The first report of a new disease that several years later would be named thromboangiitis obliterans (TAO) was made by a German pathologist Carl Friedländer in 1876; it was subsequently also reported by Viennese physician Felix von Winiwarter in 1879 [1]. Von Winiwarter pointed out characteristic features distinguishing this condition from atherosclerosis, specifically hypertrophy of the tunica intima, thrombosis and fibrosis of the vascular wall. The author believed that this disease resulted from excessive overgrowth of the tunica intima, and he therefore referred to it as endarteritis obliterans. However, the first report describing TAO was published by another Austrian, pathologist Leo Buerger, as part of a histological examination of eleven amputated limbs. His paper, entitled "Thromboangiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene", was published in 1908. In it he wrote: "There is an interesting group of cases characterized by typical symptoms which the Germans have described under the name »Spon- tan-gangrän«. […] The disease occurs frequently, although not exclusively, among the Polish and Russian Jews, and it is in the dispensaries and hospitals of New York City that we find a good opportunity for studying it in its two phases, namely in the period which precedes and in that which follows the onset of the gangrene" [2].

More than 120 years have passed since this description of TAO was published. During this period, have we gotten closer to understanding the reasons behind this condition or arrived at more appropriate diagnostic methods? It seems that a clearly affirmative answer cannot be given.
Epidemiological Problems

The actual prevalence of TAO has not been established precisely due to at least two reasons: 1. geographical differences in the prevalence of this condition, and 2. the lack of non-invasive diagnostic methods enabling differentiation between TAO and obliterative atherosclerosis in individuals with a mild degree of ischemia (e.g., stage IIA according to Fontaine). India, Korea and Japan have the highest prevalence of TAO (according to various authors up to 50% of patients with peripheral artery disease are affected), while the corresponding numbers for Western Europe are in the range of 0.50–5.6% [3]. Contrary to frequently repeated data in the literature (including data published by the authors of this review) regarding a particularly high prevalence of TAO among Ashkenazi Jews, the condition does not affect this group more frequently than the population of Western Europe, not exceeding 5% of individuals with peripheral artery disease, as was recently highlighted by Prof. Raphael Adar [4]. Furthermore, little data was gathered regarding the general population. In the 1970s and 1980s, the prevalence of TAO in North America was estimated at 8–11.6/100 000; it is known that this figure has decreased considerably in the last 30 years due to unexplained reasons [5].

A lower frequency of TAO diagnoses in the 1960s and 1970s (which can be called a “pseudo-decrease in incidence”) can be explained by the implementation of novel diagnostic methods. Józef Kaniak, a scientist experienced with TAO, wrote in the early 1980s: “Between 1928 and 1956, when the arteriographic examination was not performed so commonly, the diagnosis of Buerger’s disease was overused and this condition was ascribed to most cases of peripheral artery disease. Implementation of novel diagnostic methods and, in particular, angiographic examination, has revealed typical atherosclerotic lesions in many cases that were originally classified as Buerger’s disease” [6].

In contrast, the decrease in the incidence of TAO observed in the 1980s, although widely noted, is not so easy to explain. According to Wysokiński et al. [7], in the period from 1971 to 1980, 18% of all patients with peripheral artery disease treated at their facility in Wroclaw, Poland, were TAO patients, while in 1990 this percentage amounted to only 4%. In those authors’ opinion, the decrease was most evident in 1980–1986.

The decrease in the general incidence of TAO occurred simultaneously with a relative increase in the prevalence of this condition among women (Fig. 1). According to data collected by the Mayo Clinic, women comprised 15.8% of the newly diagnosed cases of TAO in the period from 1976 to 1980, while in 1996–1999 this percentage increased to 36.4% [8]. In a study by Sasaki et al. conducted in the Japanese population in the late 1990s [9], the percentage of women affected with TAO amounted to 9.3% and was several times higher than in the 1980s.

Table 1 summarizes the number of patients who were hospitalized due to TAO at the Clinic of Angiology, Arterial Hypertension and Diabetology at the Wroclaw Medical University between 2002 and 2010. As shown, only small fluctuations in the number of patients have occurred during recent years, with the rate of hospitalization amounting to approximately 20–30 individuals per year. After a transient increase in the percentage of women hospitalized due to TAO (up to 27% in 2003), no female patient with this condition has been hospitalized during the last two years. It is, however, difficult to assess whether this is an established tendency.

Table 1. Number of hospitalizations due to TAO at the Clinic of Angiology, Arterial Hypertension and Diabetology at Wroclaw Medical University (Poland) in 2002–2010

<table>
<thead>
<tr>
<th>Year</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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<tbody>
<tr>
<td>No. of hospitalizations</td>
<td>33</td>
<td>31</td>
<td>35</td>
<td>33</td>
<td>25</td>
<td>22</td>
<td>18</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>18</td>
<td>26</td>
<td>18</td>
<td>17</td>
<td>13</td>
<td>14</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Percentage of female patients (%)</td>
<td>21</td>
<td>27</td>
<td>15</td>
<td>5</td>
<td>6</td>
<td>15</td>
<td>7</td>
<td>0</td>
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</tr>
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Fig. 1. A 40-year-old female patient with a diagnosis of TAO and involvement of the hands and feet. Necrosis of the distal part of the forefinger; ischemia of all fingers of both hands (authors’ own image)
Is TAO an Infectious Disease?

In one of his later papers, Leo Buerger clearly suggested that TAO is an infectious condition, although he was unable to identify the microorganism responsible [10]. Numerous other authors have called the existence of this etiological factor into question, suggesting that Buerger was wrong. However, after 100 years of scientific research there is some evidence that supports the association between TAO and infection.

One of the important characteristics that distinguish individuals with TAO from other angiologic patients is a higher prevalence of periodontal disease, resulting from a lack of proper hygienic habits and tobacco smoking. For instance, in a study by Chen et al. [11] based on objective methods of assessing periodontal status, significant abnormalities were markedly more frequent in individuals with TAO than in smokers free from this condition (89.5% vs. 28%).

Another direction of research pertains to the presence of antiphospholipid antibodies in TAO patients. Maslowski et al. [19] observed that TAO patients are characterized by a markedly higher prevalence of anti-cardiolipin (aCL) antibodies (36%) as compared to patients with obliterator atherosclerosis (8%) or the controls (2%). In those authors’ opinion, higher titers of aCL are associated with a higher risk of major limb amputation (i.e., above the knee). Also, a previously mentioned study by Chen et al. [16] documented a higher prevalence of antibodies against β2-GPI in TAO patients. However, it has not been established thus far whether the presence of antiphospholipid antibodies is a secondary phenomenon, similar to many infectious diseases (such as HBV, HCV, HIV and CMV) [20] or autoimmune conditions (e.g. systemic lupus erythematosus). A literature review published by de Godoy et al. [21] suggests that diseases of the coagulation system and TAO constitute independent entities, and that the presence of aCL in TAO can only be associated with a more severe manifestation of TAO.

Coagulation Disorders in TAO

Many studies have documented an association between TAO and the presence of coagulation system abnormalities. The first group of those studies pertained to the presence of antiphospholipid antibodies in TAO patients. Undas et al. [1] revealed that TAO patients with higher titers of IgG antibodies against Treponema denticola, Porphyromonas gingivalis, and Actinobacillus actinomycetemcomitans as compared to the controls, and Iwai et al. [15] confirmed the presence of bacterial DNA (absent in healthy individuals) in 13 out of 14 specimens of involved arterial walls obtained from TAO patients. Aside from the immune response to the presence of bacterial antigens in the arterial wall, there is also a possibility that bacteria can induce the synthesis of autoantibodies in the mechanism of antigen mimicry. Chen et al. [16] analyzed the homology of amino acid sequences in P. gingivalis and T. denticola and that of β2-glycoprotein I (β2-GPI). They concluded that TAO is associated with a higher prevalence of antibodies against β2-GPI, along with greater severity of periodontal disease and higher antibody titers against the antigens of these bacteria. This finding can explain previous literature reports (see below) of a higher prevalence of antiphospholipid antibodies in this group of patients.

The hypothesis of the pathogenic influence of bacteria forming physiological oral microflora in individuals with TAO is further supported by findings from Kubota et al. [17]. Four weeks after the intravenous administration of P. gingivalis to rats, thrombosis was observed in 83.3% of popliteal artery specimens. A higher predisposition to the aforementioned autoimmune reaction, observed in some populations, may result from the influence of genetic factors. For instance, Chen et al. [18] observed that TAO patients are characterized by a higher prevalence of the TT allele of the CD14 monocyte receptor, which is responsible for binding bacterial lipopolysaccharide.
Injury to the Vascular Endothelium and Activation of the Inflammatory Response

The functioning of the vascular endothelium can be assessed by means of both imaging studies and laboratory tests. Ultrasonography is a method used to assess the response of the brachial artery to post-ischemic reactive hyperemia (flow-mediated dilatation, or FMD). Idei et al. [28] revealed that patients with TAO have lower FMD values as compared to the controls, although they do not differ significantly from individuals with obliterate atherosclerosis in terms of this parameter. Importantly, the response of the brachial artery wall to nitroglycerine administration remained unchanged, suggesting that dilatation dysfunction results predominantly from endothelial injury. In contrast, Azizi et al. [29] did not observe altered responsiveness of the brachial artery to ischemia, although they documented higher rigidity of the aorta in TAO patients.

A markedly higher number of studies address the morphological and biochemical markers of endothelial injury and dysfunction. Halacheva et al. [30] used histochemical methods and electron microscopy to determine that TAO is associated with elevated expression of both selectin E (responsible for the initial stage of leukocyte adhesion to endothelial cells and not detected under physiological conditions) and ICAM-1 and VCAM-1 integrins (providing strong adhesion of leukocytes to the endothelial surface), along with the morphological features of endothelial activation. In another study [31], the expression of VCAM-1 was revealed in the region of tunica intima (patent vessels) and vasa vasorum (obliterated vessels). This probably leads to an increase in the concentration of circulating adhesion molecules, as observed by Czarnacki et al. [32] with regard to selectins P, L and E.

Only a few authors have analyzed the concentrations of cytokines in the course of TAO. Slavov et al. [33] revealed that TAO patients are characterized by an elevated serum concentration of interleukin 6 (IL-6), along with enhanced synthesis of IL-6 and IL-12 by peripheral blood mononuclear cells and reduced expression of IL-10. Czarnacki et al. [32] also observed elevated concentrations of endothelin 1, but only in TAO patients with active ischemic ulceration.

Possible relationships between tobacco use and TAO include an allergic-hyperergic reaction to antigens in cigarette smoke, the presence of antielastin antibodies, decreased activity of proteinase inhibitors of and a genetic propensity (certain HLA antigens) [34].

Clinical Signs

One of the largest studies of TAO patients (n = 850) was presented by Sasaki et al. [9] from Japan. At diagnosis, 8% of the patients were
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Qualified as Fontaine’s stage I and 29.6% to stage II; 23.9% had resting pain and 38.1% showed trophic ischemic lesions. Involvement of the upper limbs and migrating phlebitis were observed in 25% and 16% of the cases, respectively (Fig. 2). Ates et al. [35] reported different characteristics of the disease in a study of a Turkish population (n = 344). The most frequent manifestations in this group included cooling of the affected limb (90.6%), changes in skin coloration (84.3%) and ischemic ulceration (53.1%), followed by intermittent claudication (48.2%), and resting pain (46.5%); simultaneous involvement of upper and lower limbs (4.6%) or isolated involvement of upper limbs (2%) were rarely reported. An analysis of TAO patients treated at the present authors’ center between 1970 and 1995 (n = 377) identified intermittent claudication (44%) and paresthesia (15%) as the most frequent symptoms, followed by resting pain (9%) and ischemic ulceration (7%); migrating superficial phlebitis and Raynaud’s syndrome occurred in 23% and 2% of the patients, respectively [7].

However, these data refer to previous years and seem not to hold true for currently hospitalized patients. At present, most cases of TAO diagnosed in individuals with resting pain or ischemic ulceration represent higher stages of the disease. In the current authors’ opinion, the potential reasons for this situation include: 1. the development of ambulatory care for patients with peripheral artery disease and probable inclusion of TAO patients in the “preterm atherosclerosis” group; 2. limiting angiographic examination (or CT angiography) to cases of critical ischemia, which results in a lack of clear and irrefutable evidence needed for a diagnosis of TAO; 3. the increasing popularity of ultrasonographic examination, during which the features of TAO are sometimes difficult to observe; 4. caution in diagnosing this condition. However, since the therapeutic recommendations for the early stages of both TAO and “premature atherosclerosis” are quite similar (quitting smoking, antiplatelet agents, walking exercise) there are no perceived detrimental consequences for TAO patients.

TAO is rarely associated with the involvement of other vascular areas, e.g. celiac arteries, large vessels, or coronary arteries; in such cases the diagnosis is usually established post factum, based on the results of imaging studies.

Diagnostic Criteria

None of the diagnostic criteria for TAO have been accepted by the international community, although Shionoya’s criteria [36], Papa’s scoring system [37] and Olin’s criteria [3] are frequently referred to in the literature. Common features of all these systems include detecting the disease at 40 to 50 years of age, tobacco smoking and the presence of certain clinical and angiographic characteristic, along with the exclusion of diabetes and autoimmune disorders. However, the clinical manifestations of TAO reported in the last several years suggest that a change in attitude towards this condition is needed. Many patients, particularly those with a history of ischemia-related amputation, show low levels of physical activity and develop obesity and carbohydrate metabolism disorders. Moreover, some patients show signs of a generalized atherosclerotic process co-existing with the features of TAO [38], pointing to the usefulness of the diagnostic criteria published by the Japanese Ministry of Health [9], rarely referred to in either Polish or international literature. Although characterized by a “more liberal” attitude towards diabetes and tobacco smoking, these guidelines precisely define the number of inclusion and exclusion criteria needed to diagnose TAO. Furthermore, the system requires an angiography (Table 2).

Corkscrew collaterals constitute such a specific characteristic of the disease that their shape serves as a criterion in the classification of clinical manifestations. Fujii et al. [39] identified four types of collaterals in TAO patients, differentiated by their helical sign; these collaterals are observed in 64% of the cases. Type I is characterized by a large helical sign and “tree-root” appearance, while type IV represents a tiny helical sign. In those authors’ opinion, types III and IV are a negative prognostic factor because they are associated with a high risk of ulceration: the presence of type III collaterals was associated with 4.64 OR of ulceration (95% CI: 1.63–48.52), and type IV with 11.33 OR (95% CI: 1.22–105.56). It is probable that the role of ultrasonography in the diagnosis and monitoring of TAO patients will increase in the future (Fig. 3).
Differential Diagnosis

From a practical point of view, in addition to obliterative atherosclerosis, the following important (but unfortunately, rarely included) conditions should also be considered in differential diagnosis.

**Thoracic Outlet Syndrome**

Thoracic outlet syndrome (TOS) is associated with considerable diagnostic difficulties. It results from neurovascular disorders within the upper limbs associated with the compression of a neurovascular bundle in the upper thoracic outlet. TOS can be classified as congenital (anatomical malformations, e.g. a cervical rib) or acquired (most commonly post-traumatic). Usually, the neurovascular bundle is compressed at a site of anatomical narrowing, such as the scalene fissure, the costocervical or coracothoracic space. In most cases (90–95%), it is manifested by neurological symptoms, with vascular involvement observed in 5–10% of the cases. Numbness and pain in the hands are among the reported symptoms; pain is exacerbated in certain positions (TAO patients also complain that there is an exacerbation of pain due to the elevation of limbs). CT angiography performed in a position that provokes the symptoms can be helpful in establishing a diagnosis by documenting the significant restriction in flow. In more advanced stages of the disease, associated with constant compression of the subclavian artery and sometimes with compensative development of a subclavian aneurysm, the symptoms of critical hand ischemia may develop (Fig. 4) [40].

**Peripheral Embolism and Atherothrombotic Embolism**

The diagnosis is usually unproblematic if these complications develop in an older individual, e.g. with atrial fibrillation or massive atherosclerotic...
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Problems with differentiating between these conditions and TAO can occur in the presence of a crossed (paradoxical) embolism, in young smokers and in individuals with a persistent foramen ovale, particularly co-existing with a flaccid inter-atrial septum (Fig. 5). However, the correct diagnosis is usually suggested by the rapid onset of the condition, the typical involvement of one site (e.g., one limb or finger) and the results of contrast echocardiography.

Drug-Induced Vasculitides

Drug-induced vasculitides caused by cannabis (cannabis arteritis) and cocaine are of growing importance, because they may be responsible for many cases of peripheral arterial insufficiency in adults under 50 years of age. In most cases of cannabis arteritis, claudication precedes the development of necrosis or gangrene of the toes, and often involves arteries below the knee (in ultrasonography or computed tomography, the lesions are indistinguishable from TAO). A history and toxicological profile are helpful, but making a correct diagnosis may be challenging [41].

Infectious Endocarditis

Infectious endocarditis (IE) is a septic condition that has a bacterial etiology in > 90% of the cases, and occasionally is of fungal origin. IE most commonly involves the aortic and mitral valves. Predisposing factors include congenital and acquired cardiac malformations, heart valve prostheses, immunosuppression, intracardiac electrode placement and intravenous drug abuse. Non-specific complaints (weakness, high-grade fever or persistent low-grade fever, increased perspiration, arthralgia and myalgia, loss of weight) predominate, along with symptoms associated with left heart involvement (murmurs associated with insufficiency of the involved valves, cardiac failure, embolic symptoms from CNS, celiac or limb arteries, including pain and peripheral vascular disorders, such as cutaneous and subungual splinter-like petechiae, painful, red Osler’s nodes localized on the fingers and toes, or non-painful hemorrhagic spots on the palms and soles – so-called Janeway lesions) [42]. In the case of an embolism caused by larger bacterial conglomerates, the signs of acute limb ischemia or peripheral microembolism can develop. The diagnosis is established on the basis of the clinical manifestations, the results of transthoracic or transesophageal echocardiography and blood culture. IE should be distinguished from the rare non-infectious Libman-Sacks endocarditis associated with systemic lupus erythematosus (SLE), in which papillomatous clots usually form on the mitral valve [42].

Popliteal Entrapment Syndrome

This anomaly develops predominantly in younger males (estimated prevalence 0.2–3.5%) and involves the segment of popliteal artery located within the popliteal fossa. Intermittent claudication is the most frequent manifestation, but cases of acute ischemia associated with popliteal artery thrombosis have also been reported. The diagnosis is based on angiography and ultrasonography performed on the dorsal and plantar flexure of the foot [43].
Takayasu’s Disease

This chronic large-vessel vasculitis usually affects younger women, who comprise 80–90% of all patients. Most commonly, the disease involves the aorta and the proximal segments of its branches, usually the carotid and subclavian arteries; however, cases of lower limb artery involvement within the aorto-iliac segment have also been reported. Initially, the symptoms are non-specific, subsequently progressing to symptoms associated with occlusion of the carotid and upper limb arteries. They can also encompass signs of CNS ischemia (focal disorders, vertigo, seizures), ophthalmic disturbances (blindness, glaucoma, cataract, numerous arteriovenous anastomoses of retinal vessels) and cardiac symptoms (injury to the aortic valve, arrhythmia, myocardial ischemia and heart failure) followed by arterial hypertension resulting from narrowing of the kidney artery, and complaints related to celiac artery involvement (paroxysmal stomach ache, diarrhea, bleeding from the alimentary tract). Frequently, individuals with more severe changes develop aneurysms that usually co-exist with multiple narrowed arterial lumina. The diagnosis can be supported by detecting the signs of activation of the inflammatory response and by imaging studies (ultrasonography, CT angiography and conventional angiography) revealing features that are absent in TAO patients: thickening of the vascular wall along with segmental smooth-walled narrowing, sometimes accompanied by dilatation of the vascular lumina [44].

Primary Systemic Small- and Medium-Vessel Vasculitis

Isolated cutaneous small-vessel vasculitis (previously referred to as leukocytoclastic vasculitis) is characterized by clinical manifestations that are different from those seen in TAO. Also, there are no signs of limb ischemia. At times, necrosis of a distal limb segments can be observed in the course of vasculitis associated with spontaneous mixed cryoglobulinemia (Fig. 6); however, the presence of cryoglobulins is detected in these cases, and the ankle-brachial index is normal. Aside from the presence of p-ANCA and c-ANCA type antibodies, the diagnosis of ANCA-positive inflammation (Wegener’s granulomatosis, Churg-Strauss syndrome, and microscopic vasculitis) can be suggested by co-existing features of internal organ involvement, most frequently glomerulonephritis [45]. Cutaneous polyarteritis nodosa, a form of medium-sized vasculitis, is characterized by the presence of livedo reticularis and necrotic lesions, particularly involving the calves, sometimes with concurrent systemic symptoms (arthralgia, fever), but without occlusion of the below-knee arteries. The diagnosis is made on the basis of histological examination. Behçet’s disease, another vasculitis affecting large-, medium- and small-sized vessels, can be distinguished from TAO on the basis of eye complications (uveitis, hypopyon), oral and urogenital aphthous ulcerations, as well as arthralgia; but superficial phlebitis can occur in both conditions [45].

Secondary Systemic Vasculitis

Secondary systemic vasculitis can involve a vessel of any size, but most commonly refers to small vessels; manifestations include erythema elevatum, nodes, urticarial efflorescence, livedo reticularis, or skin ulceration and necrosis. This condition can be associated with systemic connective tissue disorders (systemic sclerosis – Fig. 7), rheumatoid arthritis, SLE, Sjögren’s syndrome, PM/DM), non-specific enteritis, malignant neoplasms (usually lymphoma), infections (HCV, HBV, HIV), and can occur as an adverse reaction to prescription drugs. Non-inflammatory Raynaud’s microangiopathy is the predominant feature of systemic sclerosis (SSc), sometimes leading to chronic ischemia of fingers and the development of non-healing finger pad ulceration. Obliterating fibrosis of the tunica intima can be observed in histological specimens of the involved capillaries, and results from proliferation/edema of endothelial cells and subendothelial deposits of collagen. However, the typical histological features of necrotic vasculitis and the signs of critical limb ischemia (ulceration and dry necrotic lesions of palms and soles) can be observed in some SSc patients, usually in individuals with a limited...
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Form of this disease (ISSc – limited systemic sclerosis), positive for anti-centromere antibodies, and/or with the symptoms of Sjögren’s syndrome. In most cases, systemic vasculitis associated with mixed cryoglobulinemia develops secondarily to HCV infection [46].

Peripheral Arterial Thrombosis

Peripheral arterial thrombosis is an uncommon presentation of hereditary thrombophilias (antithrombin, protein C and S deficiency, factor V Leiden and prothrombin G20210A gene mutation); however, these may occur in acquired thrombophilias, particularly in the course of myeloproliferative neoplasms, i.e. essential thrombocythemia and polycythemia vera. The diagnosis is made on the basis of laboratory tests (blood count) and blood marrow biopsy [47].

Hypotenar Hammer Syndrome

Hypotenar hammer syndrome (HHS) is a rare form of ischemia involving fingers of the predominant hand, excluding the thumb. The disease is more prevalent in men than women, especially in individuals who are exposed to repeated blunt injuries of the hypotenar region. Most commonly, HHS is characterized by ischemia of the 4th and/or 5th finger, co-existing with such symptoms as pain, vasomotor disorders, paresthesia and cold intolerance. In advanced cases, symptoms can be accompanied by trophic lesions of the skin and finger necrosis. The diagnosis is verified on the basis of imaging studies, mostly angiography, confirming the presence of thrombosis or aneurysm located in the distal segment of the ulnar artery. Treatment and prevention of HHS include protection of the hand from mechanical injuries and quitting tobacco smoking. Additionally, anticoagulants and antiplatelet agents are administered, along with surgical revascularization and cervical sympathectomy. Thenar hammer syndrome (THS) is a similar, but even rarer, condition, characterized by thumb and/or index finger ischemia resulting from chronic post-traumatic thrombosis or thromboembolic complications associated with an aneurysm located in the distal segment of the radial artery [48].

Antiphospholipid Syndrome

This disease is caused by autoantibodies directed against protein-phospholipid complexes and manifests as recurrent episodes of venous and/or arterial thrombosis (Fig. 8) and pregnancy failures. It can have primary or secondary etiology, the latter most commonly associated with SLE. Livedo reticularis is the most typical dermal manifestation of APS; ulceration and necrotic lesions in various locations occur more rarely. Peripheral artery thrombosis can be accompanied by symptoms of acute or critical limb ischemia. The diagnosis is based on a history of vascular thrombosis and/or pregnancy failure and the presence of antiphospholipid antibodies detected at least twice at an interval of 12 weeks or more (moderate or high titers of lupus anticoagulant, and/or IgG or IgM class anti-cardiolipin antibodies, and/or antibodies against β2-glycoprotein I). Antinuclear antibodies are detected in 45% of individuals with primary APS and thrombocytopenia is observed in 30% of the patients [49].

Fig. 7. Fingertip ulceration in a 35-year-old patient with diffuse systemic sclerosis. (authors’ own image)

Fig. 8. Necrosis of the distal parts of the fingers in a 41-year-old female patient with antiphospholipid syndrome, systemic lupus erythematosus and rheumatoid arthritis (authors’ own image)
Persistent Sciatic Artery

Persistent sciatic artery is a rare but clinically important developmental anomaly occurring in 0.1% of the population. It is observed when the sciatic artery does not undergo physiological regression during fetal development and persists as the predominant artery of the lower limb. Usually, this condition is associated with hypoplasia of the superficial femoral artery, which supplies only the upper part of the thigh. Persistent sciatic artery derives from one of the ramifications of the inferior gluteal artery and travels through the posterior aspect of the thigh along with the sciatic nerve, eventually passing into the popliteal artery. Its anatomical course means it is exposed to repeated injury, which frequently leads to thrombosis or aneurysm with resulting thromboembolic complications. Clinically, persistent sciatic artery can manifest as an aneurysm located in the gluteal region and acute, subacute or chronic limb ischemia. Arteriography is the gold standard for diagnosing this condition; among other anomalies, the examination reveals an unusually large internal iliac artery. Management of the complications resulting from the presence of a persistent sciatic artery usually involves the implantation of a femoropopliteal bypass [50].

Infection with Anaerobic Clostridium sp. Bacilli

Infection with anaerobic clostridium sp. bacilli (predominantly gas gangrene caused by C. perfringens) leads to the putrid decay of tissues, exacerbated by injury and ischemia. Gangrene develops only at anatomical sites that communicate directly with the external environment (and are thus accessible to the bacteria), such as the skin, particularly if exposed to crush injuries. The infected wound is surrounded by edema, redness and blisters filled with purulent exudate (so-called ichor) with a characteristic putrid smell. The proliferating bacteria release gas to the surrounding tissues, which can be detected by palpation and is visible in radiographs. In addition to the specific clinical manifestations and a history of recent injury, a proper diagnosis is supported by the results of an anaerobic culture of the wound content [51].

Bristleworm Poisoning

Bristleworms are venomous marine annelids. Contact with their venom most commonly occurs in connection with water sports, usually diving. A urticarial rash develops at the site pricked by bristleworm bristles and is accompanied by pain and burning paresthesia; inflammatory lesions and necrosis of the skin occur less often [52].

Calcinosis Cutis

Calcinosis cutis refers to the accumulation of calcium deposits in the skin. Dystrophic calcinosis, which usually develops in response to an injury, is the most frequent form of this condition. Other established causes include connective tissue disorders, hyperparathyroidism, tumors of the skin, chronic venous insufficiency and occupational exposure to calcium compounds. Skin lesions present as hard, whitish/yellowish papules, plaques or nodes that can undergo painful ulceration. Skin necrosis, including the fingers, can develop in more severe cases. The diagnosis is based on radiographic and histopathological examination, both of which reveal the presence of calcium deposits within subcutaneous tissue [53].

Ergot Alkaloid Poisoning

This disease is caused by a fungus – Claviceps purpurea – that parasitizes cereal grains. Its sclerotia, known as ergot, contain toxic alkaloids, mostly ergotamine and ergotoxine, which cause hallucinations and uterine and vascular smooth muscle spasms, leading to miscarriage and tissue necrosis. Ergotism, as the agent responsible for mass human poisoning, was first mentioned in the Middle Ages. The disease had two principal forms: convulsive (ergotismus convulsivus) and gangrenous (ergotismus gangraenosus). The latter form was also known as “Saint Anthony’s fire” after monks of St. Anthony’s Order who treated the victims of ergot poisoning during the medieval period. The symptoms of ergot alkaloid poisoning can be classified as convulsive (epileptic seizures, nausea, vomiting, headache), central (hallucinations, psychosis, hysteria and mania), and gangrenous (loss of peripheral pulse, loss of sensation, edema and dry necrosis of distal body parts, resulting from persistent arterial spasm). At present, overdosing with ergotamine-containing anti-migraine agents, or ingestion of its hallucinogenic synthetic derivatives (mostly LSD), are the most common causes of ergotism [54].

Frostbites

They are injuries of the skin resulting from exposure to low temperatures, usually as a consequence of total body hypothermia. Distal parts of the body, including the fingers and toes, are
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particularly susceptible to frostbite. Depending on the severity, transient vasomotor disorders may be observed – pallor or livid coloration of the skin, edema, burnin, and pain (grade I), blisters filled with serous fluid (grade II) and superficial or deep skin necrosis (grade III, Fig. 9), which can lead to the spontaneous amputation of the frostbitten body part [55].

Trench Foot/Immersion Foot Syndrome

Trench foot/immersion foot syndrome is caused by prolonged exposure of the feet to wet, unsanitary and cold conditions (Fig. 10). Unlike frostbite, trench foot does not require freezing temperatures. The term “trench foot” comes from the trenches soldiers fought in during WWI; nowadays, the condition occurs most frequently in homeless people [56]. Erythema and numbness or tingling sensations occur initially, followed by tenderness and cyanosis due to vasoconstriction. Later painful foot swelling and hyperemia develops as a result of vascular paralysis. Advanced trench foot involves maceration of the skin, blisters, infected sores and gangrene, which can lead to a need for amputation. Dampness, tight shoes, immobility, as well as smoking and peripheral arterial disease contribute to tissue damage [56].

Cystic Adventitial Disease

Cystic adventitial disease (CAD) is a rare condition of unknown etiology, affecting peripheral arteries, commonly the popliteal artery, and responsible for abrupt-onset intermittent claudication. The lesion (cyst) can be visualized in computed tomography, magnetic resonance imaging or even ultrasonography, and can be distinguished from TAO on the basis of morphology, distribution and coexisting symptoms of TAO [57].

Pseudoxantoma elasticum

Pseudoxantoma elasticum is an uncommon hereditary disease, involving the skin, the cardiovascular system (arterial stenoses and intermittent claudication) and the gastrointestinal tract. The diagnosis is usually made in childhood or adolescence, and the presence of characteristic skin lesions as well as eye complications help in reaching the appropriate diagnosis [58].

References

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