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Influence of endovascular treatment on the vascular endothelium in patients with peripheral arterial disease: a systematic review

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Abstract

Peripheral arterial disease (PAD) is a major public health problem. Endothelial dysfunction represents an important mechanism in the development and progression of atherosclerosis, in part attributable to inflammation, platelet and smooth muscle activation, and arterial stiffening. The aim of this study was to explore the impact of lower limb revascularization on endothelial function in patients with PAD. We performed a comprehensive search of the academic literature using the PubMed and Embase databases to screen suitable records. Following the application of our search strategies, a total of eight studies were included in this review. Despite the limited available evidence, the dearth of academic literature suggests that revascularization has a positive effect on endothelial functioning. The effects of endovascular revascularization on endothelial functioning in patients with PAD are subject to further research.

Key words: peripheral artery disease; endothelial function; endovascular therapy; systematic review

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Introduction

Atherosclerotic peripheral arterial disease (PAD) is a major public health concern that affects more than 200 million people worldwide [1]. The estimated lifetime prevalence of PAD is 19%, 22%, and 30% in White, Hispanic, and Black populations, respectively [2, 3]. In 3–4% of patients, amputation is inevitable [1]. Endothelial dysfunction represents the key pathophysiological event in the development and progression of atherosclerosis [4] due to inflammation, platelet, and smooth muscle activation, and arterial wall stiffening.

Several diagnostic tools for peripheral atherosclerosis have been developed, including the use of markers for endothelial dysfunction. These include flow-mediated dilatation (FMD), the reactive-hypere-

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mia index (RHI), and arterial pulse waveform analysis (aPWA) [5, 6]. The majority of patients with clinically symptomatic lower limb atherosclerosis are now treated with percutaneous transluminal angioplasty (PTA), which normalizes blood flow and might have a beneficial effect on endothelial functioning. In turn, better endothelial functioning is associated with faster peripheral perfusion recovery after exercise in patients with intermittent claudication and slower progression of new atherosclerotic lesions [7].

The role of endothelial dysfunction in the pathogenesis of PAD is well-known. In contrast, the effect of angioplasty on endothelial function is less clear. In addition, very few studies have included patients with atherosclerotic lower limb ischemia [8–14]. The goal of this systematic review was to appraise the effects of angioplasty on endothelial functioning in patients with PAD.

Material and methods

Data sources and search strategy

This systematic review was conducted in compliance with the PRISMA guidelines [15]. A comprehensive literature search was undertaken using PubMed and Embase databases. The search strategy included three domains of MeSH terms and keywords combined using "AND," whereas each domain was created using "OR." The first domain contained terms related to endovascular treatment; the second contained terms related to vascular disease; and the third contained terms related to the definition of PAD. Search results were then imported into Mendeley (mendeley.com) for the selection of appropriate studies and removal of duplicates. All databases were systematically searched by six independent researchers using identical search terms. Eligible studies were screened based on titles and abstracts in accordance with the inclusion and exclusion criteria. Full-text articles were then obtained and screened. Investigators independently examined all studies to decide on which ones to include in this review. Any discrepancies were resolved via consensus.

Study eligibility

We included case-control and cohort studies that prospectively or retrospectively analyzed patients with lower extremity PAD. Lower extremity involvement was confirmed based either on an ankle-brachial index (ABI) below 0.90, or patients having undergone interventions for this condition as indicated in their medical records. Furthermore, only studies that investigated the influence of endovascular procedures on endothelial function were included.

Data extraction

Six authors were divided into three groups; extracted studies were also divided into three groups. Each group of studies was independently assessed by two authors, who performed the literature search, selected the studies, extracted the data, and assessed the quality of the studies. Data were systematically extracted from the full-text articles. Multiple studies based on the same sample, or duplicate publications of the same study, were also checked for additional data. The following data were categorized: first author name, publication year, location of investigation, study design, and population (total number of patients, age, sex, illness progression, type of endovascular equipment used, duration of follow-up, study outcome, results, and conclusions).

Results

The full search identified 1113 hits, of which 1078 were excluded after the title and abstract inspection. The remaining 35 articles were screened by full-text inspection, leading to the exclusion of another 27 articles (Fig. 1). The remaining eight articles were analyzed, as summarized in Table 1. Among these studies, one was published in 2005, one was published in 2008, and the remaining six were published between 2010 and 2020. In total, three studies originated from Switzerland, two studies originated from Poland, one study originated from the United States of America, one study from Finland, and one study from Austria. Seven studies had a case-control study design, of which all were retrospectively analyzed. One study was conducted as a prospective, randomized controlled trial.

Patient characteristics

A total of 466 PAD patients were enrolled across all studies included in this review, with an average age ranging between 63.5 ± 9.03 and 71.5 ± 8.5 years. In total, 395 patients were classified as claudicants, while 68 patients had chronic limb-threatening ischemia. Endothelial function was analyzed in most of the studies based on FMD, RHI, and intima-media thickness (IMT). In two studies, the analysis was based only on arterial stiffness parameters [10, 11]. Endovascular procedures in all studies included the use of balloon catheters and stents when indicated. One study [12] compared the DCB (Drug-Coated Balloon) to POBA (Percutaneous Old Balloon Angioplasty). The results of PTA were analyzed based on the occurrence of restenosis (i.e. a decrease in lumen diameter to less than 50% based on Doppler ultrasound), pain-free walking distance (PFWD), maximal walking distance (MWD), Rutherford scale, ABI (ankle-brachial index — change at least by

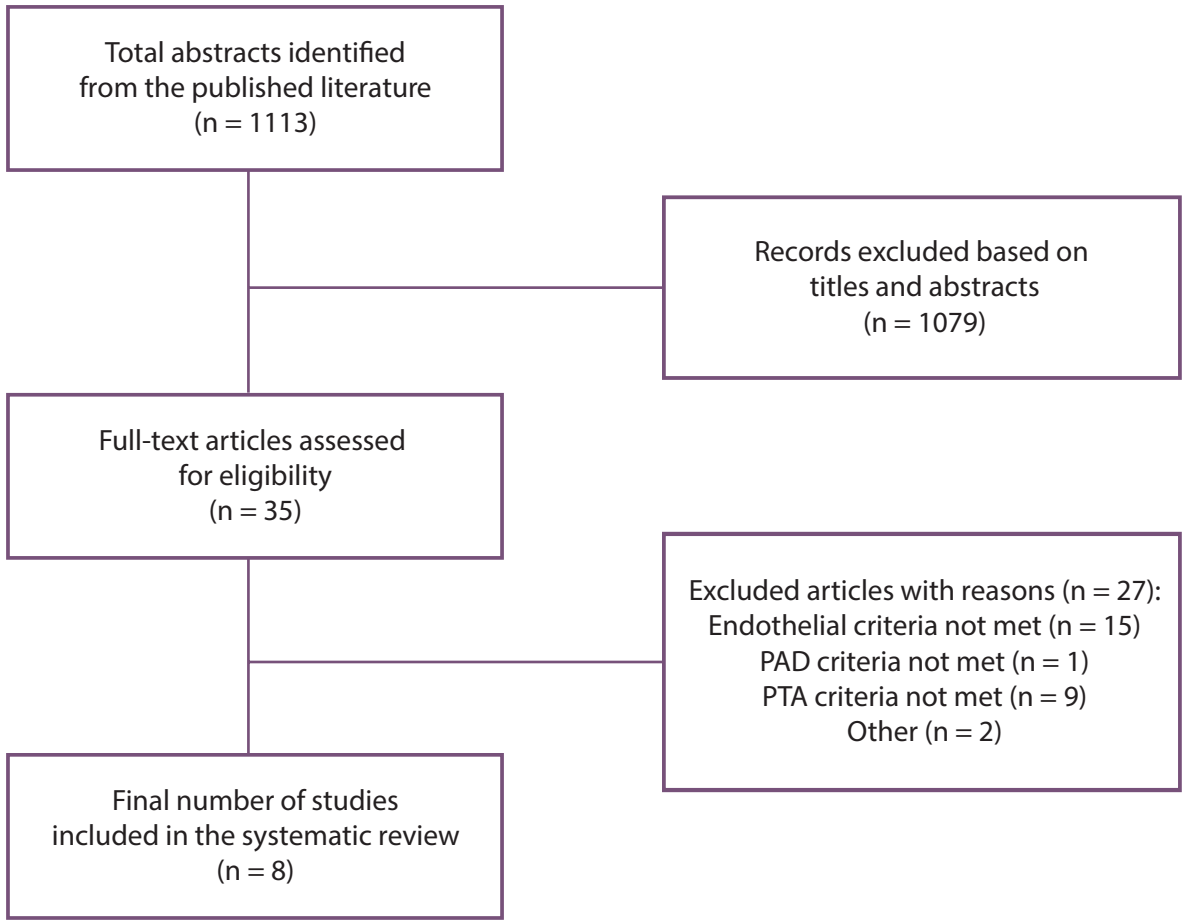

Figure 1. PRISMA flow chart

0.1) and TBI (toe-brachial index — change at least by 0.1). The duration of the follow-up period length ranged between 30 days and 12 months.

Flow-mediated dilatation

Of the eight studies, four compared FMD before and after PTA, as summarized in Table 2. Hafner and colleagues [9] measured FMD at baseline (3.53 ± 3.56%). They compared FMD in patients with and without restenosis. No baseline differences in FMD were found between patients with and without restenosis (3.55 ± 3.64% vs. 3.52 ± 3.48%; $p = 0.716$). There was however no significant change in FMD from baseline to 12-month follow-up (3.34 ± 4.18%, $p = 0.710$) [9]. Kaczmarczyk et al. [14] found significant, but transient, improvements in FMD after PTA, with a subsequent drop in FMD over a 6-month follow-up period (4.1 ± 2.9% at baseline vs. 4.88 ± 2.9% at 1 month vs. 3.4 ± 2.5% at 6 months, $p = 0.04$). Husmann et al. [16] measured FMD in patients undergoing PTA compared to those treated conservatively. The authors found a significant increase in FMD after PTA compared to baseline (4.96 ± 1.86% at baseline vs. 6.44 ± 2.88% at 1 month, $p = 0.02$). Pawlaczyk and colleagues [8] measured FMD in three patient groups: those treated with PTA, those who underwent bypass, and those treated with exercise only. They reported a significant improvement in FMD in the PTA group over the course of the study (3.88 ± 1.92% at baseline vs. 6.69 ± 2.23% after 3 months, $p < 0.01$).

Reactive-hyperemia index

Two studies [12, 14] included in this review primarily compared RHI values before and after PTA, as summarized in Table 2. Shafe et al. [12] measured RHI after endovascular revascularization in two groups of patients: DCB-treated patients and POBA with stenting-treated patients. There was a significant increase in the RHI after revascularization compared with values before revascularization, whereas the RHI did not change significantly during the 90-day follow-up period (1.43 ± 0.20 before revascularization, 1.58 ± 0.21 after revascularization, and 1.57 ± 0.22 during the follow-up, $p < 0.01$). Kaczmarczyk and colleagues proved no change in RHI values related to PTA (1.7 ±

0.7 before PTA vs. 1.7 ± 0.9 after 1 month vs 1.6 ± 0.5 after 6 months of follow-up, p = 0.62) [14].

Intima-media thickness

In total, three studies examined the relationship between PTA and its effects on restenosis using IMT values, as summarized in Table 2. Hafner et al. [9] compared IMT between patients with and without restenosis [9]. The authors found a trend towards a lower IMT in the patient group without restenosis (0.277 mm ± 0.138 mm) compared to the group with restenosis (0.314 ± 0.145 mm), although this was not statistically significant. Using a cut-off level of 0.21 mm for IMT, a statistically significant association between increased IMT and restenosis was however evident (p = 0.009). Kaczmarczyk et al. [14] found that baseline IMT decreased significantly six months after PTA administration (0.96 ± 0.29 mm before PTA vs. 0.93 ± 0.26 mm after six months follow-up, p < 0.01). There was however no relationship between IMT and reste-

Table 1. Summary of included studies

Author [year]	Country	Study type	Participants	Inclusion criteria	Exclusion criteria	PAD diagnostic criteria	Intervention (number of patients)	Follow-up [months]	Parameters of endothelium
Hafner et al. 2010	Austria	Prospective study	128; CLI/non-CLI = 0/128	Intermittent claudication no history of revascularization procedures on the affected side	Acute myocardial infarction, unstable angina pectoris or stroke, uncontrolled hypertension, decompensated congestive heart failure, pregnancy, life expectancy lower than 1 year, contraindications for anticoagulation and/or antiplatelet therapy, wound infection	Symptoms, digital subtraction angiography	PTA (n = 128), Stent implantation (n = 28)	12	FMD NMD IMT
Husmann et al. 2008	Switzerland	Prospective open, randomized controlled trial	33; CLI/non-CLI = 0/33	Symptomatic PAOD (R2-3) due to femoropopliteal obstruction	History of lower limb or coronary revascularization, an acute ischemic event within the last 3 months, chronic inflammatory disorders, moderate or severe renal insufficiency, severe liver disease, incompressible tibial arteries, persistent claudication after angioplasty	Clinical examination, ABI, color duplex sonography	PTA (n=17); Conservative treatment (n=16)	1	FMD
Jacomella et al. 2013	Switzerland	A prospective, non-randomized, controlled trial	61; CLI/non-CLI = 0/61	Symptomatic PAD (R2-3) ≥ 6 months without improvement during non-supervised walking exercise and substantial limitation in walking capacity affecting patient's quality of life	R4-6, cardiac arrhythmia, chronic inflammatory vascular disorders, failed revascularisation defined as more than 50% residual stenosis after the procedure	Symptoms	PTA (n = 61)	3	AIx
Kaczmarczyk et al. 2020	Poland	Prospective study	72; CLI/non-CLI = 30/40	CLI, stable PAD (R2,3)	End-stage kidney disease, age > 85 years, pain related to limb ischemia not allowing to obtain a horizontal position, patients with incompressible tibial arteries	Clinical examination, ABI, TBI, color duplex sonography, angiography	PTA (n = 72), stent implantation if necessary	12	FMD RHI, IMT, aPWA

→

Author [year]	Country	Study type	Participants	Inclusion criteria	Exclusion criteria	PAD diagnostic criteria	Intervention (number of patients)	Follow-up [months]	Parameters of endothelium
Pawlaczyk et al. 2016	Poland	a prospective, non-randomized study	79; CLI/non-CLI = 0/79	Symptomatic PAD, R3, patency of the popliteal artery along with at least 2 of 3 arteries in the ischemic limb, full arterial patency within the nonaffected lower extremity	Previous vascular surgery, angioedema, true or dissecting aneurysms of any artery, cancer, neurological disorders, inflammatory disorders, allergies, chronic venous insufficiency, kidney failure requiring RRT, neurogenic diabetic ulcers, poorly controlled or untreated arterial hypertension, extensive skin lesions, current use of phlebotropic agents, steroids or immunosuppressants	duplex Doppler ultrasound, Angio CT, ABI	PTA with stenting (n = 30); bypass (n = 29); treadmill training (n = 20)	3	FMD NMD
Peltokangas et al. 2018	Finland	Prospective study	24; CLI/non-CLI = 0/24	ABI < 0.9 or ABI > 1.3, symptomatic PAD, stenosis in SFA based on MRI angiography, planned PTA of the SFA	Pacemaker, risk of treatment interference by participation in the trial	Symptoms, ABI < 0.9 or ABI > 1.3, MRI angiography	PTA of the SFA (n = 24; 26 limbs)	1	Pulse wave analysis
Shafe et al. 2020	Iran, USA	A prospective, non-randomized study	86; CLI/non-CLI = 49/37	Symptomatic PAD (R2-5), R2-3 with symptoms > 3 months (with conservative treatment); ABI < 0,9; TBI < 0,7	Thrombotic lesions, lesions only within BTK segments, access via the upper limb	Symptoms, ABI < 0,9; TBI < 0,7	DCB (n = 46); POBA with stent implantation (n = 40)	3	RHI
van der Loo et al. 2005	Switzerland	Prospective study	29; CLI/non-CLI = 1/28	Planned femoropopliteal PTA (Fontaine stages II–IV)	Non-atherosclerotic diseases, bypass graft lesions, concomitant stent implantation, patients in whom the procedure was primarily not successful, history of carotid thrombendarterectomy, carotid stenting or carotid stenosis > 50%	Angiography, duplex ultrasonography	Femoro-popliteal PTA (n = 29)	6	IMT wall shear stress

nosis after the 12-month follow-up period. Van der Loo et al. [13] evaluated the relationships between PTA and restenosis with IMT. The authors found no relationship between the occurrence of restenosis and baseline IMT (IMT 0.89 mm [0.77–1.03 mm]) without restenosis vs. 0.86 mm (0.81–0.90 mm) with restenosis).

Studies assessing arterial stiffness parameters

In total, three studies included in this review examined the influence of PTA on arterial stiffness [10, 11, 14]. Peltokanges et al. [11] found that PTA causes only small, non-significant changes to PW-derived parameters for the treated limb immediately after treatment [11]. However, changes in amplitude ratios, time differences, and area ratios for the treated lower limb reached statistical significance between the follow-up visit and post-treatment state, as well as between the pre-treatment and follow-up visit. Jacomella and colleagues [10] compared arterial stiffness parameters between patients treated with PTA and those managed conservatively [10]. Their study found that revascularization was associated with a significant reduction in

Table 2. Comparison of parameters of endothelial functions before and after PTA

	References	Number of patients	Follow-up [months]	Before PTA [mean ± SD]	After PTA [mean ± SD]	p-value	
FMD (%)	Hafner 2010	128	12	3.53 ± 3.56	3.34 ± 4.18	0.710	No differences
	Husmann 2008	17	1	4.96 ± 1.86	6.44 ± 2.88	0.02	↑
	Kaczmarczyk 2020	72	6	4.1 ± 2.9	3.4 ± 2.5	0.04	↓
	Pawlaczyk 2016	30	3	3.88 ± 1.92	6.69 ± 2.23	< 0,01	↑
PW-derived parameters	Jacomella 2013*	61	3	31.5 ± 1.1	28.8 ±1.1	0.01	↓
	Kaczmarczyk 2020**	72	6	67.4 ± 12.9	65.6 ± 15.6	0.8	No differences
	Peltokangas 2018***	24	1	0.52 (0.45–0.57)#	0.34 (0.27–0.44)#	< 0,001	↓
RHI	Kaczmarczyk 2020	72	6	1.7 ± 0.7	1.6 ± 0.5	0.62	No differences
	Shafe 2020	86	3	1.43 ± 0.2	1.58 ± 0.21	0.0001	↑
IMT [mm]	Hafner 2010	128	12	No restenosis group 0.256 ± 0.133 Restenosis group 0.326 ± 0.134	NA		
	Kaczmarczyk 2020	72	6	0.96 ± 0.29	0.93 ± 0.26	0.006	↓
	van der Loo 2005	29	6	No restenosis group 0.90 (0.85–0.97)# Restenosis group 0.89 (0.84–0.93)#	No restenosis group 0.89 (0.77–1.03)# Restenosis group 0.86 (0.81–0.90)#		No differences No differences

*Augmentation Index
**Pulse pressure
***Ratio of the amplitude of diastolic wave B and the systolic maximum
#Data given as medians (interquartilranges)
FMD — Flow-Mediated Dilatation; PW — Pulse Wave; RHI — Reactive Hyperaemia Index; C-IMT — Carotid Intima-Media Thickness; B-IMT — Brachial Intima-Media Thickness; AIx — Aortic Augmentation Index

AIx (Augmentation Index) from 31.5 ± 1.1 to 28.8 ± 1.1 after 3 months ($p = 0.01$). In contrast, there was no significant change in AIx in the conservatively treated group from baseline to follow-up (29.9 ± 1.1 to 29.9 ± 1.1, $p = 0.83$). Kaczmarczyk et al. [14] showed that most of the measured arterial stiffness parameters (pulse pressure, augmentation index, central augmentation index, central augmentation pressure, and central augmentation index-HR75) decreased after PTA, and showed a consistent decrease at the 6-month follow-up, although this was not statistically significant [14]. Other parameters, like ejection duration, subendocardial viability ratio [SEVR], stiffness index, and reflection index, showed a non-significant decrease after PTA. However, all measures except SEVR increased from baseline during the 6-month follow-up.

Discussion

The aim of our study was to determine whether endovascular procedures, the most frequent method of revascularization, improve endothelial function in patients with PAD.

Endothelial dysfunction plays a key role in the pathophysiology of atherosclerosis and contributes to an increased risk of developing lower limb ischemia [17, 18] as well as other adverse cardiovascular sequelae [19]. Heiss et al. [19] called endothelial function a "barometer" for cardiovascular health, and suggested it could be a useful tool for assessing the effectiveness of novel treatment strategies. Multiple comorbidities in PAD patients, including obesity, hypercholesterolemia, hypertension, and diabetes, might in fact be related to endothelial dysfunction. All efforts focused on the im-

provement of endothelial parameters should therefore benefit patients by reducing overall cardiovascular risk.

Endothelial dysfunction disrupts the balance between vasodilation and vasoconstriction. Nitric oxide (NO) is a potent vasodilator and decreased NO bioavailability in PAD patients is strongly correlated with poor FMD [19]. The use of brachial artery FMD has been reported since 1992. It is now the most common method used to assess endothelial functioning in clinical research [20]. Several other non-invasive tests have since been developed in order to assess endothelial function. In 2002, reactive hyperemia-peripheral arterial tonometry (RH-PAT) was first described as a method for assessing peripheral vascular endothelial function. The use of RHI since then has increased rapidly [21].

FMD assesses the endothelial response to shear stress in the brachial artery as a result of hyperemia, whereas RHI corresponds to actual hyperemia. The Framingham Heart Study reported no statistically significant relationships between signals obtained using RH-PAT compared to FMD, suggesting that they reflect distinct aspects of vascular function [22]. Several studies have investigated the relationship between cardiovascular events and endothelial function. Nonetheless, the number of studies comparing FMD and RHI as predictors of adverse cardiovascular events is limited [23–25]. In a systematic review and meta-analysis, Matsuzawa et al. [26] found that both FMD and RHI have significant value in the prediction of future cardiovascular events after adjustment for other risk factors.

Carotid-femoral pulse wave velocity (cf-PWV) is another non-invasive method used to assess endothelial function and is considered the gold standard for estimating regional arterial stiffness. Arterial stiffening increases systolic and pulse pressure, promotes left ventricular hypertrophy and dysfunction, and impairs the capacity for myocardial perfusion [27]. It is an independent predictor of all-cause and cardiovascular mortality in PAD patients [28]. Indeed, arterial stiffening is associated with most cardiovascular disease endpoints, including heart disease, stroke, and chronic kidney disease. The studies included in this review suggest that revascularization might have a positive effect on endothelial function; however, this topic remains unclear, due to a small number of available studies.

Hafner et al. [9] found no significant effect for FMD as a predictor of restenosis 12 months after PTA treatment. The authors however suggested that the selective enrolment of participants with advanced PAD might have affected their results. In contrast, three studies [8, 14, 16] revealed significant improvement in FMD one to three months after successful revascularization. Kaczmarczyk and co-workers [14] also described the transience of this effect, with a significant decrease in FMD evident after six months [14]. Husmann et al. [16] described the beneficial effects of endovascular revascularization, which restored blood flow and increased tissue perfusion, in turn making walking training possible [16].

Studies included in this review that examined the RHI did not provide cohesive data. Shafe and colleagues [12] compared RHI measured before and after drug-coated balloons angioplasty and bare-metal stent placement. Improvements in RHI persisted for at least 3 months, irrespective of which intervention was used. In contrast, Kaczmarczyk et al. [14] reported a decrease in RHI directly after PTA and six months later, however, results were not statistically significant. Three studies included in our review [10, 11, 14] assessed the influence of PTA on arterial stiffness parameters, of which two showed a favorable effect on endothelial function. However, Kaczmarczyk et al. [14] found no effect of PTA on arterial stiffness parameters.

In a recent systematic review conducted by Normahani and colleagues [29], the authors evaluated the effect of lower limb revascularization on endothelial function. Their review focused on the impact of revascularization as a whole (surgical and endothelial) on various vascular measures, including perfusion (assessed using laser Doppler method, transcutaneous pressure of oxygen [TcPO2], and heat washout technique), flow (evaluated using ABI) and finally endothelial function (evaluated by using FMD, endothelin (ET)-1, NO concentrations, plasma soluble intercellular adhesion molecules (sICAMs), soluble vascular adhesion molecules (sVCAMs), C-reactive protein (CRP), lymphocyte CD11a/CD18, and neutrophil CD11b/CD18, among others) [29].

We however limited our focus to endovascular treatment and restricted our review to the most reliable markers of endothelial function. This approach simplified the review process and allowed the core message to be highlighted.

Conclusions

In conclusion, findings from this review suggest that revascularization might have a positive effect on endothelium function in patients with PAD. Further investigations focused on the assessment of endothelial function after endovascular revascularization might have therapeutic implications. Further research is needed to develop new methods of revascularization and materials used during this procedure which might have a positive and permanent effect on endothelial function.

Conflict of interests

None.

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ORIGINAL ARTICLE

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Safety and efficacy of venous mechano-chemical ablation of the great saphenous vein

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Abstract

Introduction: *Endovenous mechano-chemical ablation of the incompetent great saphenous vein (MOCA) is a new technique that combines mechanical endothelial injury and infusion of a sclerosant agent.*

Material and methods: *This is a prospective study was conducted on 40 patients who presented with the chronic venous disease at Kasr Al Ainy outpatient vascular surgery clinic with CEAP classification namely C2-C6.*

Results: *A total of 40 patients were presented with great saphenous vein incompetency, the mean age was (30), 23 patients were male and 17 were female. The vein occlusion rate at one month was 93 percent and at six months was 87 percent respectively.*

Conclusions: *Endovenous mechanochemical ablation is a safe and effective method for the management of incompetent great saphenous veins compared to open surgery.*

Key words: ablation; mechanocheical; incomptent; endovenous

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Introduction

During the last decade, there have been many types of minimally invasive procedures used for the management of great saphenous vein incompetency as endovenous laser ablation and radiofrequency ablation [1].

These techniques have a higher success rate of up to 95% at 5 years follow-up compared to surgical methods [2].

However, these techniques depend on the delivery of a high dose of thermal energy to the walls of the veins under tumescent anesthesia guided by ultrasound which is time-consuming, painful, and have many complications such as skin burns and thrombosis [3].

Recently a new technique was used using the device ClariVein™ by a combination of mechanical injury of the vein walls together with an infusion of a sclerosant agent [4].

Material and methods

Study method and population

This is a prospective study that included 40 patients who presented with chronic venous disease. At Kasr Al Ainy outpatient vascular surgery clinic. 40 patients underwent endovenous ablation by Flebogrif™.

All patients willingly consented after explaining to them the points aforementioned in the study protocol.

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Table 1. CEAP CLASSIFICATION (Clinical classification)

CEAP CLASSIFICATION (Clinical classification)
C0: no visible or palpable signs of venous disease
C1: telangiectasia or reticular veins
C2: varicose veins
C3: edema
C4a: pigmentation or eczema
C4b: lipodermatosclerosis or atrophic blanche
C5: healed venous ulcer
C6: active venous ulcer

Inclusion criteria

Patients with chronic venous insufficiency according to the CEAP classification namely C2–C6 (Table 1). Patients with refluxing great saphenous vein.

Exclusion criteria

— Patients with a history of stripping of the great saphenous vein.
— Obstruction or incompetence of the deep venous system.
— Peripheral arterial disease (ABI < 0.9).
— Superficial thrombophlebitis of a great saphenous vein.

Preoperative preparation

All patients did preoperative: (Complete blood count, Coagulation profile, Kidney function, Liver function).

Preoperative duplex

Duplex Ultrasound scanning was done to document the patency of the deep venous system and to evaluate the extent and severity of the reflux of the superficial veins (GSV, small saphenous vein, and perforators) and measuring the dimensions of the veins of patients in standing position.

Mechano chemical ablation procedure

In this study, we used the Flebogrif© device (Balton, Warsaw, Poland). We used the 90 cm catheter.

This catheter was designed as a typical diagnostic catheter. This catheter has a metal shank, attached to 5 thin, curved, springy wires with sharpened ends. After being pushed out of the catheter, these wires deployed into a cat's claw pattern. When the whole device (catheter and shank with open claws) is being pulled out, sclerosing foam is injected.

The patient is laid supine and is prepped first using povidone iodine. After applying sterile surgical drapes. The GSV is located below the knee under ultrasound guidance. Local anesthesia of xylocaine 1% is injected at the desired point of puncture. The GSV access is established below the knee joint using a 6 French sheath.

Following placement of the starter wire, the Flebogrif© device is deployed up to a point 3 cm before the saphenofemoral junction. The chemical sclerosant agent used was aethoxysclerol 3% with a ratio of 1 cm sclerosant for every 5 cm of the vein. Foam preparation of the aethoxysclerol was done using a ratio of 1 cm foam to 4 cm of air using the Tessari technique.

The device's abrasive metal nails are deployed and the device is withdrawn backward with simultaneous injection of the sclerosant agent, inducing mechano-chemical ablation.

Postoperative

Patients were observed for any hematoma formation or any intolerable pain. Patients are prescribed class II thigh-high elastic stockings to be worn for three months. They were discharged the same day home. Follow-up duplex was done immediately post-operative, 1 month and 3 months, and 6 months.

Results

A prospective study was conducted on 40 patients presented with great saphenous vein incompetency, the mean age was (30.73 ± 6.96) years, 23 patients were male (57.5%) and 17 were female (42.5%).

9 of our patients were complaining of active ulcers (C6) and 31 patients presented with visible varicose veins, edema, lipodermatosclerosis, and healed ulcers (C2–C5).

All of our patients complained of unilateral lower limb affection except for one patient; a young gentleman who had bilateral lower limb affection but the more severe left lower limb for which he was operated upon.

Diameter of GSV

Diameter comparison of upper thigh great saphenous vein dimension at the time of presentation, 3 days postoperative and one month postoperative, initially the mean diameter of GSV was 9 mm, immediately postoperative was 5 mm, and one month postoperative the mean diameter was 3 mm (Table 2).

Table 3 shows the P-value with a significant reduction in GSV diameters postoperatively and at one month.

Table 2. Comparison of GSV diameters pre and post-operative

	Age	GSV diameter initially	GSV post-op	GSV 1 month post-op
Mean	31	9	5	3
Standard deviation	6.96	0.61	0.22	0.19
Minimum	21	8	4	2
Maximum	44	10	5	3
Median	30.00	8.50	4.50	2.80

Table 3. P-value of GSV pre and post-operative

	Mean	Standard deviation	P value compared to initial
GSV diameter initial [mm]	8.51	0.61	–
GSV diameter post op [mm]	4.53	0.22	< 0.001
GSV diameter 1 month [mm]	2.71	0.19	< 0.001

Three-month and six-month follow-up duplex results

The courses of the treated GSV, deep veins, and axial veins were investigated by Duplex ultrasound for visibility, compressibility, blood flow, and reflux. A re-canalization of GSV or failure of intervention was defined as a patent segment of the treated vein more than 5 cm in length. The criterion for a varicose vein was a visible or palpable varicosity with a diameter of more than 3 mm.

At 3 months post-operative two of the cases had a recanalized Great saphenous vein while At 6 months four of the patients had a visual recanalized GSV.

Improvement in symptoms

Comparison between the pre-operative and post--operative serial measurements revealed a significant decrease in pain on the stand ($p < 0.0001$) and a non-significant difference regarding wound healing ($p > 0.05$) (Fig. 1).

Post-operative complications

We had no complications in the form of hematoma bruising or severe pain or deep venous thrombosis in the follow-up window of 6 months interval.

Discussion

Mechanochemical ablation of a great saphenous vein considered a new management strategy that is very promising and competes with surgical and non-surgical treatments that are adopted for venous disease of lower limbs. Previous studies to assess the success of using mechanochemical ablation to treat the chronic venous disease of the great saphenous vein were done using the ClariVein™, Flebogrif™ devices. Despite that, the results were very hopeful [5].

A Polish study (2021) performed on nine Merino sheep aimed to assess the effectiveness of mechanosclerotherapy of venous veins with a new device — Flebogrif® — based on an animal model. They concluded that the simultaneous use of Flebogrif® and a sclerosant (lauromacrogol) yielded better results of vein lumen reduction than the use of Flebogrif® alone. The preliminary study showed no direct damage done to the vein wall by Flebogrif and a slight increase in wall diameter. In combination, Flebogrif® + sclerosant was observed to increase the connective tissue of the intima [6].

Previous studies on the efficacy of the Flebogrif device show very promising results. The study included 200 patients, 170 females and 30 males treated with ablation with Flebogrif™ to treat varicose veins, initial technical success of the surgery was achieved in all cases. During the first 3-month follow-up, recanalization of the vein occurred in 8 patients. Results showed a statistically significant decrease in the severity of clinical symptoms in comparison to ones before the intervention and between particular days of the observation during the 3-month follow-up. In comparison to our results, we had successful venous occlusion rates where at three months intervals only one patient had a recanalized GSV and at 6 months two patients had a recanalized GSV. Also out of the 40 patients studied 9 had active venous ulcers and 5 completely healed and 4 had partially improved [7].

In a different study also using the Flebogrif device conducted by Piotr Ciostek Et al in 2015 to treat GSV disease and assess the efficacy and safety of this device in such disease, 40 cases were treated with mechano--chemical ablation using the Flebogrif device. Efficacy of the procedure at follow-up was 97.4%, 94.9%, 89.7%, and 89.7% at 1, 3, 6, and 12 months respectively [8].

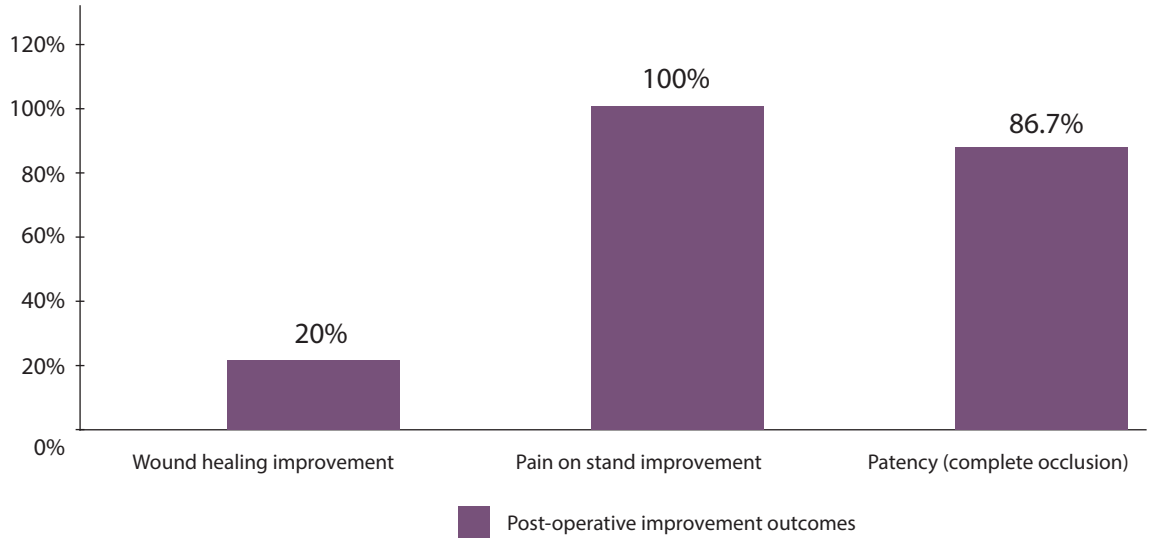

Figure 1. Postoperative outcome

Another randomized trial was done to compare the intra-procedural pain using the ClariVein device and RFA using the visual analog score. Pain values were also recorded at 3- and 6-month follow-ups. About 170 cases were followed over a 21-month period from 240 screened. Patients in ClariVein group experienced less maximum pain significantly during the procedure by Visual Analogue Scale versus RFA 34 mm, $p < 0.003$) and number scale versus RFA $p < 0.002$). 'Average' pain scores were also significantly less in the first group. Results of our trial show significant improvement in the pain score p-value < 0.001 [5].

A study using the ClariVein device was done on patients for the management of symptomatic varicose veins at the Charring Cross NHS Hospital in London. 119 patients have been randomized, with 60 patients using Clarivein and 59 to RFA. Results show that 66% of patients were at one-month follow-up, and the complete or proximal occlusion rates were 92% for both groups. At one month follow-up, the clinical and the quality of life scores for both groups had similar improvements. Compared to our study the vein occlusion rate at one month was 93 percent and at six months was 87 percent respectively [7].

In the meantime, there is no randomized control trial to compare the results of mechanochemical ablation versus endovenous laser ablation.

From our study, we have also come to find that there are fewer complications as regards complications of mechanochemical ablation compared to other interventions. A total of 808 cases were managed with RFA and EVLA (2057 procedures). The success rate of RFA was 98.4%, that equivalent to EVLA at 98.1%. The success rates of thermal ablation for each vein were: GSV, 98.5%; SSV, 98.2%; ASV, 97.2%; and PVs, 82.4%. The overall thrombotic complication rate was 10.5%. The thrombotic complications include endovenous heat-induced thrombosis (EHIT; 5.9%) and acute superficial venous thrombosis (4.6%). The rate of a thrombotic complication after the procedures for each vein was: GSV, 11.8%; SSV, 5.5%; ASV, 6.5%; and PVs, 2.4%. The thrombotic complication rate was 7.7% for RFA and 11.4% for EVLA ($P < 0.007$) [9].

In a systematic review and meta-analysis conducted by (Alozai et al 2022), five articles met the inclusion criteria, reporting 348 procedures in 392 patients. 4 studies reported the 3-month anatomic success, and 3 studies reported 12-month anatomic success. The 3-month anatomic success rate was 95.6% (95% CI, 93.2–98.0%). The 12-month anatomic success rate was 93.2% (95% CI, 90.3–96.1%). Major complication reported within 3 months was deep vein thrombosis (0.3%) while thrombophlebitis and hyperpigmentation had occurred in 13.3% to 14.5% and 3.3% to 10.0% of patients, respectively, within 3 months. [10].

Conclusions

Mechanochemical ablation is a minimally invasive day-case treatment solution for cases with chronic venous disease. It is an emerging treatment for the management of chronic venous disease that avoids the complications of surgery ranging from anesthetic problems to other complications.

Conflict of interest

None.

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VIA MEDICA

REVIEW ARTICLE

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Influence of endarterectomy on the structure and function of the retina and optic nerve

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Abstract

Carotid arteries are the main blood vessels supplying the brain, neck, and face as well as ophthalmic arteries. Internal carotid arteriosclerosis is strictly associated with ophthalmic symptoms caused by damage to the optic nerve. This condition can manifest as an ocular ischemic syndrome or anterior ischemic optic neuropathy. One of the surgical procedures that treat carotid arteriosclerosis is an endarterectomy. It has been proved that this surgical procedure can additionally reduce intraocular pressure and improve visual acuity, best corrected visual acuity (BCVA), visual field, a bioelectrical function of the optic nerve and retina, and perfusion of the optic nerve head. It has been also observed that the procedure does not affect retinal nerve fiber layer thickness and ganglion cell layer. The aim of this review was, to sum up information on the influence of endarterectomy on the function of the optic nerve based on the up-to-date internet database.

Key words: endarterectomy; internal carotid artery; optic nerve; perimetry; electrophysiology

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Introduction

Carotid arteries are the main blood vessels supplying the brain, the neck, and the face as well as ophthalmic arteries [1]. Plaque forming in these arteries leads them to be hardened and narrower thus increasing the chances of carotid atherosclerotic diseases. Internal carotid arteriosclerosis is one of the main causes of stroke and transient ischemic attack worldwide. This condition has been strictly associated with ophthalmic symptoms and evidence shows that it may lead to ischemic lesions of the retina and optic nerve in 15–46% of involved patients [2]. As a matter of fact, when an embolus originating from the carotid artery reaches the ophthalmic artery, it may cause a wide variety of ocular problems that can be considered the first symptoms of carotid stenoses, such as transient monocular visual loss, central retinal artery occlusion and central retinal artery branch occlusion [3–5]. Ocular ischemic syndrome (OIS) and anterior ischemic optic neuropathy (AION) are also associated with significant carotid artery stenosis and may lead to ocular blood flow reduction and cause damage to the optic nerve. The main symptoms include permanent (AION) or transient (OIS) visual loss and ischemic ocular pain. Generally, it is important to observe ophthalmic symptoms as they may foreshadow possible future cerebrovascular complications [2, 6].

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Carotid arteriosclerosis can be treated with surgery — the atherosclerotic plaque can be removed by endarterectomy or angioplasty and stenting [1]. A broad range of research has highlighted that endarterectomy can improve multiple visual parameters in patients with severe ICA.

The aim of this review is to summarize the findings concerning the impact of endarterectomy on the function of the optic nerve, accumulated and published in the literature in the last five years.

Methodology

Two reviewers have independently searched electronic databases using search terms: "internal carotid endarterectomy and visual field", "influence of ICE on the optic nerve function", "atherosclerosis and optic nerve function", "ICE and vision", internal carotid endarterectomy and electrophysiology", "internal carotid endarterectomy and optical coherent tomography" to obtain information on the influence of internal carotid endarterectomy on the function of the optic nerve.

Background

Atherosclerotic cardiovascular diseases (CVD) are associated with the buildup of fats, cholesterol, and other substances in and around the arteries and form of plaque. These diseases are a leading cause of mortality worldwide [7]. In 2020, in people aged 30–79, the prevalence of increased carotid intima-media thickness was estimated to be 27.6%, the presence of plaque — 21.1% and of carotid stenosis — 1,5% [8].

Internal carotid arteriosclerosis (ICA) prevents proper blood flow in the brain and has been widely associated with ophthalmologic symptoms. This condition can be treated surgically by endarterectomy, angioplasty and stenting. However, treatment may differ depending on symptoms, as surgical intervention on asymptomatic patients is still disputed. Undergoing an operation is recommended for asymptomatic patients with high-grade stenosis (70–90%) or symptomatic ones with moderate (50–69%) or high-grade stenosis [1].

Carotid endarterectomy (CEA) restores the blood flow in the vessels and prevents the brain and eye from damage due to hypoperfusion. It has been documented that CEA can reduce intraocular pressure (IOP) as well as improve visual acuity, visual field, a bioelectrical function of the optic nerve and retina, and perfusion of the optic nerve head. It has been also observed that CEA doesn't affect retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL).

Yan et. al performed a study on 15 patients with severe internal carotid stenosis (> 70%) but who did not suffer from ocular symptoms [9]. They underwent carotid endarterectomy (CEA) and complex ophthalmic examination before and after surgery. Upon surgery, the number of patients with low visual acuity (20/200 – 20/60) decreased while the number of patients with middle level of visual acuity (20/50–20/28) increased presenting partial improvement. Additionally, results showed that IOP levels decreased after surgery and the mean value of IOP was reduced from 17.41 ± 2.59 to 15.95 ± 2.50 mm Hg [9]. However, previous studies obtained controversial results, one found IOP to be significantly decreased after CEA [10], while Guclu et al. drew opposite conclusions [11]. Overall, although the mechanisms underlying these dynamics are not well understood, it was suggested that CEA might cause ophthalmic hemodynamic changes to IOP.

Another research showed that CEA can significantly improve the parameters of both static and dynamic visual fields. Konstantiniuk et. al. conducted a cohort study on 29 patients suffering from carotid artery stenosis [12]. Of 11 of the presented preoperative impairment of visual field parameters, 18 had those parameters preoperatively normal. The subjects had a full ophthalmic examination of both eyes before and after endarterectomy comprising the assessment of dynamic visual field (Goldmann perimetry). In a group of 11 patients, 8 experienced postoperative improvements in the visual field parameters. In the group of 18 patients, 3 experienced minor impairments; in two cases there were respectively, focal and temporal impairments in the contralateral eyes. In the third case there were both focal improvements and impairments. In the rest 15 patients, the vision remained unchanged, after the ICA [12].

Furthermore, other studies support the idea that CEA is associated with the subjective improvement of different visual symptoms after CEA, such as blurred vision, amaurosis fugax, and visual acuity [13, 14]. A study conducted by Yan et al., aiming at the analysis of changes in the visual field, highlighted how both kinetic and static visual field parameters significantly improved after CEA [9]. Researchers also showed that eyesight appeared to be enhanced after CEA was performed on patients suffering from anterior ischemic optic neuropathy or ocular ischemic syndrome [2, 6, 15]. Different studies underlined improvements in visual acuity or perimetric parameters after the surgery [16, 17].

Moreover, CEA may have a positive effect on the bioelectrical function of the retina and optic nerve in patients with significant ICA. In their research Yan et. al. assessed flash visual evoked potentials (FVEPs), pattern visual evoked potentials (PVEPs), and electroretinogram (ERG) before and after CEA. The outcome of FVEPs and PVEPs showed that the latency of the P2 wave

was significantly shortened in both eyes and that the P100 latency was only slightly reduced, while its amplitude increased. However, differences in P100 were not statistically significant. The results of ERG showed that the oscillatory potential amplitudes statistically significantly increased [9]. Supporting these results, a previous study reported latency diminution and amplitude increase, reinforcing eyesight improvements and the recovery of visual function upon CEA [10]. Finally, another study analyzed different electrophysiological parameters of the optic nerve function in patients with the acute ocular ischemic disorder. Both the threshold of electrical sensitivity and the level of liability of the optic nerve appeared to be improved after the surgery [2].

Perfusion of the retina and optic nerve head is further ophthalmic parameters enhanced after CEA. Lahme et al. investigated optic nerve head (ONH) perfusion in patients with severe asymptomatic carotid artery stenosis [18]. The study analyzed 25 eyes of 25 participants suffering from this condition and compared them to 25 eyes of 25 healthy individuals. Optical coherence tomography angiography (OCT-A) was performed before and after the carotid surgery. The results showed that, in patients with ICA, the flow density of the radial peripapillary capillary (RPC) layer of the ONH was significantly lower than in healthy controls. Additionally, the flow density in the RPC of ONH was improved after CEA in both ipsilateral and contralateral eyes [18].

Finally, retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) parameters are generally considered to be unchanged before and after CEA. Pierro et al. enrolled 30 patients with unilateral carotid artery stenosis and 30 healthy patients as controls [19]. All participants underwent complex ophthalmic examination including OCT and OCT-A scans, and RNFL, ganglion cell layer (GCL) as well as choroidal (CT) thicknesses were assessed. RNFL and GCL were similar between the study group and controls and remained unchanged after the surgery [19]. Other studies confirmed that RNFL thickness remained unchanged before and after CEA and specifically no connection between retinal blood flow and RNFL thickness in glaucoma patients was found [9, 20]. Overall, researchers speculated that these results suggest that blood flow velocity does not affect the caliber of the retinal blood vessels.

Conclusions

Improved artery blood flow following endarterectomy demonstrated a positive effect on the function of the optic nerve and it can, to some degree, enhance and restore visual functions in patients with severe carotid artery stenosis. Multiple results of studies proved that the surgery can reduce IOP and improve different ophthalmic parameters such as visual acuity, BCVA, visual field, the bioelectrical function of the optic nerve and retina, and perfusion of the optic nerve head. It has been also observed that the procedure does not affect RNFL and GCL thickness.

Conflict of interest

None.

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Irisin — the future of ischemic stroke therapy?

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Abstract

Irisin is a recently discovered hormone, synthesized mainly by the muscles. Expression of irisin and its precursor named FNDC5 was also found in the heart, kidneys, liver, pancreas, adipose tissue, and brain including cortical neurons, hippocampus, cerebellum, hypothalamus, and spinal cord.

The purpose of this study is to review the latest research on the properties of the irisin and its cytoprotective effect against neuronal damage and to draw attention to its possible clinical use in the treatment of stroke. Notch pathway activity increases after ischemic damage, stimulating the repair of the affected brain area. Irisin activates the Notch pathway which inhibits the activity of microglia, secretion of inflammatory factors, and finally leads to reduction of the brain edema. Studies revealed that irisin increases levels of brain-derived neurotrophic factor (BDNF), leading to enhancement of survival and migration of the neurons, and protecting nerve cells from damage during the ischemic stroke. It was also found that irisin maintains mitochondrial integrity, reduces oxidative stress, and exerts a protective effect on the blood-brain barrier.

Irisin entails a neuroprotective effect, reducing the extent of the infarcted area and the degree of brain damage. Stimulation of the irisin expression by physical activity or its exogenous administration remains the subject of research that raises hope for development of the new therapeutic options for diseases, especially ischemic stroke.

Key words: ischemic stroke; irisin, apoptosis; FNDC5 protein; BDNF; blood-brain barrier; brain injury; neuroprotection; exercise

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Introduction

Ischemic stroke remains one of the most important causes of neurological morbidity and mortality all over the world. According to the data from 2021, ischemic stroke affects 9.5 million people worldwide, causing 2.7 million deaths annually [1, 2]. Recent studies have shown that stroke causes a loss of 52 million years of life as a result of premature death and disability, being one of the leading causes of reduced life expectancy, and a deterioration in the quality of life. Over 70% of strokes remain the ischemic type. Additionally, there is a slight predominance of stroke among men [1]. The increasing incidence of stroke among young adults (45 years old, and younger) remains currently a significant issue [3, 4].

Due to the enormous importance of this problem, it is necessary to develop effective methods of preventing stroke complications. Currently, high hopes are placed on the newly discovered myokine, named irisin which

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was found to be released from skeletal muscles during physical exercises [1–6].

The aim of the study is to reveal the current state of knowledge about the cytoprotective properties of the irisin and to draw attention to the therapeutic potential and possible clinical usage of this myokine in the treatment of stroke.

We designed our literature review to include studies that addressed the role of irisin in ischemic stroke. The literature search was performed using PubMed for studies restricted to clinical trial, review, comparative and multicenter studies published from 2007 to 2022, using the following medical subject headings (MeSH) terms: ischemic stroke, irisin, apoptosis, FNDC5 protein, BDNF, blood-brain barrier, brain injury, neuroprotection, exercise. The most suitable articles were manually collected based on preliminary abstracts review on the subject of the influence of irisin on brain ischemia. The references of searched articles identified additional ones that also matched, so these were included in the final review with 36 articles and 2 websites in total.

The current state of knowledge

The main places of irisin synthesis are skeletal muscles and its secretion takes place immediately after physical exercises [5, 6]. Studies have shown that irisin affects the liver, pancreas, adipose tissue, bone, and brain with its variety of effects [7]. First of all, irisin involves the regulation of metabolic pathways and protects cells from apoptosis [8].

Released in skeletal muscles, it stimulates the uptake of glucose and fats, and their metabolism while limiting gluconeogenesis and glycogenolysis. In the liver, it stimulates the gluconeogenesis process and inhibits glycogenolysis and lipogenesis. It regulates the level of glucose in the blood serum, not only due to the fact of aforementioned processes but also by affecting the pancreas. Irisin stimulates pancreatic cells to secrete insulin and glucagon. Furthermore, it provides protection from apoptosis and enhances the regeneration of the beta cells. Bone tissue is another site of irisin action. Bones retain adequate mass and strength because irisin reduces the activity of osteoclasts. Irisin also has a beneficial effect on white adipose tissue, turning it brown, inhibiting the accumulation of lipids, increasing glucose uptake, and inhibiting lipolysis [7].

Physical activity increases the secretion of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) — which is a transcriptional coactivator and metabolic regulator [9]. The increased level of PGC-1α drives the expression of FNDC5 — the irisin precursor. FNDC5 is a transmembrane glycoprotein. It consists of a signal peptide and several domains. Proteolytic cleavage of FNDC5 is necessary for the formation of functional irisin. The final step is post-translational modification including glycosylation [10].

Neural stem cell proliferation, neuronal differentiation, gliogenesis, and microglial activity are regulated by the Notch pathway [11]. Its activity increases following ischemic damage and stimulates the repair of the affected areas of the brain.

Administration of irisin activates the Notch pathway that inhibits the activity of microglia and secretion of inflammatory factors such as Il-1β, and TNF-α, and finally reduces edema of the brain tissue. Caspase-3 activity is also reduced, inhibiting thereby neuronal apoptosis [11] (Fig. 1).

Studies have shown that the activity of the Notch intracellular domain (NICD) increases 24 hours after ischemic stroke, which proves an increased activity of the aforementioned Notch pathway. The process of neuronal differentiation can be demonstrated by labeling nerve cells with NeuN dye. Studies revealed that the levels of NeuN-positive cells increase after prior administration of exogenous irisin. The NeuN dye binds to mature neurons, indicating that neuronal differentiation takes place. On the other hand, the concentration of pro-inflammatory factors, including TNF-α and IL-1β, is significantly reduced after the administration of irisin [11]. This allows us to conclude that irisin reduces inflammation in the course of a stroke.

Irisin influence on caspase-3 levels and neural cells apoptosis

Caspase-3 appears to be a crucial enzyme in the pathways of cerebral cell apoptosis. Brain ischemia leads to the involvement of two overall apoptosis pathways, intrinsic — initiated by mitochondria injury, and extrinsic — initiated by cell surface death receptors, both mediated by caspase-3 [12, 13]. An important role in cell death through apoptosis plays oxidative stress that leads to blood-brain barrier (BBB) dysfunction through structural and functional disturbances of endothelial cells' mitochondria [14, 15]. Thereby, cytochrome C (Cyt-c) is released from the mitochondrial membrane to the cell's cytoplasm, whereas proapoptotic Bax protein shifts inversely, activating the caspase family (including caspase-3), and inducing endothelial apoptosis. These events cause BBB damage and following dysfunction that leads to brain edema [15, 16]. Guo et al. (2021) revealed that exogenous irisin administration inhibits Bax and Cyt-C transits that lead to a decrease in caspase-3 activity and a reduction of endothelial cell apoptosis [15]. The above-mentioned study used a mouse model of traumatic brain injury (TBI), exploring both exogenous irisin and in vivo irisin synthesis, triggered by endurance exercise, influencing BBB after TBI. Both

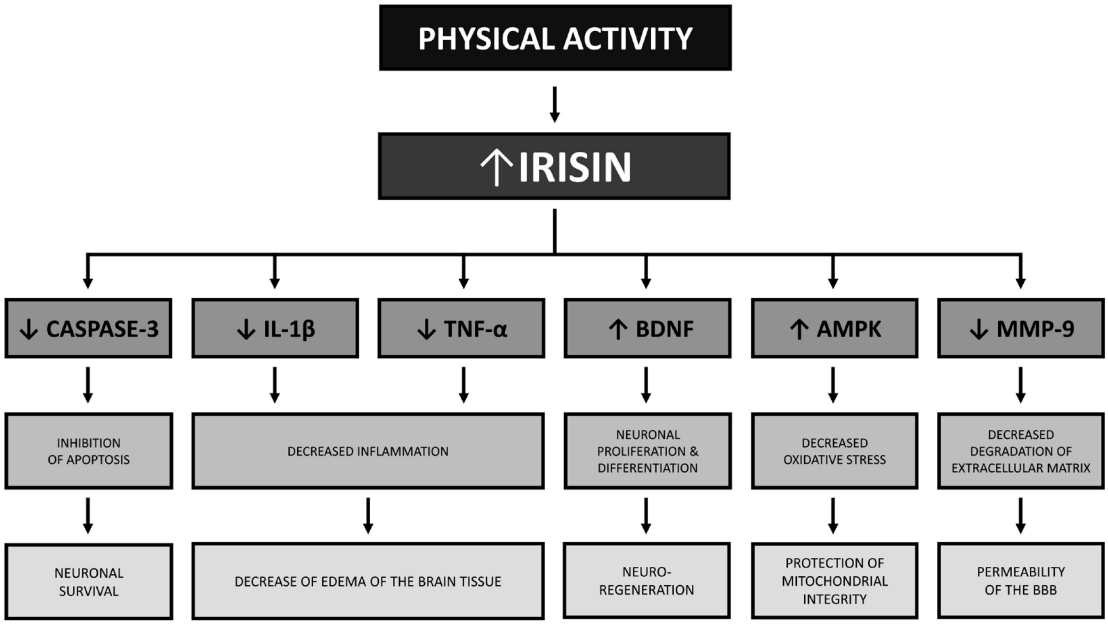

Figure 1. The effect of increased irisin concentration on various neural cell pathways; IL-1β — interleukin-1beta, TNF–α — tumor necrosis factor-alpha; BDNF — brain-derived neurotrophic factor, AMPK — AMP-activated protein kinase, MMP-9 — matrix metalloproteinase-9

exogenous irisin and endurance exercise appeared to diminish BBB damage in mice. Furthermore, the authors demonstrated that irisin may ameliorate BBB dysfunction after TBI by uncoupling protein 2 (UPC2) expression enhancement on the neural mitochondrial membrane [15]. Uncoupling proteins remarkably affects mitochondrial physiology, engaging in, inter alia, redox signaling. UPC2 might decrease reactive oxygen species production, reducing mitochondrial membrane potential [17]. It may result in a reduction of oxidative stress and inflammatory response [15].

Jin et al. (2019) investigated the influence of irisin on cleaved caspase-3, using in vivo and in vitro ischemia/ /reperfusion (I/R) brain injury models. The investigators found that pretreatment of irisin was associated with a significant reduction of the cleaved caspase-3 levels after I/R brain injury in comparison with the I/R injury group without irisin treatment in both in vivo and in vitro models. These results point out the neuroprotective properties of irisin that are associated with the inhibition of neural cell apoptosis [11].

The role of BDNF and AMPK

Brain-derived neurotrophic factor (BDNF) is a protein synthesized in the neurons as a pro-isoform and released after proteolytic changes. BDNF expression in the central and peripheral nervous systems is dependent on various factors, such as stress, nutrition, metabolism, or behavior. BDNF mediates neuronal differentiation, axonal sprouting, or dendritic arbor proliferation, and controls synaptic plasticity, long-term depression (LTD), and long-term potentiation (LTP), playing a very important role in the learning and memory processes [18]. Irisin may affect BDNF through PGC-1α/FNDC5 axis during endurance exercise, exerting a neuroprotective effect [19, 20]. Asadi et al. (2018) explored the influence of recombinant irisin on the BBB permeability, infarct size, neurological outcomes, BDNF expression, and apoptosis, using a mouse model of ischemic stroke by occlusion middle cerebral artery with following reperfusion. The study revealed that intracerebroventricular administration of recombinant irisin at doses of 0,5; 2,5; 7,5 and 15 μg/kg significantly decreased the size of infarction; however, better neurological outcomes were observed at doses of 7,5 and 15 μg/kg. At level 7,5 μg/kg irisin significantly reduced brain edema, lowered apoptotic cells, and enhanced BDNF immunoreactivity in the infarcted brain regions. It was found that the irisin administration did not affect BBB interruption.

The authors concluded that irisin reduces brain damage following ischemic stroke in a dose-dependent manner, diminishing apoptosis and leading to increasing BDNF expression in the ischemic brain area [21]. BDNF appears as an essential regulating factor following irisin action during ischemic stroke. It may also have a beneficial impact on neuronal survival and migration [19, 22] (Fig. 1).

Regarding 5'-AMP-activated protein kinase (AMPK), it appears as an endogenous protective protein, responding to deleterious stimuli, including cerebral ischemia, or neurodegenerative diseases. It regulates energy metabolism in the brain, influencing cell survival, growth, obsolescence, and death. AMPK plays an important role in ischemic stroke, reducing oxidative stress, ameliorating neuron apoptosis, affecting autophagy, improving mitochondrial dysfunction, protecting neurons from excitotoxicity of glutamate, reducing neuroinflammation, and promoting angiogenesis [23] (Fig. 1).

It was shown that irisin may mediate the expression of both BDNF and AMPK through physical activity [19]. Fan et al. (2020) revealed, in their in vitro study, that irisin activates the AMPK pathway, leading to the protection of cardiomyocytes and mitochondria against hypoxia-reoxygenation injury, under high glucose stress conditions [24].

Similarly, Zhang et al. (2020) revealed a protective irisin role against ischemia/reperfusion acute kidney injury, mediating by AMPK [25]. Despite poor evidence in the literature, linking directly neuroprotective role of irisin, mediating by AMPK in ischemic stroke, the above-mentioned studies indicate this possibility and further investigations are needed [19].

The role of MMP-9

The scope of damage caused by ischemia and reperfusion is significantly dependent on blood-brain barrier (BBB) disruption and subsequent edema formation. Matrix metalloproteinase MMP-9, by participating in the degradation of the extracellular matrix, leads to an increase in the permeability of the blood-brain barrier, which can cause early brain edema, inflammatory infiltration, and, consequently, neuronal injury [26, 27].

In the studies using the middle cerebral artery occlusion (MCAO) ischemic stroke model in rats, it was shown that intravenous administration of irisin prior to the induction of stroke significantly improved parameters related to the extent of the stroke. A significant reduction in the volume of infarcted cerebral tissue was observed in the irisin pretreatment group (23.00% vs. 34.83%). In the pathomorphological analysis using Evans blue, a decrease in permeability of the blood-brain barrier and a decrease in the activity of MMP-9 metalloproteinase was observed in this group. Maintaining the integrity of the blood-brain barrier resulted in a reduction of edema and limited excessive build-up of water in the brain tissue (Fig. 1). Also, the neurological deficit score was lower in irisin--treated rats. The above results suggest that increased concentrations of irisin, by inhibiting MMP-9, may have a neuroprotective effect, leading to a reduction in the level of neurological deficit [28].

Irisin as a prognostic factor

There are indications that serum levels of irisin may be used as a prognostic marker in patients with ischemic stroke. Irisin level in patients with 6-month survival was significantly higher compared to patients who died. Moreover, irisin had a higher predictive value as compared to FBG, Hs-CRP, HCY, IL-6, and clinical assessment according to the NIHSS scale. Most noteworthy, among patients with high concentrations of irisin, poor functional outcome (i.e. modified Rankin Scale (mRS) of 3–6) is less frequent, resulting in higher chances of recovery [29, 30].

Neuroprotection of the physical activity in ischemic stroke

It is commonly known that exercises have a beneficial effect on brain function. Physical activity causes releasing of many molecules, proteins, and metabolites involved in cell metabolism and the repair of their injuries. Exercises stimulate a series of changes to ensure the amelioration of the brain's vascularization and release neuroprotective and angiogenesis factors, which are promoting increased brain blood flow and avoidance of injuries [31]. According to the same study active subjects show statistically significant reductions in vessel tortuosity and an increased number of small vessels in comparison to less active persons [32]. In combination with creating new collateral vessels that might explain the role of activity in neuroprotection. Preconditioning exercise as a mild stressor protects the brain from injury by inhibiting apoptosis and induces brain ischemic tolerance. These effects have a lot of mechanisms. Preconditioning exercises reduce infarct volume and neurological deficits, activate the protective and repair functions of astrocytes, and reduce oxidative damage in neurons [33]. Moreover, this activity has a positive impact on the components of the blood-brain barrier preventing its interruption and subsequent formation of edema [34].

During physical exercise, many metabolic pathways are activated, including the release of osteocalcin by bones, beta-hydroxy-butyrate by the liver and FNDC5/ /irisin by muscles. All of the aforementioned substances are responsible for increasing the level of BDNF, which shows a neuroprotective effect, reducing the scope of cognitive impairment due to ischemia, as studies concluded [35]. Studies have shown that irisin can decrease inflammatory factors, such as IL-6 and TNF-α, which may limit inflammation-related damage to the brain. The protective properties of irisin are also associated with a decrease in the concentration of MMP-9 responsible for the destruction of the blood-brain barrier. The similarity of irisin effects to other neuroprotective substances secreted during exercise leads to the conclusion

that irisin is also an important mediator of the protective effect on the brain. This conclusion is supported by the fact that low serum irisin level was a predictor of poor early functional outcomes in patients with ischemic stroke. As irisin is mainly secreted by muscles during physical activity, it may play a key role in connecting exercise with the protection of brain function [36].

Conclusions

Irisin secretion is associated with physical activity. This myokine plays a key role in relieving inflammation, inhibiting apoptosis, as well as maintaining mitochondrial integrity, and reducing oxidative stress which is connected with cell injury. Irisin exerts a cytoprotective effect on neurons, reducing the extent of infarcted area and the degree of brain damage. There is a correlation between physical activity, irisin levels, and the likelihood of a positive neurological outcome during ischemic stroke. Irisin also has an effect similar to other neuroprotective substances secreted during physical activity, suggesting its importance in alleviating the effects of ischemia on brain tissue. Its multidimensional effect raises hope that it can be used as a prognostic factor, which may enable the development of new therapeutic strategies in patients after ischemic stroke. However, further investigations are still needed, in particular on large groups of patients, which in the future may provide a foundation for the development of new therapeutic options for ischemic stroke.

Conflict of interest

None.

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CASE REPORT

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Superficial temporal artery aneurysm

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Abstract

The superficial temporal artery (STA), an end branch of the external carotid artery, is a major artery of the head. Due to its location, where skin and fat tissue remain the only protection of the artery, it can be easily damaged while head injury, causing an aneurysm to form. So far around four hundreds of cases of STA aneurysms have been described in the literature.

We present a 37-year-old woman with a painless pulsatile mass of approximately one centimeter above the left ear and headaches in the left temporal area. In the past, she was a victim of domestic violence with a few head trauma.

The STA aneurysm was confirmed in ultrasound imaging. The patient did not meet the criteria for the diagnosis of giant cell arteritis. She was presented for a vascular surgery consultation and qualified for surgical resection of the aneurysm. In addition, the patient was diagnosed with hepatic hemangioma and mild aortic and mitral valve regurgitation.

According to the available literature, STA aneurysms have mostly been reported as post-traumatic. The gold standard for STA aneurysm treatment is surgical resection. The procedure was reported as safe, as well as a low grade of recurrence or complications during the procedure was shown in the literature.

Key words: *superficial temporal artery aneurysm; head injury; headache; temporal mass; angio-computed tomography scans*

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Introduction

The superficial temporal artery (STA), an end branch of the external carotid artery, is a major artery of the head. It begins within the parotid gland and passes superficially over the posterior root of the temporal bone [1]. Due to this location, where the skin and fat tissues remain the only protection of the artery, it can easily be damaged by head injury. The first case of STA aneurysm was reported in 1742 by Thomas Bartholin. Since then, around four hundred cases of STA aneurysms have been described [2]. The most common clinical presentation is a painless, growing, pulsatile mass in the temporal area and headaches on the involved side. STA aneurysms can be divided into true aneurysms or pseudoaneurysms [3]. Pseudoaneurysms are mostly post-traumatic aneurysms, due to the artery being prone to injury because of its anatomy [4].

The purpose of this paper was to present the case of a 37-year-old woman admitted to the Department and Clinic of Internal Medicine, Angiology, and Physical Medicine for diagnosis, in whom a post-traumatic STA aneurysm was finally diagnosed.

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Case report

Anamnesis and physical examination

The 37-year-old woman was admitted to the Clinic due to a painless pulsatile mass of around one centimeter above the left ear and headaches localized in the left temporal area. The mass had been noticed three months before the patient was admitted to the Clinic. The patient reported that the mass has grown in her observation since then. She neglected fatigue, fever episodes, and night sweats. She denied mandibular claudication and symptoms of polymyalgia. On physical examination, there was no hyperesthesia in the temporal area. Moreover, no sight problems were recorded. She has undergone a neurological examination with no abnormalities found. In the past, she was a victim of domestic violence with a few head traumas. As cardiovascular risk factors are concerned, she was an active smoker. To estimate the 10-year risk of developing cardiovascular disease the Framingham Risk Score as a sex-specific algorithm was used [5]. Taking age into consideration, she was considered at low cardiovascular risk.

Laboratory tests

The results of the majority of performed laboratory tests were normal including peripheral blood count with leukocytes differentiation, erythrocyte sedimentation rate, C-reactive protein, fibrinogen, troponin, parameters of kidney function assessment, ions (natrium, kalium, calcium, and phosphate), liver function and injury tests, thyroid function parameters, iron, and vitamin B12 concentrations, uric acid, and total protein, as well as coagulation parameters (prothrombin time and activated partial thromboplastin time). In terms of lipid profile parameters, a slightly elevated concentration of total cholesterol (195 mg/dl) and low-density lipoprotein cholesterol (140 mg/dl) was found, with reduced high-density lipoprotein cholesterol (38 mg/dl) and a normal level of triglycerides (96 mg/dl). The concentration of selected cancer markers was determined, showing an increased concentration of CA 125 (51.4 U/ml), with the correct concentration of alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA).

Imaging and functional tests of the cardiovascular system

During hospitalization in the Department and Clinic of Internal Medicine, Angiology, and Physical Medicine in Bytom the left STA aneurysm was confirmed during clinical examination and ultrasound imaging. STA on a length of 6 mm, was widened up to 4 mm with a thickening of the aneurysm wall up to 1.1 mm and a suspicion of a thrombus in the aneurysm (Fig. 1). The intima-media complex was thickened to 1.2 mm within the common carotid bulb, and apart from this the carotid and vertebral arteries in the ultrasound study were normal. Angio-computed tomography scan of carotid, vertebral, and brain arteries was performed in which a lack of posterior left connecting artery of the brain was found. The asymmetry of the carotid and vertebral arteries was also described, with the dominance of the left vertebral artery and the right internal carotid artery. Carotid, vertebral, and intracranial arteries aneurysms were excluded. The patient did not meet the criteria for the diagnosis of giant-cell arteritis. Thus, she was not qualified for an STA biopsy. She was presented for a vascular surgery consultation and qualified for surgical resection of the aneurysm.

The performed ECG examination revealed a sinus rhythm with a frequency of 60 per minute. Transthoracic echocardiography showed only mild mitral and aortic valve regurgitation, and apart from this, the morphology and function of the heart structures and the great arterial trunks were normal. A Doppler ultrasound examination of the lower extremity arteries was performed, which showed the correct blood flow spectrum. Measurements of the ankle-brachial index (ABI) and the toe-brachial index (TBI) were within the normal range. Measurement of the pulse wave velocity in the femoro-cervical section using the Sphygmocor XCEL apparatus showed a value that did not indicate increased vascular stiffness (6.2 m/s). The values of central and peripheral arterial pressure and the parameters of the pulse wave analysis were normal, in addition to a slightly increased augmentation index (AIx 36%, AIx75 29%).

Other diagnostic procedures

During hospitalization, the patient underwent an ultrasound examination of the abdominal cavity, in which a focal lesion of the liver with the morphology of the hemangioma was described, as well as a single parietal atherosclerotic plaque in the abdominal aorta, which was confirmed by computed tomography of the abdominal cavity and pelvis with contrast. In addition, a uterine myoma was described by computed tomography. An ultrasound of the thyroid was also performed, which showed a slightly increased volume of the gland (19.1 ml) and heterogeneity of the parenchyma, with no obvious focal changes (moreover thyrotropin and free thyroid hormone levels were normal). The chest radiograph was described by the radiologist as normal.

Discussion

An aneurysm is a widening of the artery caused by a weakness of the artery wall, classified according to the integrity of the three layers of the vessel wall into

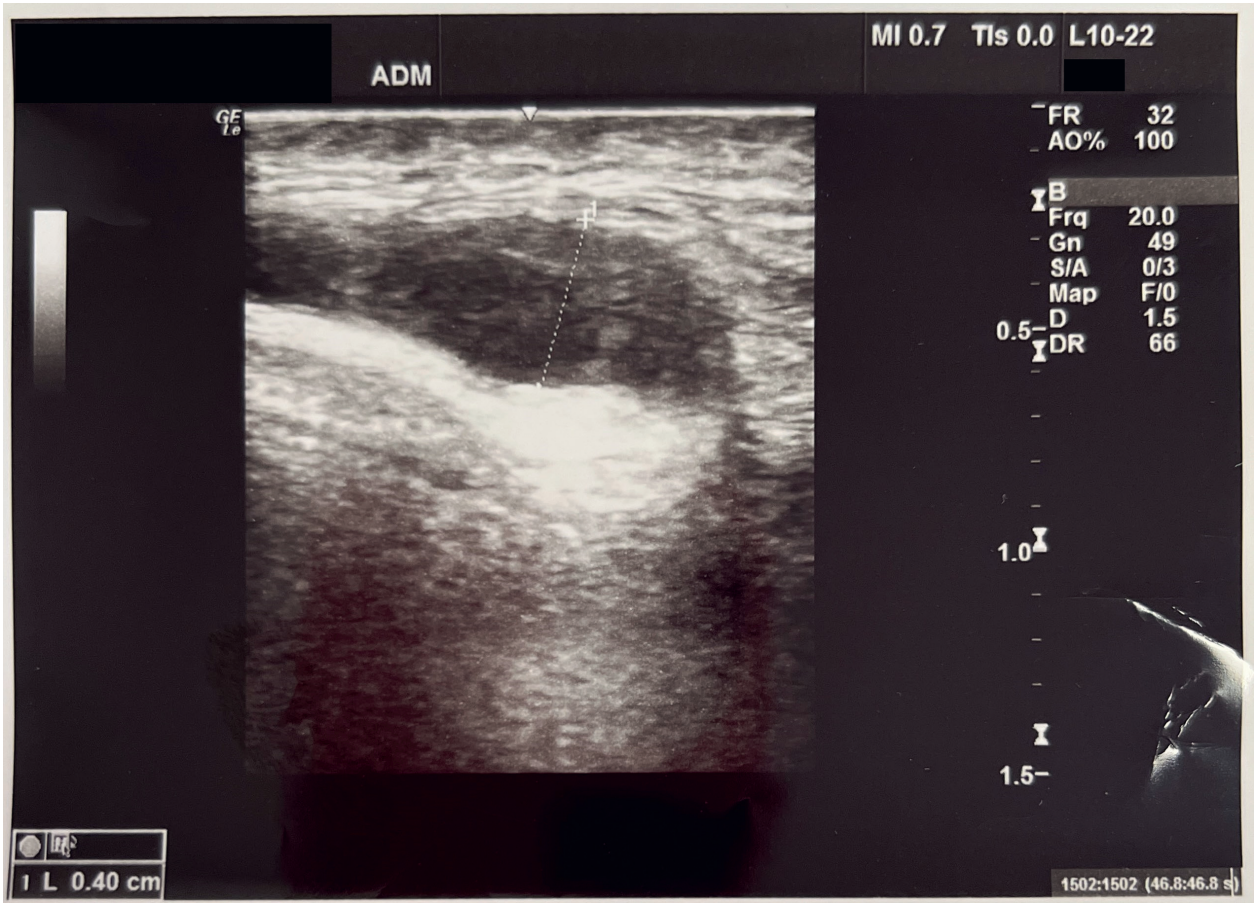

Figure 1. Superficial temporal artery aneurysm in ultrasound doppler exam

true, false (pseudoaneurysms), and dissecting aneurysms [6]. So far, STA aneurysms were mostly reported as post-traumatic aneurysms [7]. Only 5% of the cases are considered spontaneous aneurysms with congenital or atherosclerotic components accountable [8]. Due to STA location and the course through shallow subcutaneous connective tissues, it can be easily damaged while head injury, injections (e.g. botox), hair transplantation, or during plastic and reconstructive surgery in the temporal area [9–11]. Some studies have also been reported on STA aneurysms caused by mask-wearing during the COVID-19 pandemic. The STA aneurysms were located at the pressure point created by the rubber mask [12]. Articles commented on this issue suggest that any blunt or penetrating trauma to the temporal area may result in STA aneurysm development, due to partial transection or contusion of the arterial wall and its necrosis. Developed hematoma that further becomes organized, and its progressive dilatation explains the delayed appearance of the pulsating mass [13]. As reported, the delay in the appearance of pulsatile masses is from two to six weeks [14]. STA aneurysm should be taken into consideration while painless, pulsatile mass in the temporal area is being examined [15]. In addition, headaches on the affected side, ear discomfort, dizziness, and neurological defects were also reported in some cases, however, most of the patients have had no symptoms [16]. Subcutaneous hematoma, dural arteriovenous fistula, inflammatory diseases such as giant cell arteritis, sebaceous cyst, dermoid cyst, neoplastic diseases such as facial nerve schwannoma or parotid gland tumor, meningocele, lymphadenopathy are the conditions that should be involved in the differential diagnosis of temporal mass [17]. Giant cell arteritis is the most common form of vasculitis observed in adults [18]. A careful diagnostic path should be taken because if the diagnosis is missed and no treatment is implied, it can lead to irreversible blindness [19]. The diagnosis of STA aneurysm can be made based on the patient's history and physical examination, and then confirmed with different imaging modalities. In most cases, proper physical examination is sufficient for diagnosis due to their vascular signs such as a pulsatile mass thrill. However, when the aneurysm is thrombosed the vascular signs might not be present [20]. In most cases, the diagnosis was confirmed by

ultrasound imaging and angio-computed tomography [21]. In some patients, magnetic resonance angiograms or catheter angiograms were performed [22]. All of the imaging modalities presented give a good STA aneurysm visualization and permit one to exclude other diagnoses. If the patient is not suspected of a vasculitis no biopsy of the temporal artery is required [23].

Although STA aneurysms have a relatively benign course, when compared with aneurysms of larger caliber arteries, they may lead to severe hemorrhage and be associated with a difference of bothersome symptoms, however cosmetic problems, pain, and discomfort are the main reason for the treatment [24]. The gold standard for STA aneurysm treatment is surgical resection [25]. The procedure was reported as safe and with a low grade of recurrence of the aneurysms or complications during the procedure which is shown in the literature [26]. After surgical treatment, mostly cosmetic problems were noticed, such as scars or skin defects [27]. Depending on the location of the STA aneurysm and its size some nerves can be damaged during the surgical procedure [28]. The frontozygomatic branch of the facial nerve and the auriculotemporal nerve are the most commonly injured nerves [29]. It may result in facial local peripheral paralysis or abnormal ear sensibility and parotid gland increased secretion [30].

Endovascular treatment might be considered in a selected group of patients when the aneurysm is located in a relatively inaccessible area for open surgical treatment, such as the part of the superficial temporal proximal artery. Proper dissection of these proximal lesions requires exposure of the parotid and facial nerve before ligation and resection of the aneurysm, which increases the rate of possible complications during surgery [31]. Coil embolization, as an alternative treatment method, is highly effective, leaving no facial scar, but thickening in the temporal area may still be palpable [32]. In a subacute aneurysm, lasting for more than three weeks, and a chronic aneurysm, lasting for more than three months, ultrasound-guided thrombin injection was reported as a safe and successful treatment. However, it can cause distal tissue necrosis [33].

Conclusions

STA aneurysm is a rare pathology, caused mainly by blunt trauma to the temporal area. Accurate examination with different imaging modalities, mostly ultrasound imaging, permits the proper diagnosis. Surgical ligation and resection of the aneurysm is the gold standard of treatment; however, endovascular treatment can be a safe and effective procedure in some cases.

Conflict of interest

None.

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CASE REPORT

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Unilateral lower extremity lymphedema as a first symptom of primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)

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Abstract

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), is a rare and aggressive variant of extranodal lymphoma. We report the case of a 64-year-old woman with unilateral lymphedema of the lower limb as the first and only symptom of PCDLBCL-LT for six months. Violaceous nodules were the second symptom and they progressively developed on the edematous calf. Initially, they were diagnosed as warty overgrowths, which are common skin changes in the course of chronic lymphedema. The lack of improvement in the violaceous nodules after compression therapy prompted to perform a skin biopsy. Histopathological evaluation revealed the presence of PCDLBCL-LT. In this article, we want to highlight the challenges of making a diagnosis of PCDLBCL-LT. To our knowledge, no other study has reported on lymphedema as an initial symptom of PCDLBCL-LT.

Key words: lymphedema; primary cutaneous diffuse large B-cell lymphoma; leg type (PCDLBCL-LT); violaceous nodules; warty overgrowths; methotrexate-associated lymphoproliferative disorder (MTX-LPD)

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Introduction

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is a rare medical condition. It accounts for 15% of all primary cutaneous B-cell lymphomas (CBCL) and 4% of all primary cutaneous lymphomas (PCL). It usually affects elderly women in the 7th decade of life with a strong predilection for the lower limbs. However, in some cases (15–20%) it may affect other parts of the body [1, 2]. Compared to other primary cutaneous lymphoma (PCL) subtypes, PCDLBCL-LT is a more aggressive variant that manifests with rapidly growing red or violaceous nodules. It is characterized by a poor prognosis with a 5-year survival rate of 40–50% [1, 3, 4]. Regarding histological features, large B-lymphocytes with numerous mitotic figures and a diffuse growth pattern are seen, as well as a strong expression of B-cell lymphoma 2 (Bcl-2), CD-20, B-cell lymphoma 6 (Bcl-6) and multiple myeloma oncogene-1 (MUM-1) of those cells. In about 10% of cases, MUM-1 can be negative while CD-10 is usually negative [5].

Case report

A 64-year old woman with a 28-year history of rheumatoid arthritis (RA) treated for 27 years with methotrexate (MTX) and low doses of glucocorticoids,

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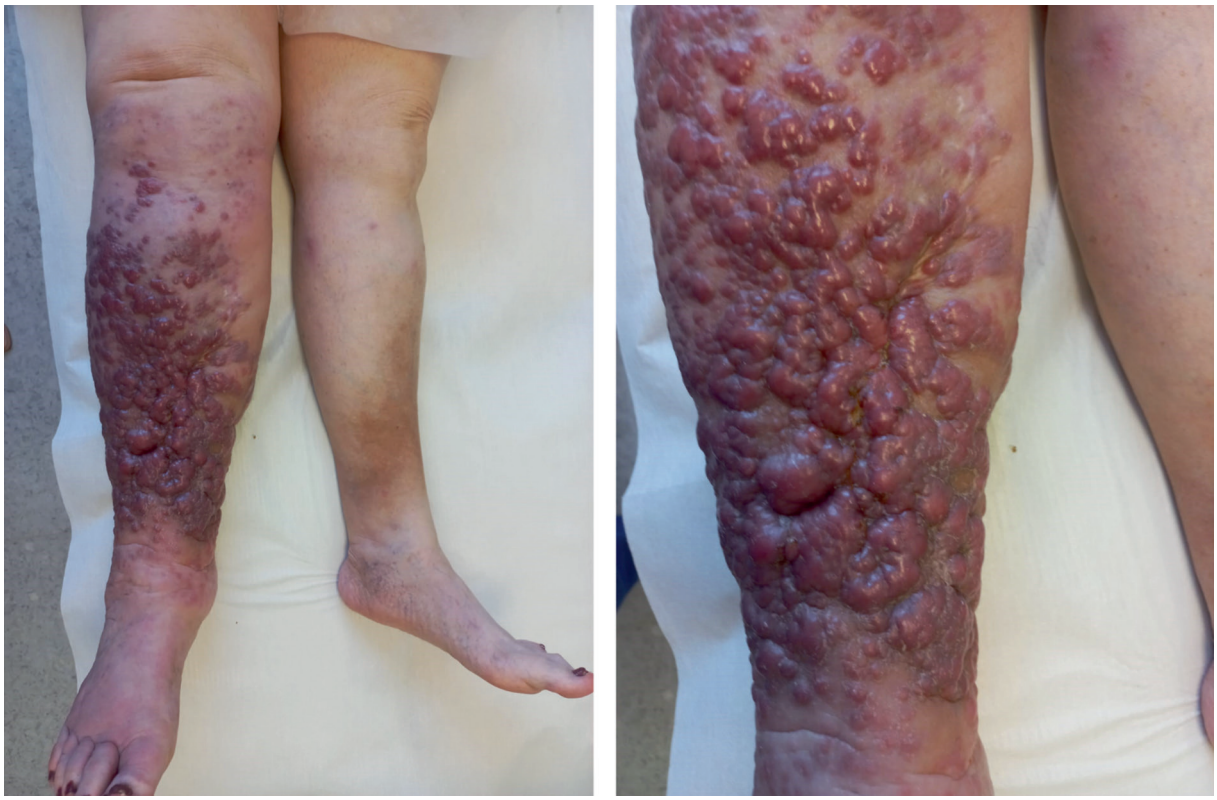

Figure 1. Lymphedema and violaceous nodules of lower right extremity in the course of primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) in our patient

and after a colostomy performed 4 years earlier due to perforation of the diverticulum ulcer, was referred to the department of angiology due to lymphedema of the right lower limb. Lymphedema was first noticed ten months earlier and gradually progressed. Doppler ultrasound examination ruled out deep vein thrombosis (DVT). After 4 months of lymphedema, compression therapy was applied with slight effect. Finally, six months after the appearance of the first signs of edema a number of papular changes developed on the affected leg. Skin lesions were consulted dermatologically and treated with topical ointments without a positive effect. Later, the papules developed into hard, bluish nodules.

The physical examination at the time of admission to the hospital revealed a lymphedema of the right lower limb accompanied by numerous violaceous nodules on the edematous skin (Fig. 1). The nodules were also present on the left knee. There were no clinical signs of systemic disease, such as weakness, emaciation, enlarged lymph nodes, or low-grade fever. The violaceous nodules were not painful. Laboratory parameters showed a moderately elevated concentration of C-reactive protein — 17 mg/L (normal value: 0–5 mg/L) and a significantly elevated concentration of lactate dehydrogenase — 1078 U/L (normal value: 0–248 U/L). Other laboratory parameters were within normal limits. Based on the medical history and clinical symptoms, skin cancer was suspected and diagnostic tests were scheduled.

First, contrast-enhanced computed tomography (CT) of the chest, abdomen, pelvis, and lower extremities was performed. The skin lesions visible in the CT of the right leg can be described as nodular thickening of the skin and subcutaneous tissue, covering the entire circumference of the limb without features of pathological contrast enhancement (Fig. 2). The CT showed no other abnormalities, such as enlarged lymph nodes, which may explain the presence of lymphedema in the lower limb.

Histopathology revealed a highly atypical population of large malignant lymphoid cells with immunoblast and centroblast morphology and an inconsistent growth pattern. Cancer cells have invaded the dermis in a destructive way. The subcutaneous tissue was also involved. Immunohistochemical staining revealed the presence of large lymphoid cells positive for CD-20, CD79a, Bcl-2, and p63 and negative for CD-10, TdT, MUM-1. The proliferation rate assessed by Ki-67 staining was close to 100%. Mitotic figures were numerous (approximately 30/10 HPFs). The final diagnosis of PCLBCL-LT was made based on histopathological findings (Fig. 3).

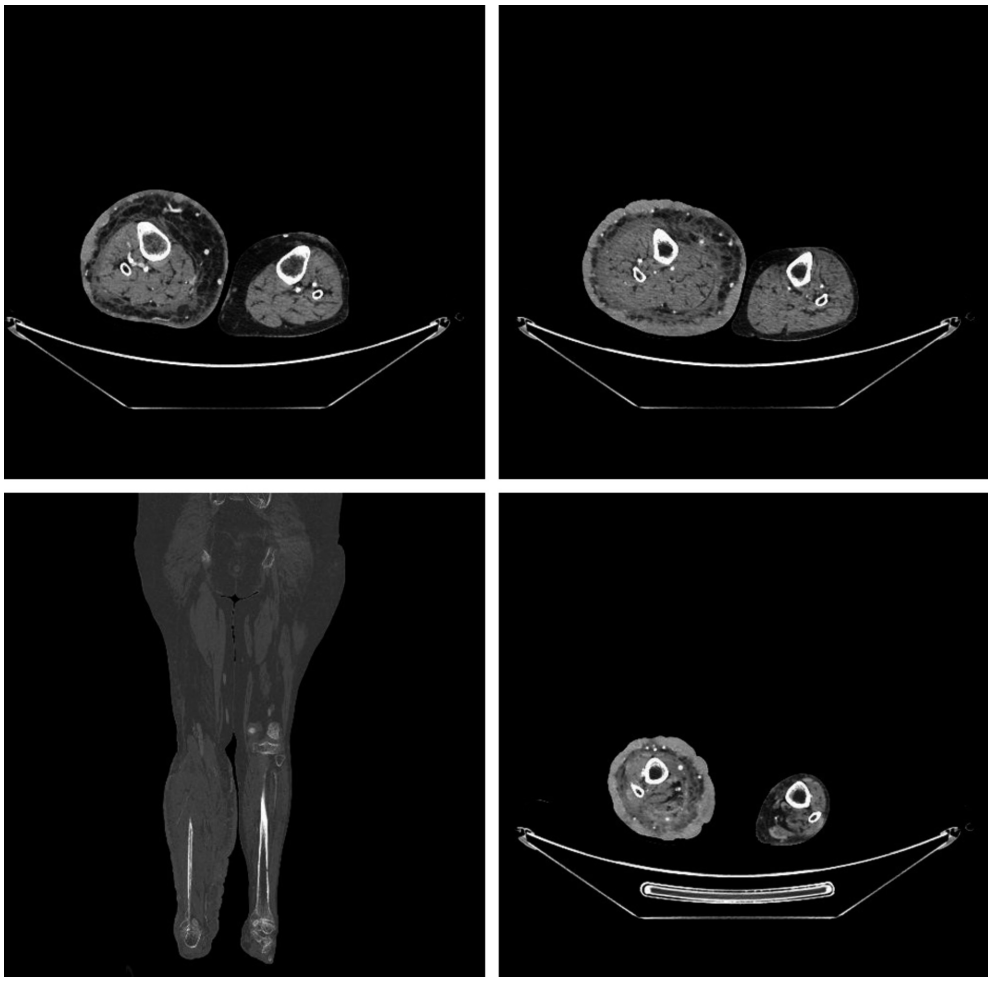

Figure 2. Contrast-enhanced computed tomography (CT) scans of the lower extremities in our patient with primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)

In order to start the treatment as early as possible, the patient was referred to the department of hematology, where a PET-CT examination was performed and chemotherapy was started using the R-CHOP protocol. During this time, the nodules spread to the forearms, but they disappeared shortly after starting treatment. MTX was discontinued from RA treatment immediately after diagnosis.

Discussion

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is an extranodal variant of non-Hodgkin lymphoma. The clinical presentation is most often manifested as rapidly growing tumors, plaques or violaceous nodules within one or both lower extremities [1, 4, 6]. However, skin manifestations of PCDLBCL-LT are clinically heterogeneous and may sometimes take unusual forms, e.g. verrucous plaque-like lesions, multiple nodules with widespread garland-like patches, bluish-reddish multicolored rainbow patterns or even annular patches with erythematous, well-defined borders that resemble erythema chronicum migrans [7–10]. Moreover, in many cases of PCDLBCL-LT, the appearance of skin lesions may suggest a benign nature and contribute to the delay in making the correct diagnosis [7–10]. Considering the wide spectrum of the clinical picture of PCDLBCL-LT and its rarity, it is worth highlighting the challenges in the diagnosis of patients with this disease entity.

The violaceous nodules on the calf of our patient developed 6 months after the appearance of the first symptoms of lymphedema. Therefore, they were initially thought to be warty overgrowths, which are common skin lesions in chronic lymphedema. There are many synonyms for warty overgrowths in the literature, including verrucous papillomatosis, papillomatosis cutis lymphostatica, lymphostatic verrucosis, lymphatic papillomatosis, lymphedematous keratoderma, verrucous elephantiasis and elephantiasis nostras verruciformis [11]. According to the International Society of Lymphology, warty overgrowths correspond

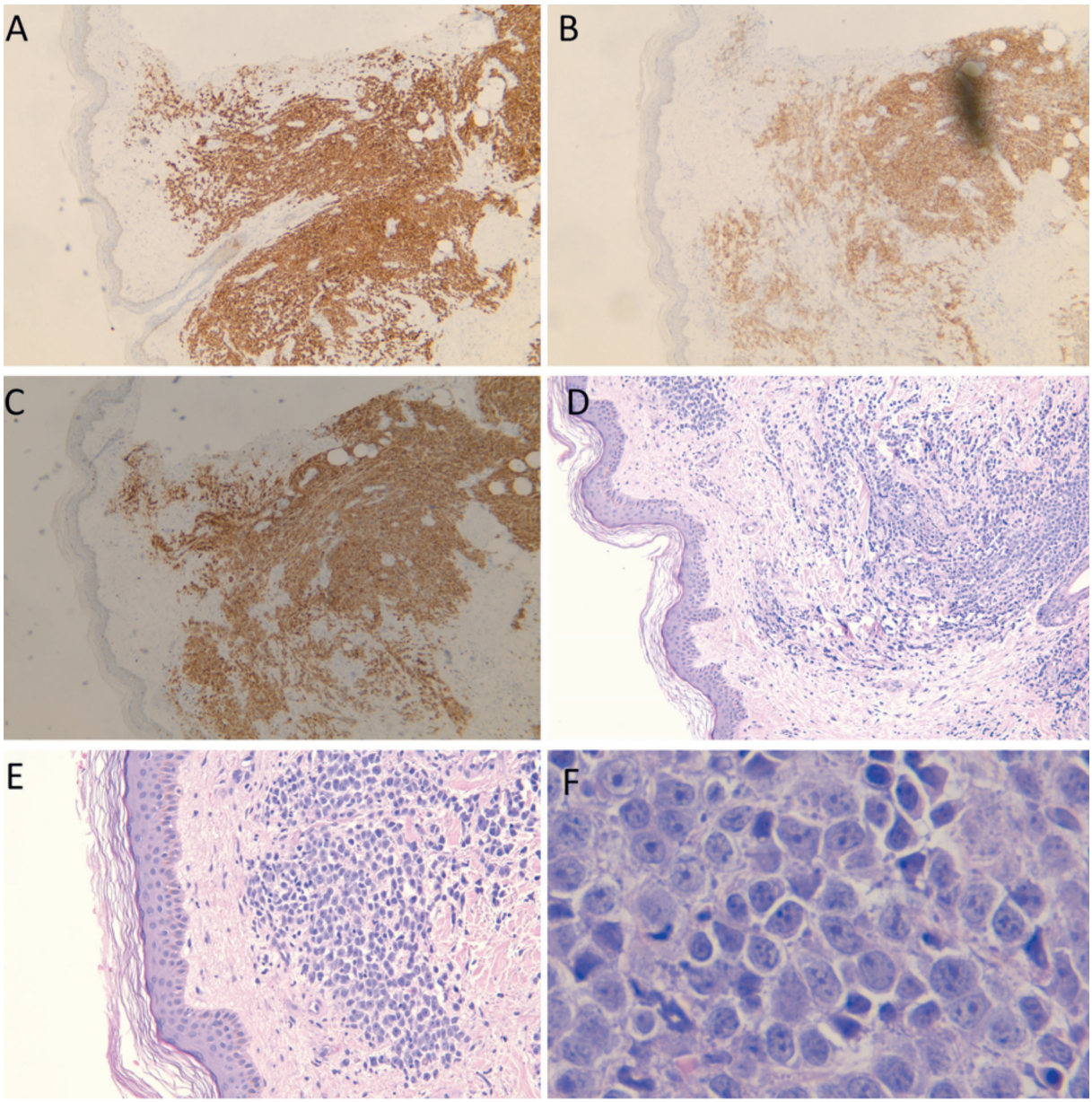

Figure 3. Histopathology of primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) in our patient. Positive staining for Bcl-2 **(A)**, CD-20 **(B)**. Staining for Ki-67 showed an intense nuclear reaction in almost 100% of lymphoma cells **(C)**. Highly atypical infiltration of large lymphocytes growing in the form of discohesive sheets of cells infiltrating the dermis, with spared epidermis — magnification ×10 **(D)**; magnification ×20 **(E)**. Lymphocytic infiltrate is composed of large, highly atypical cells with immunoblast (single nucleus) and centroblast (multiple, small nuclei) morphologies **(F)**

to stage III lymphedema [12]. They occur after a rather long course of lymphedema and disappear or decrease after compression therapy. Nevertheless, we would like to point out the similarity between these two skin abnormalities and the importance of properly performed diagnostics, including an early skin biopsy. Figure 4 presents photos of warty overgrowths in the course of lymphedema, which may imitate skin lesions in the course of PCDLBCL-LT. In other reports, it was pointed out that skin lesions in the course of PCDLBCL-LT may also mimic such diseases as cellulitis, sporotrichosis [13], DVT, lymphangiosarcoma (which was also initially taken into account in the differential diagnosis in our patient) or even erythema migrans, which is often observed in Lyme disease [10]. Taking all this into account, the initial diagnosis of PCDLBCL-LT can be difficult and often may be preceded by numerous misdiagnoses.

Unilateral lower extremity lymphedema as the first and initially the only symptom of PCDLBCL-LT in our patient additionally hindered the diagnosis. Malignancy and its treatment is the most common cause of secondary lymphedema in developed countries [14, 15].

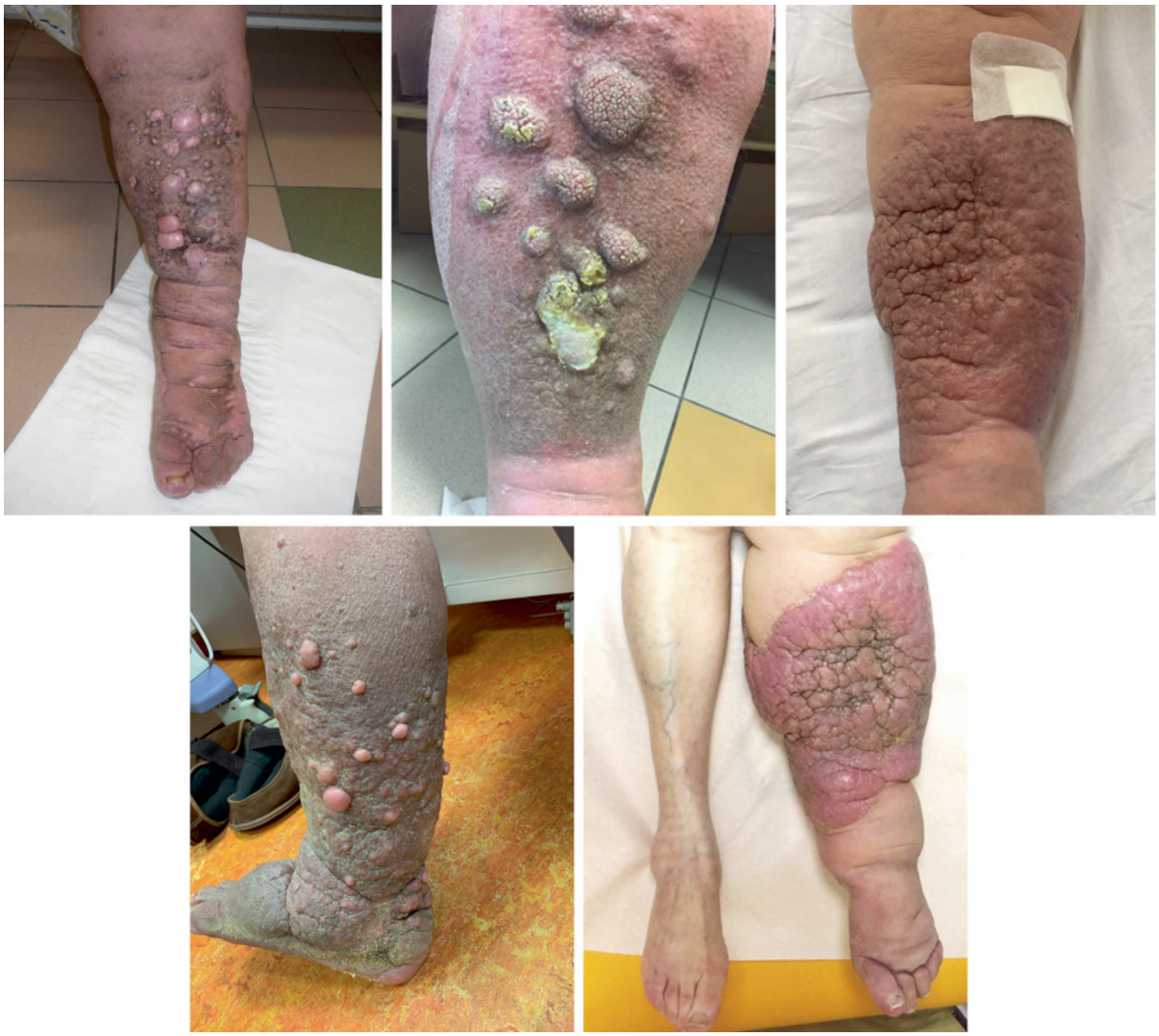

Figure 4. Warty overgrowths in the course of long-standing lymphedema in other patients admitted to our department, which may resemble skin lesions in primary cutaneous diffuse large B-cell lymphoma, leg type (PCLDBCL-LT)

However, malignant lymphedema is usually accompanied by other symptoms of systemic involvement. Lymphedema in the course of lymphoma is a result of obstruction of lymphatic vessels by cancer cells. A retrospective study of 4676 patients with lymphedema showed that 11 of them had lymphoedema caused or aggravated by lymphoma, including 1 case of upper limb edema, 9 cases of lower limb edema and 1 case of systemic edema. However, in patients from this study, apart from lymphedema, clinical symptoms such as weakness, emaciation, pain or lymphadenopathy were also observed [16]. In our patient, lymphedema and skin lesions were the only symptoms of PCDLBCL-LT. Hawkins et al. [17] presented ten cases of unilateral leg edema as the only symptom of lymphoma. However, our case refers to primary cutaneous lymphoma and to the best of our knowledge, there has not been a reported case of unilateral lymphedema as the initial symptom of PCDLBCL-LT.

On the contrary, there are several reports that PCDLBCL-LT may be a rare complication of long-standing lymphedema [18]. Thirteen such cases were described in the literature [19]. The time between the occurrence of lymphedema and the development of PCDLBCL-LT skin lesions ranged from 40 years to only 1 year [19, 20]. In general, long-standing congenital or acquired lymphedema is a well-known risk factor for many other malignancies, including lymphangiosarcoma, squamous cell carcinoma, malignant melanoma, and Kaposi's sarcoma [18]. Impaired lymph drainage may result in an area prone to cancer, including lymphoma. Considering that lymphedema was the first symptom in our patient, it cannot be ruled out that PCDLBCL-LT may be a complication of lymphatic system insufficiency also in our case. However, the absence of another

cause of lymphedema in our patient and the short time between the onset of lymphedema and the appearance of skin lesions rather preclude such a sequence of events.

It is also worth noting that our patient used MTX as a treatment for rheumatoid arthritis for 27 years. There are reports about lymphoproliferative disorder (LPD) which occasionally develop in rheumatoid arthritis as induced by MTX (MTX-associated LPD; MTX-LPD) [21–24]. As in our patient, approximately half of MTX-LPD cases occur at primary extranodal sites, including the skin [21]. It has also been reported that discontinuation of MTX treatment results in spontaneous remission in many patients with MTX-LPD, without additional treatment [21, 25, 26]. In our patient, immediately after establishing the diagnosis, MTX was discontinued, however, taking into account the extent of skin lesions in our patient, it was decided to start chemotherapy.

The optimal management for PCDLBCL-LT includes immunochemotherapy, consisting of R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) as the first-line treatment and radiotherapy as a therapeutic option. A large study showed that the use of the R-CHOP regimen resulted in an increase in the 5-year survival rate from 46% to 66% [27]. Early initiation of treatment reduces the risk of extracutaneous dissemination, and thus increases the chances of complete remission [27]. According to the literature, the time from onset of symptoms to diagnosis and treatment of primary cutaneous lymphomas ranges from 1 to 24 months, with a median of 7 months [16].

In conclusion, PCDLBCL-LT may cause many diagnostic difficulties, therefore, increased clinical awareness of physicians of all specialties is required that this neoplasm should be considered in the differential diagnosis in patients with unilateral lower extremity lymphedema. Delay in proper diagnosis has a significant impact on prognosis.

Conflict of interest

None.

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VIA MEDICA

CASE REPORT

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Isolated thigh ischemia in the course of iliofemoral arterial obstruction

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Abstract

A 72-year-old female presented rapidly developing ischemia of the skin and subcutaneous tissue of the antero--medial aspect of a thigh. An atypical clinical manifestation of ischemia led to delayed diagnosis and treatment that resulted in the development of large tissue loss in the anteromedial aspect of the thigh. Endovascular recanalization of recurrent occlusion in the ilio-femoral segment with rotational thrombectomy together with a multi-step local surgical treatment resulted in healing of the lesion.

Key words: chronic limb-threatening ischemia; thigh necrosis; thigh ischemia; percutaneous rotational thrombectomy

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Introduction

Chronic Limb Threatening Ischaemia (CLTI) most commonly results from the progression of atherosclerotic occlusive lesions in the arteries that supply blood to the limb [1]. The estimated incidence of the disease is 500–1000 per one million individuals per year [2]. The most important risk factors are smoking, older age, diabetes, and dyslipidemia [3, 4]. The disease most commonly manifests with rest pain followed by ulcers and gangrene. Once these lesions occur limb loss is imminent unless promptly revascularized [5]. Typically, the rest pain and gangrene affect the distal parts of the limb such as the toes, forefoot, or heel [6]. With a prolonged duration of ischemia, the lesions extend to the more proximal and deeper structures [7]. The purpose of this paper is to present a case of an atypical clinical presentation of recurrent CLTI with rest pain and gangrenous lesions affecting only the anterior surface of the thigh that was successfully treated with advanced endovascular techniques.

Case report

A seventy-two-year-old woman presented to a vascular surgery department because of severe pain in an anterior aspect of her right thigh. Seven months earlier because of an exacerbation of chronic right limb ischemia manifested by a short distance intermittent claudication and rest pain at night, she had undergone an endarterectomy of the external iliac artery (EIA) and common femoral artery (CFA) through a femoral approach. Due to proximal residual stenosis in the common iliac artery (CIA), a balloon expandable stent (9 × 58 mm) had been implanted. At that time superficial femoral artery (SFA), deep femoral (DFA), and popliteal artery (PA) were patent without any significant stenosis. Both surgery and postoperative course were uneventful, and cessation of the patient's complaints

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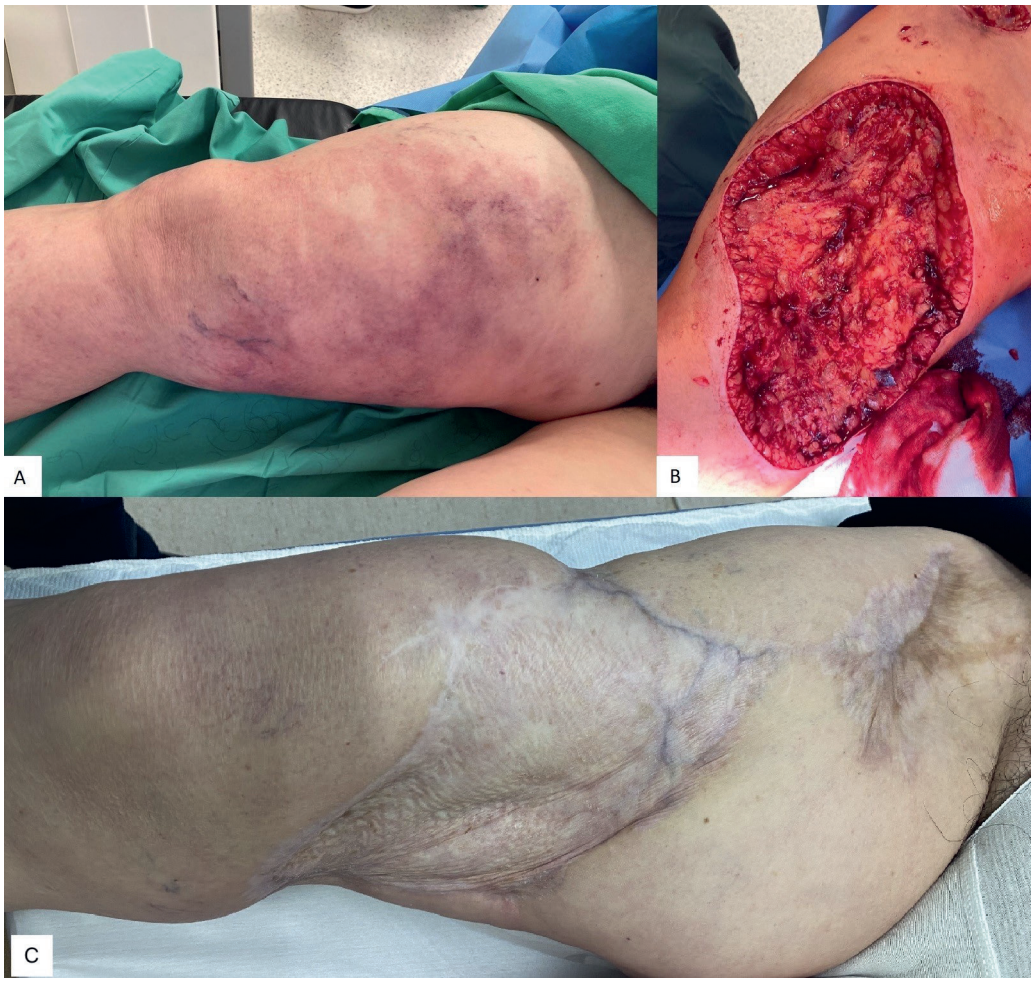

Figure 1. A. Cyanosis and edema of the anteromedial surface of the right thigh directly before surgical excision. **B.** Wound of the anteromedial surface of the right thigh directly after surgical excision. **C.** Completely healed thigh

was accomplished. Clopidogrel 75 mg and ASA 75 mg once daily and walking exercises along with cessation of smoking were recommended. Her past medical history included also percutaneous coronary intervention with drug-eluting stent implantation 10 years earlier and treatment for hypothyroidism. The patient presented typical vascular risks factors such as smoking, obesity, and hypertension.

On physical examination, tenderness, edema, and slight cyanosis on the anterior aspect of the right thigh were found. The temperature of the overlying skin was normal. The distal part of the limb was well perfused with a capillary refilling time below 2 seconds. Assuming that the patient's complaints did not result from ischemia anti-inflammatory and analgesic medications were recommended. The patient returned ten days later because of unremitting pain and extension of edema and cyanosis of the right thigh (Fig. 1A). The patient was afebrile and in a good general state. Angiography showed good patency of CIA, CIA stent, and internal iliac artery (IIA). EIA, CFA, and proximal segments of DFA and SFA were tightly stenosed (Fig. 2A). Distal parts of DFA, SFA, and PA and their branches were patent without any significant stenosis (Fig. 2B). Apart from increased concentration of C-reactive protein to 41,1 mg/l and mild anemia with hemoglobin of 10,7 g/dl, the results of laboratory tests were including serum creatinine, leucocytes, and procalcitonin were within normal limits. Percutaneous balloon angioplasty of EIA, CFA, and proximal segments of DFA and SFA with simultaneous excision of the affected area of the right thigh and groin was performed. The affected tissue had the appearance of skin and fat necrosis and involved only the skin and subcutaneous tissue without fascia and muscle involvement (Fig. 1B). Samples of excised tissue were sent for culture and intravenous treatment with clindamycin and ceftriaxone was started. On the 13th postoperative day, after the preparation with vacuum

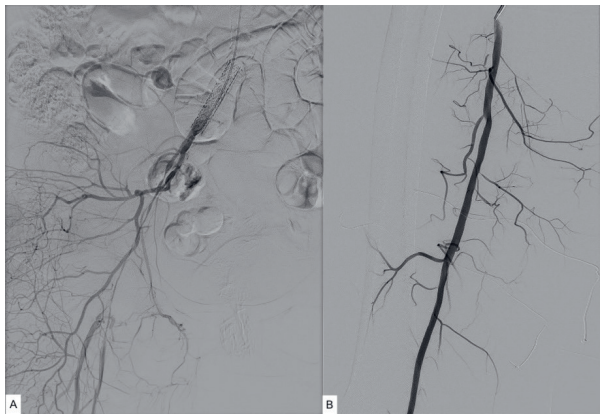

Figure 2. A. Intraprocedural arteriography showing patent common iliac and internal iliac arteries and tight stenosis of external iliac, common femoral, and proximal segments of deep femoral, and superficial femoral arteries. **B.** Distal parts of deep femoral and superficial femoral arteries and popliteal artery and their branches were patent without any significant stenosis

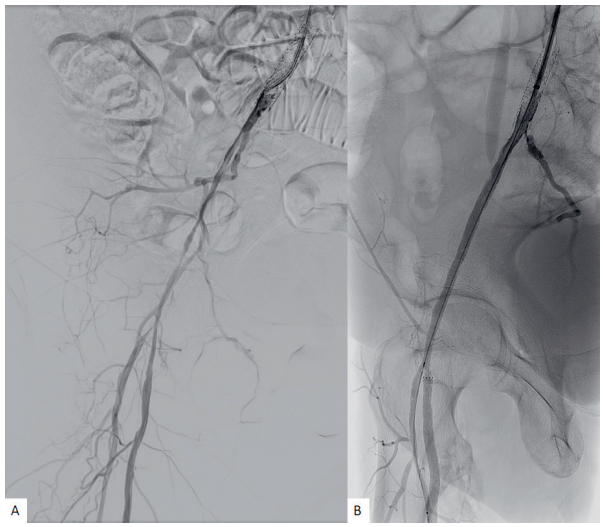

Figure 3. A. Intraprocedural arteriography showing critical restenosis of external iliac, common femoral, and deep femoral arteries. **B.** Intraprocedural arteriography after percutaneous rotational thrombectomy and superficial femoral artery stent implantation

therapy, the wound was covered with a split-thickness skin graft that healed the wound. Wound cultures were negative. The tissue culture for Actinomyces was also negative. The histopathology examination revealed the presence of foci of skin and fatty tissue necrosis with the formation of micro-abscesses.

Four months later the patient was admitted again because of the severe pain, necrosis lesions, and episodes of bleeding from the previously healed ulcer site. CT angiography showed again patent CIA and IIA, critically stenosed EIA, CFA, and proximal segments of DFA and SFA. Distal parts of DFA, SFA, and PA and their branches were patent without any significant stenosis. The wound was debrided, and samples were sent for microbiological examination. The culture revealed polymicrobial flora: *Enterobacter Cloacae ssp.*, *Staphylococcus haemolyticus* MRCNS, and *Staphylococcus epidermidis*. Despite repeated debridement and culture-guided intravenous antibiotic therapy the lesions were not healing. Taking into account the early recurrence of stenosis it was assumed that it was due to either thrombosis or intimal hyperplasia. Because of the tissue scaring after the previous procedures and the ulceration in the groin, it was decided to treat the patient endovascularly (Fig. 3A). Through a left axillary artery, a percutaneous rotational thrombectomy of right EIA, CFA, and proximal segments of DFA and SFA with Rotarex® S 8 Fr (Straub Medical) was performed. Due to a suboptimal result of thrombectomy an 8 mm self-expanding stent (Epic, Boston Scientific) was implanted in the EIA and a 6 mm self-expanding stent (Zilver Flex, Cook) was implanted in the proximal portion of SFA (Fig. 3B).

After the revascularization and debridement, the healing of the lesion was observed. Four months after the percutaneous thrombectomy the ulcer healed completely. During the 24-month follow-up, the patient remains asymptomatic without recurrence of the thigh ulceration (Fig. 1C).

Discussion

This paper reports a case of an atypical presentation of CLTI. The clinical signs of CLTI such as ulcers and gangrene most frequently affect the distal parts of the limb and penetrate to the deeper layers. In the described case the lesions involved only the skin and subcutaneous tissue of the anterior aspect of the thigh with uncompromised perfusion of the muscle of the thigh and of the distal limb. Due to atypical localization, the ischemia was initially erroneously excluded as the responsible factor and other causes of necrosis of subcutaneous tissue such as necrotizing fasciitis, actinomycosis, Clostridial cellulitis or myonecrosis or cellulitis caused by other pathogens was initially considered.

Due to the good general condition of the patient and the absence of characteristic signs such as crepitations, foul-smelling discharge, and hemorrhagic bullae as well as negative cultures Clostridial infection was discarded in the first place [8]. Actinomycosis, a disease caused by the anaerobic bacteria Actinomyces Israeli could have also given an observed clinical picture. The infection spreads by continuity provoking an inflammatory process with the formation of fistulae and abscesses discharging thick-yellow exudate. In the presented case a yellow exudate was absent and the Actinomyces

Israeli was not cultured. The inflammation of the skin and subcutaneous tissue could also have been caused by necrotizing fasciitis a polymicrobial infection of fascia and muscles characterized by rapidly progressing deterioration [9]. In our patients, the clinical progression was rather slow and neither fascia nor muscles were involved. Moreover, the culture of samples taken at the beginning of the disease was negative. Cellulitis due to other pathogens, mainly *Staphylococcus aureus* and *Streptococcus pyogenes*, was also considered [10]. This disease causes typical signs of inflammation such as local heat, redness, swelling, and pain. It is frequently preceded by minor trauma or bite [11]. In the present case, there was no history of trauma or bite, local heat was absent and, to be said again, cultures were negative. Normal levels of leucocytes and procalcitonin also argued against infection as a cause of observed symptoms. Most of all the healing of the wound after the recanalization of the external iliac artery and the recurrence of ulceration after its restenosis supports the main role of ischemia in the development of observed lesions. Between the 13th day and the 4th month after the index procedure, the patient was free of complaints which probably correspond to the time required for restenosis to develop and become clinically apparent.

The skin of the anteromedial surface of the thigh is perfused by the perforating arteries taking off mainly from SFA and DFA that were patent in the described case [12]. Moreover, the flow in these arteries as well as in the popliteal and tibial arteries must have been sufficient to maintain a satisfactory blood supply to the distal part of the limb. It could have been supposed that the perforating arteries had been injured during the previous endarterectomy. These arteries however whose number may vary from 8 to 14 are localized mainly in the mid-thigh region where the SFA was not exposed [13]. Moreover some of these arteries, so-called musculocutaneous perforators, supply blood also to the thigh muscles that did not suffer from ischemia in the presented case [14]. Also in arteriography, all branches of DFA and SFA were patent. The most probable explanation for observed ischemic lesions was a decrease in skin perfusion induced by compromised inflow. Clinical improvement after the restoration of inflow with subsequent deterioration with restenosis and ultimate healing after successful treatment of restenosis seem to confirm this hypothesis. Thus, occlusion of the external iliac and common femoral arteries may have an atypical clinical presentation in the form of progressive ischemia of the anterior surface of the thigh.

In a case of a subacute occlusion of the EIA surgical thrombendarterectomy or iliofemoral prosthetic graft would be probably the best and the most durable solution. However, because of the presence of the ulceration in the groin region, these procedures would be associated with a great risk of complications such as impaired wound healing or graft infection which may have disastrous consequences. Due to the subacute nature of arterial obstruction catheter-directed thrombolysis would have been unsuccessful and balloon angioplasty with stent implantation would have been associated with a risk of peripheral embolization. Percutaneous rotational thrombectomy is based on the action of a helical Archimedes screw that enables detachment of the occluding material, its aspiration and fragmentation, and transportation of the material out of the patient's body [15]. The use of percutaneous rotational thrombectomy removed almost completely the occluding lesion and allowed for safe and effective balloon angioplasty with stent implantation [16].

Conclusions

Chronic limb-threatening ischemia may have an atypical clinical manifestation with isolated involvement of the skin of the thigh and absence of distal limb ischemia. Percutaneous rotational thrombectomy is a safe and effective method of treatment of subacute arterial occlusion.

Conflict of interest

None.

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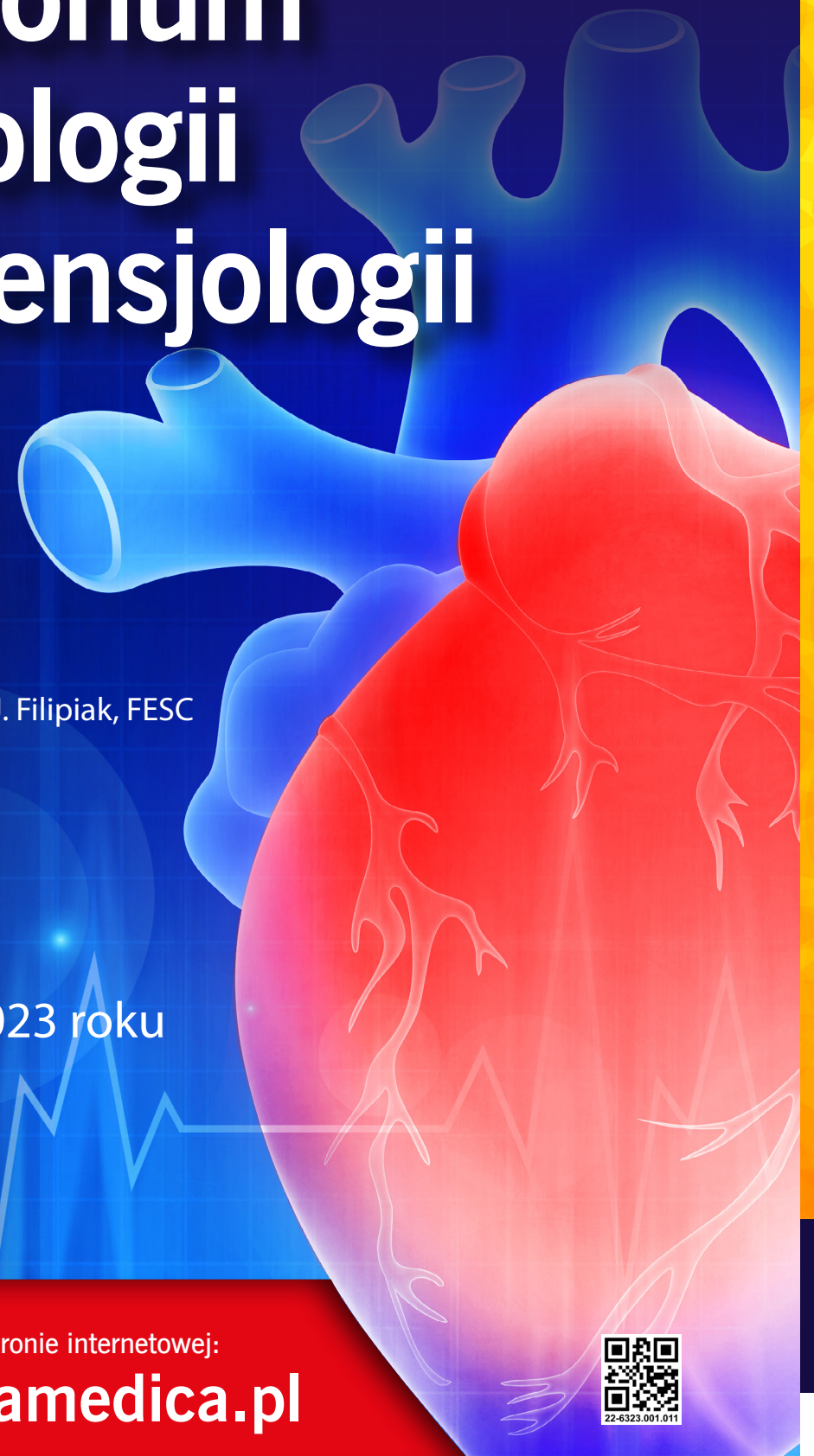

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