REVIEWS

Thromboangiitis obliterans: a rheumatologist's perspective

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Thromboangiitis obliterans (TAO), or Buerger's disease, is a segmental thrombotic acute and chronic inflammatory process in small- and medium-sized arteries and veins, primarily of the upper and lower extremities. In rare cases, cerebral, coronary, renal, and mesenteric vessels may also be affected. This review describes the rheumatologic manifestations of TAO, outlines the spectrum of diseases for differential diagnosis, and presents the updated diagnostic criteria for TAO (2023).

Keywords: *thromboangiitis obliterans; antiphospholipid antibodies; systemic connective tissue diseases.*
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For reference: *Seredavkina NV, Reshetnyak TM, Lila AM. Thromboangiitis obliterans: a rheumatologist's perspective. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2025;19(5):119–126 (In Russ.). https://doi.org/10.14412/1996-7012-2025-5-119-126*

Thromboangiitis obliterans (TO) or (Buerger's disease) - is a segmental thrombotic acute and chronic inflammatory process in small and medium arteries and veins, predominantly in the upper and lower extremities; in rare cases, cerebral, coronary, renal, and mesenteric vessels may be involved [1–3].

The first description of TO belongs to Leo Buerger (1879–1943), who presented a case of TO in 1908 and later published a monograph on the subject. In his monograph, he quoted Felix von Winiwarter (1852–1931), who, as early as 1879, described pathological findings in a patient with obliteration of almost all arteries in the lower extremities.

Patients with TO are most often men under the age of 40 who experience intermittent claudication, paresthesia, difficulty walking for long periods of time, and ischaemic disorders of the extremities – ranging from cyanosis to ulcers or dry gangrene, invariably leading to amputation of the extremities and having a significant negative impact on quality of life and working capacity. In this regard, there is an ongoing search for methods of early diagnosis and new effective treatments for OT [2, 4].

According to the World Health Organization definition, TO is a rare disease. Most patients belong to a group with a low socio-economic status. The prevalence of TO varies across regions: the disease is most common in the Middle East and Far East, Southeast Asia, Eastern Europe, and South America. A hereditary predisposition to TO has been proven (HLA-B54-MICA-1.4, HLA-A9, HLA-DRB1, HLA-DPB1), which may not manifest itself without environmental triggers (smoking, rickettsiosis, periodontal disease) [5–7].

Although the study of TO has a history spanning more than 120 years, there is still no reliable marker for its diagnosis. Imaging methods and laboratory tests have been used primarily to rule out other vascular diseases, rather than to diagnose TO itself. Several options for classification criteria for TO have been proposed.

The criteria proposed by S. Shionoya (1996) [8] have low specificity and include: 1) smoking history; 2) onset before the age of 50 years; 3) occlusion of the popliteal arteries or their distal branches; 4) either upper limb involvement or phlebitis migrans; 5) absence of atherosclerotic risk factors other than smoking (all 5 factors are mandotary). S. Shionoya's criteria were most commonly used in middle- and low-income countries in the Middle East and South Asia, mainly due to limitations in insurance coverage or access to more modern examination methods [1].

The criteria developed by J. Mills (1994), M. Papa (1996), J. Olin (2000) contain the results of instrumental examination (angiography, histological examination) and have a number of limitations and exclusion conditions, such as diabetes mellitus, obliterating atherosclerosis, systemic blood diseases associated with hypercoagulation, and systemic connective tissue diseases [4, 9].

The possibility of a link between TO and autoimmune inflammation began to be discussed in the 1990s, when it was shown that the immunological mechanism plays a definite role in changes in the vessel wall [10]. Unlike other arterial diseases, TO is characterised by the presence of a cellular thrombus with low-intensity inflammation in the vessel wall, associated with the activation of macrophages and dendritic cells in the intima [11] and, in the active phase, accompanied by the production of anti-endothelial antibodies [12]. Nevertheless, indicators of the acute phase of inflammation, local haemostasis tests and traditional "screening" autoantibodies (antinuclear antibodies, rheumatoid factor, RF) and other immunological markers (complement, circulating immune complexes and cryoglobulins) in TO remain within normal limits or are absent (Table 1). A similar pattern is observed in antiphospholipid syndrome (APS).

APS is an acquired thrombophilic disorder in which autoantibodies are produced against phospholipid determinants of cell membranes or phospholipid-binding proteins in the blood. Clinical manifestations caused by antiphospholipid antibodies (aPL) in the blood range from asymptomatic aPL carriage to life-threatening manifestations depending on the size, number, and type of occluded vessels [15]. Laboratory markers of APS include moderately positive and higher levels of IgG and IgM antibodies to cardiolipin (aCL), antibodies to β2-glycoprotein 1 (aβ2GP1) and/or a positive lupus anticoagulant (LA), recorded twice at 12-week intervals [16]; in 1997, these markers were included in the international classification criteria for systemic lupus erythematosus (SLE) [17].

Table 1. Clinical manifestations, some laboratory parameters and results of instrumental examination in vascular diseases [1–3, 13–15]

Parameter	TO	APS	Obliterating atherosclerosis	Systemic vasculitis
Clinical manifestations				
Chronical low limb ischemia	Yes	Yes	Yes	Yes (during flare with peripheral artery involvement)
Chronical upper limb ischemia	Yes	Yes	Very rarely	Yes/No (during flare with peripheral artery involvement)
Arterial thrombosis	Yes	Yes	Atherothrombosis	Yes/No#
Venous thrombosis	No#	Yes	No#	No#
Thromboplebitis migrans of low limbs	Yes	Yes	No#	No#
Fever, weakness, myalgia, weight loss	Very rarely	No	No	Yes
Test results				
CRP	N*	N*	N, possible increase ≤10 mg/l without other reasons	High positive level during flare
D-dimer	N*	N*	N*	High positive level during flare
Leukocytes	N*	N*	N*	Leukocytosis
Thrombocytes	N*	N, thrombocyto-penia is possible	N*	Thrombocytosis
Fibrinogen	N*	N*	N*	Elevated level during flare
APTT	N	N, possible prolonged APTT due to the presence of LA	N	N
Prothrombin time	N**	N**	N**	N**
Thrombin time	N**	N**	N**	N**
INR	N**	N**	N**	N**
aPL	Rarely low	High positive level positive level	No	High positive level
RF	Rarely	No	No	Often
C3-, C4- complement components	N	N (low complement is possible in lupus-like APS)	N	N
ANA	Very rarely	Very rarely	No	Very rarely

Note. APTT – activated partial thromboplastin time; INR – international normalized ratio; LA – lupus anticoagulant; ANA – antinuclear antibodies; N – normal rate; # – as a concomitant disease with additional risk factors; * – if the level increases, check for infections, rheumatic diseases, neoplasias; ** – the level may increase by many times on anticoagulant therapy.

Similar clinical manifestations (arterial thrombosis and superficial thrombophlebitis) of two different diseases – TO and APS – served as a reason for research in this area.

In 1993, C. Fernandez-Miranda et al. [18] presented the clinical and immunological characteristics of 41 patients with OT. ACL were detected in 30 symptomatic patients, and 1 of them had a highly positive IgG-aCL level.

In 2000, R. Adar et al. [19] retrospectively analysed the medical records of 188 patients with high positive for aPL. Three men diagnosed with Buerger's disease subsequently developed classic APS, one of whom, who had previously been diagnosed with TO, died at the age of 45 from catastrophic APS. Four men with SLE had clinical symptoms of chronic arterial insufficiency, but TO was not detected for some reason. A woman with recurrent spontaneous abortions prior to verification of SLE with AFS was found to have TO. These data indicate the onset of SLE or AFS with manifestations of TO.

R. Cervera et al. [20] studied data from 1.000 patients (820 women and 180 men) from 13 European countries, whose age at the time of inclusion in the study was 42±14 years. All patients met the criteria for APS: 53% - had isolated primary APS, 36% - had SLE with APS, 5% - had lupus-like syndrome, and the

remaining 6% - had APS in combination with other rheumatic diseases. The results of the study showed that leg ulcers were observed in 6%, digital gangrene - in 3%, and foot skin necrosis - in 2% of patients; however, there is no information on whether these patients underwent peripheral artery examination, and it cannot be ruled out that the symptoms were associated with TO.

L. Maslowski et al. [21] reported elevated aCL levels in patients with TO. The study included 47 TO patients, 48 - with peripheral atherosclerosis, and 48 controls. In all cases, IgG, IgM, and IgA aCL were tested using solid-phase enzyme immunoassay. The authors showed that the frequency of aCL detection in TO patients was statistically much higher than in patients with atherosclerosis and in the control group: 36% versus 8% and 2%, respectively ($p<0.01$ in all cases). ACL-positive patients with OT developed the disease at a younger age and were also more likely to undergo amputation.

TO may be accompanied by clinical symptoms typical for SLE. Today, aPL tests are performed in a wider range of clinical disciplines, therefore, in real practice, there is a decrease in the frequency of aPL positivity and, as a result, the likelihood of confirming the diagnosis after testing for these antibodies. This aspect is addressed in the recently published classification criteria for SLE, developed jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) [16]. Routine screening for aPL without clinical manifestations of disease is not recommended to avoid accidental detection. Clinical scenarios that give reason with a high probability of suspecting APS include, in particular, younger patients (under 50 years of age) with unprovoked thrombotic events, thrombosis in atypical locations, or thrombotic complications or pregnancy complications associated with a concomitant autoimmune disease [16, 22]. The main recommendation in the guidelines is the need to test all aPLs simultaneously and interpret the results taking into account the clinical picture and all laboratory markers. This is because aPLs are a set of diverse autoantibodies with overlapping but different characteristics in terms of both their detection and their relationship to clinical manifestations.

The presence of aPL was recorded in patients with peripheral arterial disease (PAD), including those undergoing TO [23]. In a meta-analysis of 21 clinical studies involving 6057 patients with PAD, LA was more common in critical limb ischaemia (CLI) and was associated with the ineffectiveness of surgical revascularisation. Overall, aPLs were statistically significantly more common in PAD than in the control group: 13% versus 4% ($p<0.05$). However, this analysis has a number of significant shortcomings and limitations concerning the interpretation of the obtained results: heterogeneity of diagnosis (TO? Atherosclerosis?) and assessment of PAD severity, which precluded comparative analysis of subgroups; in most cases, a single incomplete antibody test (only aCL and LA); positivity expressed as a percentage of patients in whom aPL were detected, without indicating their levels and immunoglobulin class; moreover, it is unclear whether LA positivity was investigated on anticoagulant treatment [23].

The aPL frequency in SLE is approximately 30–40% [24, 25]. There are several descriptions of clinical cases in which TO was diagnosed several years before the verification of definite SLE [19, 26], and isolated descriptions of the SLE onset with CLI and multilevel arterial obstructive disease [27]. Studies involving SLE patients with confirmed TO have not been conducted for a number of reasons. In SLE, the bimodal nature of mortality and the early and accelerated development of atherosclerosis have been proven [28–30]. The meta-analysis of eight studies reporting on 263 258 SLE patients and 768 487 controls showed that the prevalence of PAD was 15.8% (95% CI: 10.5%, 23.2%) in SLE patients and 3.9% (95% CI: 1.8%, 7.9%) in controls with a corresponding odds ratio of 4.1 (95% CI: 1.5, 11.6; $P<0.001$). Regardless of SLE, PAD was associated with factors such as older age, arterial hypertension, type 2 diabetes mellitus, and other clinical signs of atherosclerosis. All these factors, in accordance with most diagnostic criteria, allow TO to be ruled out. Vascular wall biopsy was not performed in these studies, and PAD was considered a manifestation of generalised atherosclerosis [30].

The next most common rheumatic disease after SLE and APS in terms of aPL detection frequency is Behзet's disease (BD), which, according to the 2012 classification, belongs to variable vasculitides [31] and in which the relationship between thrombosis and aPL is also debated. The aPL frequency (mainly aCL and aβ2GP1) in BD, according to various authors, ranges from 2 to 39% [32]. Thrombotic disorders involving both arterial and venous vessels are reported in 45% of BD patients [33]. Both APS and BD can lead to critical ischaemia of the fingers and toes, resulting in ulceration and peripheral necrosis [2]. G. Hari and N. Skeik [34] described a BD patient with CLI and analysed seven other similar cases, five of which revealed occlusion of the femoral and/or popliteal arteries and aneurysms. The authors believe that critical ischaemia developed due to a combination of vasospasm and vaso-occlusive disease against due to small vessel vasculitis.

A number of studies have noted the similarity of clinical symptoms of TO to those of other rheumatic diseases [35, 36]. It has been shown that some symptoms of rheumatic diseases preceded the diagnosis of TO and disappeared as more obvious vascular manifestations developed [37–38], which requires observation. X. Puechal et al. [37] retrospectively assessed joint damage in 83 TO patients who admitted to rheumatology and vascular surgery departments and underwent a complete clinical and instrumental examination. Clinical signs of rheumatic diseases were detected in 11 (12.5%) of 83 TO patients. Eight patients had recurrent arthralgia that started 2 to 13 years (average 10 years) before TO, as well as acute migratory short-term transient non-erosive monoarthritis affecting large joints. The preliminary diagnosis in such patients often indicated periarthicular structures involvement with a tendency to relapse. Prodromal rheumatic symptoms disappeared with the appearance of ischemic signs.

Issues related not only to diagnosis but also to treatment of TO remain relevant. For example, O. Lambotte et al. [39] reported on three TO patients, two of whom had polyarthritis at onset and one of whom had carpal tunnel syndrome. T. Takanashi et al. [40] described the onset of TO with livedo reticularis and painful erythema nodosum, which were successfully treated with prednisolone, but on prednisolone therapy gangrene of both feet developed, followed by amputation. Ischemic manifestations were resistant to high doses of glucocorticoids and mycophenolate mofetil.

J.A. Johnson and R.J. Enzenauer [38] demonstrated a combination of TO with arthritis, which was accompanied by an increase in acute phase indicators (ESR, CRP), by positive RF and ANA, but negative anti-neutrophil cytoplasmic antibodies (ANCA). After receiving angiography data, the diagnosis of primary vasculitis was revised to TO. A short course of treatment with prednisolone completely relieved the arthritis. Ischemic disorders were compensated after 90 sessions of hyperbaric oxygenation. The arthritis did not relapse subsequently.

Table 2. Diagnostic criteria of thrombangiitis obliterans [1]

The 'definitive' diagnosis of TO can be made in a person (regardless of age, gender, clinical signs and symptoms, laboratory and imaging tests) with all of these three mandatory features:
1) history of tobacco smoking (current or past smoker14 but not the second-hand smoker);
2) typical angiographic features (normal proximal arterial structure, absence of atherosclerotic plaque, lack of microaneurysm, infra-popliteal arterial occlusion, corkscrew collaterals and skip lesions);
3) typical histopathological features (particularly, intact internal elastic lamina, Infiltration of polymorphonuclear inflammatory cells in all small and medium-sized vessels' wall layers).

'Suspected' diagnosis of TO can be confirmed in the presence of one major criterion plus four or more minor criteria:
Major criteria
History of active tobacco smoking (current or past smoker but not the second-hand smoker)
Minor criteria
1. Disease onset at age less than 45 years
2. Ischemic involvement of both of the lower limbs, such as:
   – absence of any distal pulses (aa. dorsalis pedis и tibialis posterior) of both limbs, or
   – ankle brachial index less than 0.9 of both limbs, or
   – diminished Toe Brachial Index of both limbs (TBI <0,75), or
   – chronic sign of ischemia of either lower legs or feet (including hair loss, nail thickness and, skin atrophy) in addition to the absence of any distal pulses of at least one limb
3. Ischemic involvement of any of the upper limbs, such as:
   – positive Allen's test[1], or
   – absence of radial pulse, or
   – Raynaud's phenomenon
4. Thrombophlebitis migrans (history or in the physical examination)
5. Discoloration of the toes or fingers in patients with lighter skin tones as a peculiar blush ranging from a red to a red-blue shade of purple on edematous toes, in which the toes on a limb sometimes might not be affected to the same degree. It can extend to the ankle in dependent position of the limb.

[1]Allen's test: the patient is asked to clench both fists tightly for 1 minute while the radial and ulnar arteries are compressed to block them. The patient then quickly unbends the fingers of both hands, and the doctor compares the colour of the hands. A positive result is recorded if the initial pallor of the hands is quickly replaced by hyperemia. The test can be repeated with compression of the ulnar arteries.

The link between ankylosing spondylitis (AS) and TO deserves attention. H.H. Chen et al. [41] retrospectively analysed data from 30911 patients with newly diagnosed AS and 309110 healthy controls and showed that patients with newly diagnosed AS have an increased risk of developing immune-mediated inflammatory diseases, including TO: the incidence rate/10^5 years for TO in the AS group was higher than in the control group – 2.6 versus 0.2, the incidence rate ratio was 16.26 (95% CI 2.72–97.31; p<0.01).

In the above-mentioned study by X. Puechal et al. [37], two TO patients were found to have HLA-B27-positive undifferentiated spondyloarthritis. G. Lpoalco et al. [42] observed a combination of AS and TO in a young woman, and AS diagnosed 6 years before the TO manifestations. Possible explanations for the association between AS and TO include common genetic risk factors, such as HLA-B*40 [18, 43], and smoking [3].

Rheumatic manifestations are not the only "atypical" symptoms of TO. F. Fakour and B. Fazeli [36] analysed 83 articles, 80 of which were descriptions of more than one clinical case of TO and three were original studies involving TO patients. The gastrointestinal tract (GIT), heart, central nervous system, eyes, kidneys, genitourinary system, mucous membranes, joints, lymphohematopoietic system, and hearing organs were the most frequently involved in the pathological process.

Since TO was first described, there have been 46 known cases of GIT involvement in TO [36, 44]. Most patients had occlusion of the superior mesenteric artery (53%), inferior mesenteric artery (12.5%), superior and inferior mesenteric arteries (22%), and intestinal arteries (12.5%) [36]. GIT involvement can be fatal [44].

Currently, there is no consensus on whether visceral manifestation is a symptom of systemic TO or the result of thromboembolism caused by atherosclerosis of the aorta or major visceral trunks. In the differential diagnosis of visceral TO, other forms of vasculitis should be considered. The differential diagnosis should include polyarteritis nodosa, rheumatoid arthritis, spondyloarthritides, IgA-associated vasculitis, Kawasaki`s disease, giant cell arteritis, SLE, APS, eosinophilic granulomatosis with polyangiitis, small vessel vasculitis with intestinal involvement (isolated organ vasculitis), vasculitis associated with inflammatory bowel disease, and thrombosis [35, 45].

However, according to the classification of PAD, TO is not considered a type of vasculitis. TO patients are usually referred to angiologists or vascular surgeons rather than rheumatologists. This may be due to the favourable response to smoking cessation and the lack of response to immunosuppressive therapy. Cytostatics and glucocorticoids reduced the joint manifestations of TO, but exacerbated limb ischaemia and, in the case of mesenteric ischaemia, led to intestinal perforation with subsequent fatal outcome [38, 40, 44, 46].

TO is not classified as a systemic disease, and its diagnostic criteria only take into account damage to small and medium-sized arteries in the limbs, but involvement of visceral arteries has also been noted. Clinical manifestations of TO in other organs are considered to be atypical or progressive forms of TO [36]. One of the reasons for the rare detection of such disorders may be the lack of medical supervision of patients. The main obstacle to follow-up observation is the mandatory quit smoking. The unwillingness of patients to quit smoking leads to them ignoring their doctor's recommendations while the symptoms are tolerable (e.g., postprandial pain) or seeking treatment from a doctor of another speciality [36].

Due to the variability of the clinical picture of TO, a study was conducted in 2022 to develop a consensus on the diagnosis of

TO using a two-stage modified Delphi methodology [47]. The results showed that, apart from smoking, experts did not reach a consensus on the criteria for TO, including age of onset; involvement of the upper limbs or phlebitis migrans; limitation of vascular involvement of the lower extremities to infrapopliteal arteries; exclusion of risk factors for atherosclerosis and other types of vasculitis; laboratory markers and/or vascular examination results. The authors proposed a reassessment of all published diagnostic criteria for TO for their harmonisation and widespread use [47].

In 2023, an international working group was established, comprising 56 experts in the fields of angiology, vascular medicine and vascular surgery from 29 countries, who developed updated diagnostic criteria for TO (Table 2) [1].

The working group recommends the use of only selective catheter angiography with digital subtraction angiography in the absence of the major criteria or if less than four minor criteria. Nonatherosclerotic occlusion of the superficial femoral artery along with infrapopliteal arterial involvement would not be exclusive for TO diagnosis. There are no typical characteristics of TO that can be detected by computed tomography angiography, so it cannot be used to diagnose TO, but it can be used to assess any occlusion or atherosclerotic changes in the proximal arteries. The working group did not reach a consensus on the need for laboratory data for the diagnosis of TO. However, laboratory tests, including determination of glucose, lipid profile, CRP, aPTT, ANA, RF, and coagulation profile, may be useful if imaging methods do not confirm the diagnosis of TO or other vascular diseases [1].

Thus, the definite TO can be established in a patient if all three criteria are present: a history of active smoking, typical angiographic features (normal proximal arterial structure, absence of atherosclerotic plaque, lack of microaneurysm, infra-popliteal arterial occlusion, corkscrew collaterals and skip lesions) combined with typical histological features (particularly, intact internal elastic lamina, Infiltration of polymorphonuclear inflammatory cells in all small and medium-sized vessels' wall layers). The following rheumatic manifestations may be observed in TO: arthralgia, livedo reticularis, erythema nodosum, acute migratory short-term transient non-erosive monoarthritis with large joint involvement, and the presence of autoantibodies. The differential diagnosis of TO should include polyarteritis nodosa, rheumatoid arthritis, spondyloarthritides, IgA-associated vasculitis, Kawasaki`s disease, giant cell arteritis, SLE, APS, eosinophilic granulomatosis with polyangiitis, small vessel vasculitis with intestinal involvement (isolated organ vasculitis), as well as vasculitis associated with inflammatory bowel disease.

The management of TO patients is a multidisciplinary issue. According to the International Classification of Diseases, TO is coded as I73.1 (thromboangiitis obliterans), and such patients should be supervised by a vascular surgeon. However, if antibodies are detected, TO may be coded as M31.9 (necrotising vasculopathy, unspecified) and managed by a rheumatologist.

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Received/Reviewed/Accepted
14.02.2025/05.05.2025/13.05.2025

Conflict of Interest Statement

The article was prepared within the framework of the basic research project № PK 125020501434-1.

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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