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Thromboangiitis obliterans (Buerger's disease) - a review

1. Rafał Bogacz MD, https://orcid.org/0000-0002-4010-8943 Lower Silesian Oncology Center in Wrocław, Plac Ludwika Hirszfelda 12, 53-413 Wrocław,
e-mail: rafalbogacz.rb@gmail.com

2. Magdalena Gaik MD, https://orcid.org/0000-0003-3922-9016 Lower Silesian Oncology Center in Wrocław, Plac Ludwika Hirszfelda 12, 53-413 Wrocław,
e-mail: gaikmag@gmail.com

3. Ewa Uram MD, https://orcid.org/0009-0008-6460-8150 Lower Silesian Oncology Center in Wrocław, Plac Ludwika Hirszfelda 12, 53-413 Wrocław,
e-mail: ewa.uram@gmail.com

4. Inga Magda MD, https://orcid.org/0009-0004-5413-6656 5 Military Clinical Hospital SPZOZ, Wrocławska 1-3, 30-901 Kraków
e-mail: inga.magda21@gmail.com

5. Justyna Woźniak MD, https://orcid.org/0000-0003-1386-6009 Wrocław Medical University Wybrzeże L. Pasteura 1, 50-367 Wrocław,
e-mail: justyna.joanna.wozniak@gmail.com

6. Karol Womperski MD, https://orcid.org/0000-0001-9612-2974 Wrocław Medical University Wybrzeże L. Pasteura 1, 50-367 Wrocław,
e-mail: karol.womperski@gmail.com

7. Magdalena Osuch MD, https://orcid.org/0000-0002-9837-3723 J. Dietl Specialist Hospital, Skarbowa 4, 31-121 Kraków
e-mail: magdalena.osuch17@gmail.com

Corresponding author
Rafał Bogacz MD, +48605138877, rafalbogacz.rb@gmail.com
Lower Silesian Oncology Center in Wrocław, Plac Ludwika Hirszfelda 12, 53-413 Wrocław

Abstract

Introduction: Thromboangiitis obliterans (Buerger's disease) is a segmental, multilocular, nonatherosclerotic inflammatory disease that most commonly affects small and medium sized arteries, veins and nerves of the extremities. The disease is spread worldwide and mainly affects young male tobacco smokers.

Aim of study: In this review we gather and summarize available knowledge about pathogenesis, diagnosis and methods of treatment of Thromboangiitis obliterans.

Methods and materials: Search of the articles in PubMed and GoogleScholar databases was performed using following keywords: Thromboangitis obliterans; Buerger's disease; Thromboangitis Obliterans pathogenesis; Thromboangitis Obliterans diagnosis; Thromboangitis Obliterans treatment; Thromboangitis Obliterans pathophysiology; Thromboangitis Obliterans symptoms; Thromboangitis Obliterans epidemiology; Thromboangitis Obliterans risk factors; The most relevant to the topic articles were included.

Summary: Even though the causes of the disease remain unclear and treatment is still difficult, there are new experimental methods of treatment being researched that may bring a breakthrough in the future.

Keywords: Thromboangiitis obliterans; Buerger's disease; Thromboangitis diagnosis; Thromboangitis treatment

Introduction and purpose of the study

Thromboangiitis obliterans was first described by Felix von Winiwarter in 1879 [1]. It's also known as Buerger's disease after american surgeon Leon Buerger whose research on this disease highly contributed to the state of knowledge on the subject we have today [2]. The purpose of this paper is to gather and present current knowledge on diagnosis and treatment of Thromboangiitis obliterans through review of available literature.

Methods

Search of the articles in PubMed and GoogleScholar databases was performed using following keywords: Thromboangiitis obliterans; Buerger's disease; Thromboangitis Obliterans pathogenesis; Thromboangitis Obliterans diagnosis; Thromboangitis Obliterans treatment; Thromboangitis Obliterans pathophysiology; Thromboangitis Obliterans symptoms; Thromboangitis Obliterans epidemiology; Thromboangitis Obliterans risk factors; The most relevant to the topic articles were included.

Definition, pathology and pathogenesis

Thromboangiitis obliterans (TAO) is a segmental, multilocular, nonatherosclerotic inflammatory disease that most commonly affects small and medium sized arteries, veins and nerves of the extremities. [3,4,5] TAO differs from other forms of vasculitis. The thrombi in Buerger's disease are inflammatory and highly cellular with relative sparing of the blood vessel wall [3].

The cause of Buerger's disease remains unknown but there is a strong association between exposure to tobacco and disease occurrence[6]. Despite the fact that acute-phase reactants such as C-reactive protein and commonly measured autoantibodies are usually normal or negative (what makes diagnosis impossible based solely on biochemical blood test results) it is believed that abnormalities in immunoreactive process drive the inflammatory reaction [4]. Adar et al. have shown that patients with TAO present increased cellular immunity to types I and III collagen compared to those who have atherosclerosis [7]. Moreover Eichhorn et al. detected high titers of anti endothelial cell antibodies in patients with TAO [8]. Patients with Buerger's disease have poor endothelium-dependent vasorelaxation in their peripheral vasculature [9]. Plethysmography was used to assess forearm blood flow in the unaffected limb following the administration of vasodilators: sodium nitroprusside (endothelium-independent) and acetylcholine (endothelium-dependent), were infused. Patients with Thromboangiitis obliterans had a lower increase in forearm blood flow in response to

intraarterial acetylcholine than healthy individuals (14.1 vs. 22.9 ml per minute per deciliter of tissue volume, P0.01), and endothelium-dependent vasodilatation is impaired even in the nondiseased limbs of these patients. The increase in forearm blood flow in response to sodium nitroprusside was not significantly different between patients and healthy individuals (13.1 and 16.3 ml per minute per deciliter, respectively), which indicates that nonendothelial mechanisms of vasodilation are intact.

Acute, subacute and chronic phases of the disease can be distinguished. Depending on the phase in which the histopathological examination is performed, the results and the image differ. The acute phase is composed of an occlusive, highly cellular inflammatory thrombus. Polymorphonuclear neutrophils, microabscesses and multinucleated giant cells are often present. The chronic phase is characterized by organized thrombus and vascular fibrosis that may mimic atherosclerosis but TAO patients preserve the internal elastic lamina [4, 9-11].

Epidemiology

TAO mainly affects young male tobacco smokers, however cases of the disease in people chewing tobacco or taking snuff have also been reported[12]. Some studies indicate that the disease is increasingly affecting females [13,14] The disease occurs worldwide, but in some regions, such as the Far East and the Middle East, it is more common than in the United States or Western Europe [15]. The prevalence of the disease among all patients with peripheral arterial disease ranges from values as low as 0.5 to 5.6% in Western Europe to values as high as 45 to 63% in India, 16 to 66% in Korea and Japan, and 80% among Ashkenazi Jews [16]

Clinical features

TAO usually occurs in young males before the age of 45. The disease most commonly progresses with periods of exacerbation and remission. Initial signs may include paraesthesia, intermittent claudication, neuropathic pain due to nerve ischemia. At a later stage, also pain at rest. Vasomotor disorders may occur - Raynaud's phenomenon. Physical examination reveals pulse abnormalities in the dorsal pedis, tibial posterior, popliteal, radial, and ulnar arteries. Some patients have symptoms of migratory superficial phlebitis in the form of red, tender nodules. Ischaemia of the distal parts of the limbs in the later stage of the disease can lead to ischemic ulceration, tissue necrosis and amputation.

Diagnosis

Diagnosis is based on examination of the patient, laboratory tests, imaging tests such as arteriography or Doppler ultrasonography and on histopathological examination of a section of diseased vessels in the acute phase of the disease. Complete blood count with differential, glucose level, liver enzymes and renal function parameters, acute phase reactant level, as well as rheumatoid factor, ANA antibodies, Scl-70 antibodies should be performed (the disease should be differentiated from systemic scleroderma). Screening for hypercoagulopathy, including antiphospholipid antibodies is recommended. Acute phase proteins such as CRP are usually normal or may be slightly elevated during exacerbation periods. Transthoracic or transesophageal echocardiography and arteriography should be carried out if a proximal source of embolization is suspected. Arteriography often shows multiple stenoses in the distal limb blood supply and normal proximal arteries with no evidence of atherosclerosis, but it does not allow to make a diagnosis solely on its basis [17]. Allen's test should be performed in patients with leg ulcers [18]. A positive test result suggests the diagnosis of TAO.

Diagnostic criteria

Diagnostic criteria proposed by several authors can be found in the literature:

- Mills and Porter [19] have proposed major and minor criteria. Their major criteria include: onset of distal extremity ischemic symptoms before the age of 45 years, tobacco abuse, undiseased arteries proximal to popliteal or brachial level, objective documentation of distal occlusive disease by four limb plethysmography, arteriography and/or histopathology and exclusion of proximal embolic source, trauma and local lesions, autoimmune disease, hypercoagulable states, and atherosclerosis (diabetes, hyperlipidemia, renal failure, hypertension). Their minor criteria include: migratory superficial phlebitis, Raynaud's syndrome, upper extremity involvement and instep claudication.

- Papa et al. [20] have suggested a scoring system that would give positive points to patients presenting: age of onset less than 30/30-40 years, ischemic symptoms of the limbs, present Raynaud's syndrome, typical angiography/biopsy image and negative points to patients presenting: late age of onset, female/non-smokers, absent brachial/femoral pulse

- Shinoya's [21] criteria are: a history of smoking, onset before the age of 50 years, infrapopliteal arterial occlusions, either arm involvement or phlebitis migrans, and the absence of risk factors for atherosclerosis other than smoking

- Olin et al. [3] have proposed: an age of less than 45 years and current (or recent) history of tobacco use; the presence of distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers, or gangrene) documented by noninvasive vascular testing; exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus by laboratory tests; exclusion of a proximal source of emboli by echocardiography and arteriography; and consistent arteriographic findings in the clinically involved and noninvolved limbs.

Treatment

The most important factor in treatment is absolute cessation of smoking. Using tobacco in any form should be discontinued. It has proven to be the best way to stop disease progression and avoid limb amputation. Even smoking substitutes containing nicotine can keep the disease active. [22, 23] In order to relieve the pain associated with ischemia and ulceration of the limbs, analgesics should be used: paracetamol, opiate drugs, in some cases even epidural anesthesia. Antidepressants might be of additional value. Possible soft tissue and bone infections pose a major therapeutic difficulty. Antibiotic therapy should also include anaerobic bacteria in its spectrum.

Study by Fiessinger and Schafer [24] has shown that administration of iloprost (a synthetic analogue of prostacyclin PGI2) over 28 days was superior to aspirin and showed better results for patients with total relief of pain at rest and complete healing of all trophic changes. Moreover, only 6 percent of patients receiving iloprost required amputation compared to 18 percent receiving aspirin. Trials of hemolytic treatment in small groups of patients with positive results have been reported, but further research is needed to determine the usefulness of this therapy [25,26]. Surgical revascularization is usually not possible due to the multifocal, segmental nature of the disease and the fact that it mainly affects small, distal vessels. Lumbar or thoracic sympathectomy has no established clinical value and is rarely performed. Sympathectomy has been shown to provide short-term pain relief and to promote ulcer healing in some patients with Buerger's disease, but no long-term benefit has been confirmed [27].

In recent years new experimental therapy methods have been published. For critical limb ischemia, including TAO, cell-based treatments using autologous progenitor cells extracted from bone marrow or peripheral blood have been recommended. The cell suspensions are injected intraarterially or intramuscularly along the vascular beds of the limbs. Metaanalyses have confirmed the viability and safety of cell-derived therapies in critical limb ischemia as well as their beneficial therapeutic effects such as pain control, ulcer healing, pain-free walking capacity, and amputation-free survival [28-31].

Bosentan, an endothelin receptor antagonist used in pulmonary artery hypertension was recently reported to have shown promising results in the treatment of digital ulcers in TAO patients [32, 33].

Summary

Over the years of research more knowledge about the pathogenesis of TAO has been gathered. Even though causes still remain unclear, better understanding of the nature of the disease and improvement of diagnostic methods allow for faster diagnosis of patients. Effective treatment remains the biggest challenge. Although smoking cessation is currently the best method to stop the progression of the disease and avoid complications, new treatments are being researched and may bring a breakthrough in the future.

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Author contribution:

1. Rafał Bogacz: project supervision, final version of manuscript (16%)
2. Magdalena Gaik: work integrity and coherence (14%)
3. Ewa Uram: analysis and interpretation of data (14%)
4. Inga Magda: writing of the manuscript (14%)
5. Justyna Woźniak: concept and design (14%)
6. Karol Womperski: data research and analysis (14%)
7. Magdalena Osuch: intellectual content and data research (14%)

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