension and diabetes mellitus as co-morbidities while the other two did not have any other risk factors. Two of the patients were received on Non rebreathing mask (12–15 L/min) and one was maintaining saturation with oxygen supplementation with face mask (6–8 L/min). All the three patients later progressed to severe COVID-19 infection with ARDS requiring non-invasive/invasive ventilation. One of the patients had reported after two weeks of onset of symptom while the rest two presented during the second week. All these patients had raised markers of hyperinflammation such as raised neutrophil/lymphocyte ratio, serum D-dimer, ferritin, LDH and CRP levels (Table 1). These patients received standard institutional care as per the existing guidelines in the form of antipyretics, steroids, therapeutic dose of anticoagulation (enoxaparin 1 mg/kg subcutaneous twice daily), and awake proning protocol. These patients were diagnosed to have cytokine storm syndrome based on their clinical deterioration and laboratory parameters. One of the patients was also administered Inj Tocilizumab (8 mg/kg) infusion over 1 hour. However, there was no improvement in clinical or oxygenation status. These patients were then administered Inj Bevacizumab (7.5 mg/kg) infusion over 1 hour. Despite that these patients showed worsening of their clinical condition requiring invasive ventilation and later succumbed to their illness. The pre and post arterial blood gas after 24 and 48 hours did not show much improvement and these patients continued to have high oxygen requirement (Table 2). One of the patients also developed spontaneous haemoptysis as a complication to the anti VEGF therapy. The chest radiograph after 7 days showed sub optimal clearing of opacities (Figure 1A–D).

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Table 1. Demographic profile of patients

	Age	Sex	Comorbidities	Day of onset on presentation	Day of receiving Bevacizumab	Arterial blood gas before administering (pO_2/FiO_2)	ABG after 48 hours (pO_2/FiO_2)
Patient 1	73	M	Type II diabetes, hypertension	17	19	150	148
Patient 2	49	M	Nil	12	14	43	52
Patient 3	47	M	Nil	13	14	120	100

Table 2. Lab parameters of the patients

	Patient 1		Patient 2		Patient 3	
	09/04	19/04	19/04	27/04	22/04	28/7
Hb [g/dL]	12.7	15.9	11.8	12.4	10.2	15.4
TLC [cmm]	10200	26700	4500	14600	14000	25100
N/L	87/10	93/03	93/02	92/05	84/06	85/13/01/01
PLT [cmm]	166000	121000	195000	183000	127000	129000
PT/INR/PTTK	14/1.0/59.1	14.8/1.06/35.5	15.9/1.08/39.7	15.1/2.29	15.6/1.05/30	17.2/1.34/29
UREA [mg/dl]	34	11	34	59	73	89
CREAT [mg/dL]	0.8	0.2	1.1	0.7	1.3	1.5
OT/PT [IU/L]	88/	58/53	39/67	40/97	28/30	28/42
LDH [IU/L]	548	897	424	499	645	686
PROCAL	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	0.03
D.DIMER [mg/dL]	4.3	5	2.61	8	3.34	7
S. Ferretin [pg/mL]	710	650	900	804	597	984
CRP	106	98	138	100	48	24

The current SARS-CoV-2 pandemic has caused unprecedented mortality and morbidity worldwide and lack of confirmed effective therapy poses a therapeutic dilemma for the treating physician. It primarily affects the lung and has serious manifestation of ARDS which manifests as severe hypoxia in these patients. VEGF inhibitor (Bevacizumab) is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), and prevents its association with endothelial receptors. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels) and its inhibition of microvascular growth is believed to retard the growth of tissues due to which it has been used in various malignancies. has been shown to improve oxygenation, clinical and laboratory features especially C-reactive protein in Severe COVID-19 patients [1, 4]. However, this was not seen in our patients and the one of the reasons could have been delay in administration of this therapy and it was given as last resort for salvaging these patients. Based on our initial experience, we did not find any added benefit of anti VEGF therapy in severe COVID-19 patients and a larger study is needed to confirm its efficacy.

Conflict of interest

None declared.

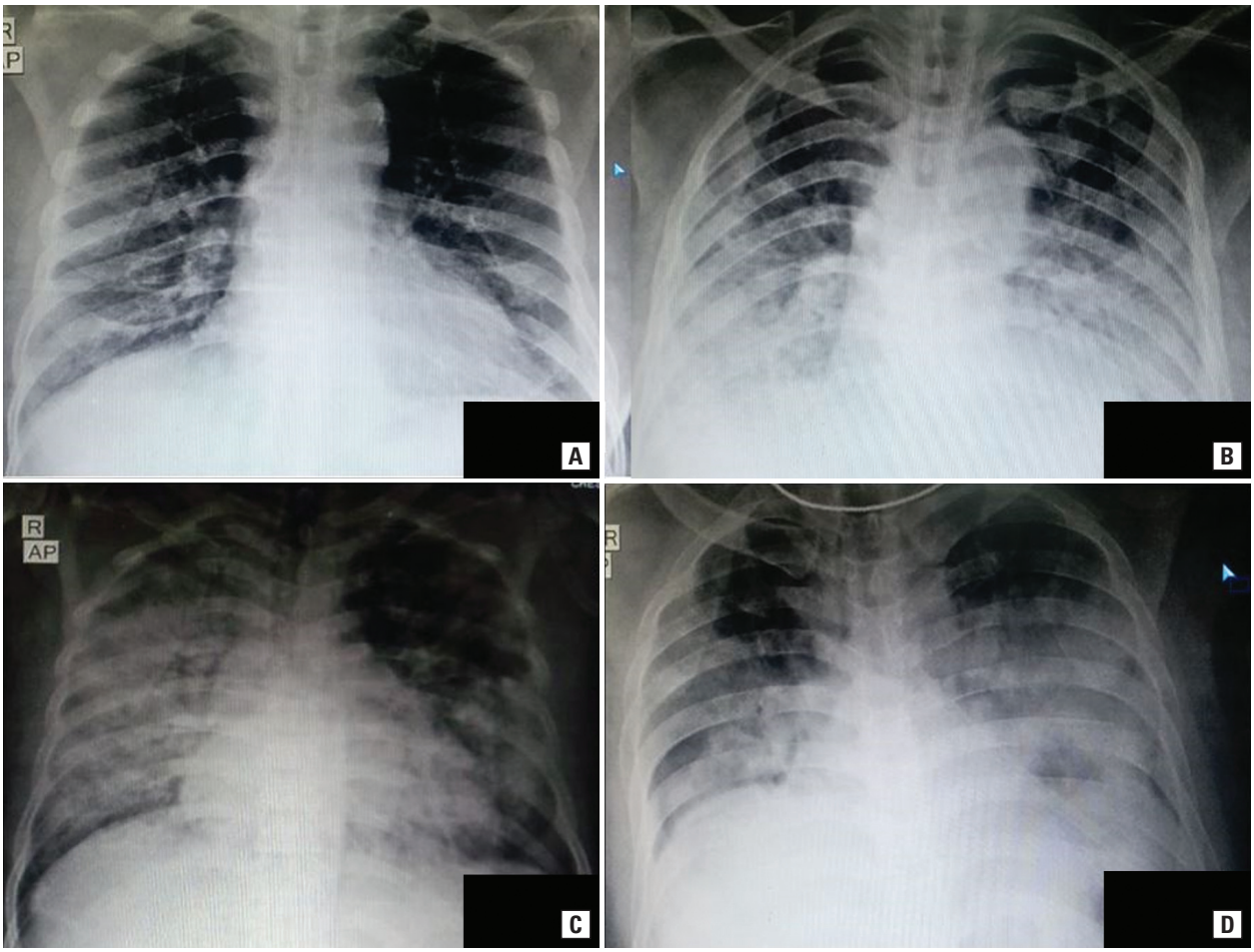

Figure 1. Chest radiograph showing bilateral air space opacities with increased opacities in radiograph **B** as compared to **A**, and **D** as compared to **C**

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Interventional closure of an unusual broncho-pleural fistula with superglue

To the Editor

Rheumatoid arthritis is a multisystemic disorder which has multiple extraarticular manifestations. One of the most common pulmonary manifestations is in the form of pulmonary nodules [1]. These patients are at higher risk of recurrent pneumothorax which can get complicated in form of broncho/alveolo- pleural fistula [2]. This can cause significant increase in morbidity. Here we report a case of recurrent pneumothorax who was diagnosed to have rheumatoid arthritis with multiple pulmonary nodules and the broncho--pleural fistula. She was successfully managed with bronchoscopic intrabronchial cyanoacrylate glue instillation.

A 42-year-old female presented to another hospital with history of progressive dyspnoea and right sided pleuritic chest pain of 4 days duration. On evaluation her chest radiograph revealed right sided pneumothorax. She was managed with intercostal drain (ICD) insertion and conservative management. ICD was removed after 7 days as her pneumothorax resolved and there was no evidence of air-leak and she was discharged. Unfortunately, patient reported again after 10 days with similar complaints and further evaluation revealed a recurrent pneumothorax (Figure 1A). ICD reinsertion was done and a persistent air-leak (Cerfolio grade-2) was also identified. During her hospital stay, she complained of pain and progressive swelling of joints of her hands and legs, especially the small joints. On evaluation, she was found to have raised rheumatoid factor levels and anti- cyclic citrullinated protein (anti-CCP) antibody and was diagnosed to have rheumatoid arthritis and was commenced on disease modifying anti rheumatic drugs. Her contrast enhanced computed tomography of chest showed numerous calcified nodules in bilateral lungs with patchy bronchiectasis and coarse reticulations (Figure 1C). There were features of mosaic attenuation with patchy areas of air-trapping seen in bilateral lungs. She underwent bronchoscopy with 6.0 mm diameter flexible video- bronchoscope (2.8 mm channel, Olympus BF-1T150, Olympus Corporation, Japan) which showed unhealthy mucosa in right lower lobe (RLL) bronchus which bled on touch. Broncho-pleural fistula (BPF) was localised by sequential occlusion with balloon occlusion catheter (Fogarty; Edwards Lifesciences, Irvine, CA, USA) to lateral basal segment of RLL. We decided to close the BPF with cyano acrylate glue. N-butyl cyano acrylate glue was filled in 2 mL syringe under strict dry condition. We used transbronchial needle aspiration needle (21G, 15mm in length, Olympus Corporation, Japan) for delivery of the glue which is otherwise used for diagnostic aspiration from mediastinal lymph nodes. It was inserted through the working channel of the bronchoscope and the glue was instilled under direct observation to the site of leak. We kept the bronchoscope about two centimetres away from the catheter tip to prevent damage to the bronchoscope and we also used additional precaution in form of Fogarty balloon which was inflated between the tip of catheter and the distal tip of scope to prevent any spill of the glue on the scope (Figure 1D). The procedure was successful and her right lung showed radiologic expansion with resolution of the leak and chest tube was

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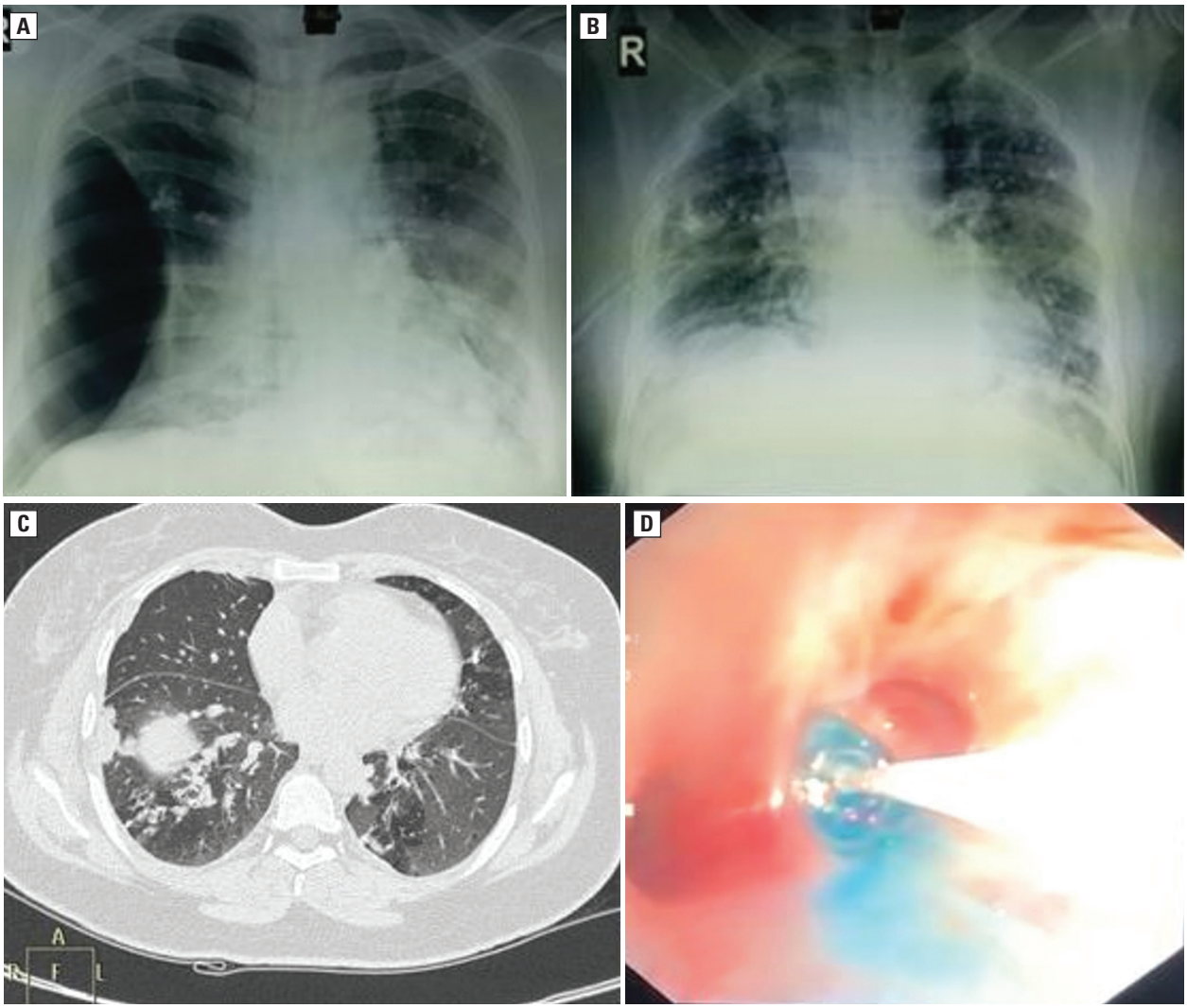

Figure 1A. Chest Skiagram showing right sided pneumothorax; **B**. Chest skiagram showing resolved pneumothorax post intrabronchial instillation of cyano-acrylate glue; **C**. Computed tomography of chest showing bilateral rheumatoid nodules; **D**. Fibreoptic bronchoscopic picture showing intrabronchial glue installation

removed 3 days after the procedure (Figure 1B). She is presently asymptomatic.

Rheumatoid arthritis is a systemic disease which causes progressive and symmetrical inflammatory destruction of joints due to antibodies [1]. It also has extra-articular manifestations in form subcutaneous nodules, vasculitis, eye involvement and pulmonary disease [2]. The pulmonary involvement of RA constitutes of pleural effusion, pneumothorax, pulmonary nodules, pulmonary artery hypertension, bronchiolitis, organising pneumonia and Caplans syndrome [2, 3] The pulmonary necrobiotic nodules can cause haemoptysis, pneumothorax and bronchopleural fistula. These patients are prone for recurrent pneumothorax and bronchopleural fistula which can cause significant morbidity and prolong hospital stay with increased chances of infection [4, 5] The management of bronchopleural fistula is a challenging task and includes surgical and endobronchial interventions. The surgical options include chronic open drainage, direct stump closure with intercostal muscle reinforcement, omental flap, trans-sternal bronchial closure, and thoracoplasty with or without extrathoracic chest wall muscle transposition [6–8]. Video assisted bronchoscopy can be both diagnostic and therapeutic in these patients as it can be used to localize the leak and allows introduction of sealants. The advantages of bronchoscopic procedure are cost effectiveness, quick action, lesser hospital stay and can also be done on out-patient basis [6–8]. The important factor which determines

success of this method is the location and size of air-leak. The success rate is higher in peripheral and alveolo-pleural fistulas less than 4 mm [7]. The leak should be directly visualised and there should be reduction or stoppage of leak on occlusion with endobronchial catheter tip [6, 8]. Video bronchoscopic guided endobronchial glue installation is effective non- operative method of closure of alveolo-pleural fistula.

Conflict of interest

None declared.

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Early corticosteroid initiation delays viral RNA clearance in respiratory secretions of COVID-19 patients

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To the Editor

Previous studies have demonstrated that a cumulative dose of methylprednisolone more than 200 mg could suppress the immune cells resulting in prolonged severe acute respiratory syndrome coronavirus 2 shedding in patients with coronavirus disease 2019 (COVID-19) pneumonia [1, 2]. In our study, we further confirm an association between early corticosteroid use and delayed viral shedding in COVID-19 patients.

In Greece, in contrast to current guidelines, many doctors in fear of the "cytokine storm" and in the absence of other drugs for the treatment of COVID-19, prescribed corticosteroids for "out-of-hospital" use (early initiation) in febrile patients with normal saturation of oxygen (SpO_2) and no evidence of pneumonia [3].

We reviewed the records of patients with early corticosteroid initiation that were later admitted to a tertiary, University hospital, the largest public reference unit in Thessaly, Greece with COVID-19 pneumonia and those of patients with late corticosteroid initiation (in-hospital initiation of corticosteroids if hypoxemia was present, according to current guidelines) [3]. Early versus late corticosteroid treated patients were propensity score matched to adjust for baseline differences.

We measured the time from COVID-19 onset to two consecutive reverse transcription polymerase chain reaction (RT-PCR) negative tests with Kaplan-Meier graphs and compared the duration of viral shedding between early and late corticosteroids treatment group with log-rank tests. The virus clearance time was calculated from the onset of symptoms to the date of the first negative RT-PCR test. Furthermore, we compared ICU admission rates and hospital length of stay in both groups. A total of 64 COVID-19 patients were included in the study and the mean age was 57.83 ± 12.66 years. Among them, 32 patients were given early home corticosteroid treatment and 32 were given corticosteroids during hospitalization due to hypoxemia (SpO_2 < 94%). All patients received dexamethasone in a dose of 6 mg per day for a 10-day period (total 60 mg). Patients' characteristics are shown in Table 1. All patients had a PaO_2/FiO_2 ratio > 200 at admission. A difference of 5.5 days in viral shedding was observed between the early and late corticosteroid initiation group as shown in Figure 1. No difference was observed in ICU admissions and hospital length of stay.

Our data demonstrates that apart from a high cumulative dose, early corticosteroid use delays viral clearance in COVID-19 patients. Further larger studies are needed to identify if this delay is associated with worse outcomes.

Conflict of interest

None declared.

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Table 1. The basic characteristics of the patients in both groups

	Early dexamethasone group (n= 32)	Late dexamethasone group (n = 32)	P-value
Mean age ± SD	55.7 ± 11.7	60 ± 13.4	0.17
Symptoms on admission			
Dyspnea (%)	37.50	37.50	> 0.99
Cough (%)	75	65.63	0.59
Anosmia/ageusia (%)	18.75	18.75	> 0.99
Myalgias/weakness (%)	81.25	46.88	0.009
Admission vital signs			
Mean temperature ± SD	37.6 ± 0.56	37.5 ± 0.76	0.63
Mean P/F ratio ± SD	291.6 ± 69	277.5 ± 33.4	0.30
Median respiratory rate (IQR)	22 (20–25)	20 (19.25–22)	0.06
Median systolic blood pressure (IQR)	129.5 (120–136)	119 (110.3–125)	< 0.001
Median heart rate (IQR)	82 (77.25–91)	86 (76–93.5)	0.54
Treatment in hospital			
Dexamethasone (%)	100	100	> 0.99
Median duration of viral shedding [days]	27.50	22	Log-rank (Mantel-Cox) test: chi square = 13.44, p-value < 0.001
Outcomes			
ICU admission (%)	0	9.38	0.24
In-hospital mortality (%)	0	6.25	0.49

ICU — intensive care unit; IQR — interquartile range; SD — standard deviation

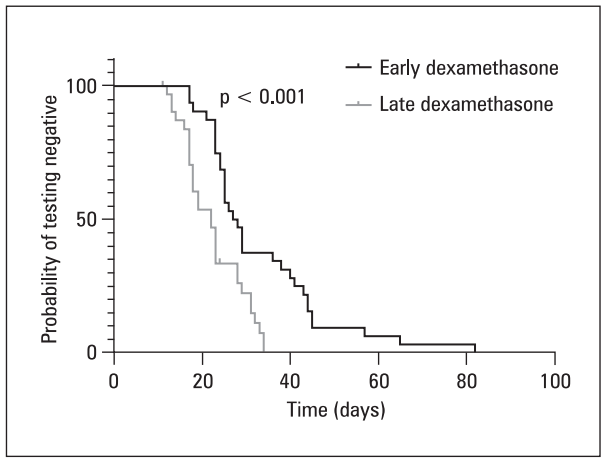

Figure 1. Kaplan-Meier presenting the comparison of days to test negative

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