Etiopathogenesis, clinical diagnosis and treatment of thromboangiitis obliterans – current practices

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Thromboangiitis obliterans (TAO) is a segmental inflammatory occlusive disorder that affects small- and medium-sized arteries, and arm and leg veins of young smokers. Several different diagnostic criteria have been offered for the diagnosis of TAO. Clinically, it manifests as migratory thrombophlebitis or signs of arterial insufficiency in the extremities. It is characterized by highly cellular and inflammatory occlusive thrombi, primarily of the distal extremities. Thromboses are often occlusive and sometimes display moderate, nonspecific inflammatory infiltrate, consisting mostly of polymorphonuclear leukocytes, mononuclear cells and rare multinuclear giant cells. The immune system appears to play a critical role in the etiology of TAO. However, knowledge about immunological aspects involved in the progression of vascular tissue inflammation, and

consequently, the evolution of this disease, is still limited. There are several studies that suggest the involvement of genetic factors and results have shown increasing levels of antiendothelial cell antibodies in patients with active disease. Vasodilation is impaired in patients with TAO. TAO disorder may actually be an autoimmune disorder, probably initiated by an unknown antigen in the vascular endothelium, possibly a component of nicotine. There are various therapies available for treatment of TAO, but the major and indispensable measure is smoking cessation. Except for discontinuation of tobacco use, no forms of therapy are definitive. Sympathectomy, cilostazol and prostaglandin analogues (prostacyclin or prostaglandin E) have been used in specific conditions. Recently, therapeutic angiogenesis with autologous transplantation of bone marrow mononuclear cells has been studied in patients with critical limb ischemia.

Key Words: *Buerger's disease; Immune system; Nicotine; Thromboangiitis obliterans*

Thromboangiitis obliterans (TAO) was first described in 1879, when Felix von Winiwarter, an Austrian surgeon who was an associate of Theodor Billroth, reported in the German *Archives of Clinical Surgery* a single case of what he described as presenile spontaneous gangrene (1). In 1908, Leo Buerger, a physician at Mount Sinai Hospital (New York, New York, USA), described the occurrence of digital gangrene among the Jewish population in New York (2). Buerger related the cellular nature of arterial thrombosis, as had von Winiwarter, and described the absence of large vessel involvement. It was Buerger who named the disorder 'thromboangiitis obliterans', and only briefly mentioned its relationship with smoking. In 1924, Buerger reported that tobacco use was probably a predisposing factor (3). Allen and Brown (4) reported 200 cases of TAO evaluated at Mayo Clinic (Rochester, Minnesota, USA) from 1922 to 1926; all were male smokers.

TAO, or Buerger's disease, is a distinct disease that often leads to vascular insufficiency. It is characterized by chronic inflammation and acute thrombosis of medium- and small-calibre arteries in the arms and legs, particularly the tibial and

radial arteries, with occasional extension to veins and nerves of the extremities (5-7).

The precise cause of TAO is still unknown and different hypotheses are suggested. A reaction to the constituents of cigarettes is recognized as a factor of initiation, progression and prognosis of this disease. Possibly, genetic modifications or autoimmune disorders are implicated (8-10). Thus, the strong relationship with smoking seems to involve direct toxicity to the endothelium by certain tobacco products (nicotine) or an idiosyncratic immune response to some agents. Most patients with TAO have hypersensitivity to extracts of tobacco. Peripheral endothelium-dependent vasodilation is impaired in the nondiseased limbs of patients with TAO, and this type of vascular dysfunction may contribute to such characteristics as segmental proliferative lesions or thrombus formation in the peripheral vessels (11).

The incidence of TAO has decreased in men, despite the relative increase in the number of female cases due to the increasing number of female smokers (12). The number of women presenting to the clinic with TAO was almost equal to

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that of men. The only difference was the higher incidence of female nonsmokers at the first consultation, but this did not influence the response to treatment or outcome (13). Cigarette smoking is regarded as the only strong contributing factor to TAO. Smoking may exacerbate Buerger's disease by inducing vasoconstriction and increasing platelet thrombosis (14), and may exacerbate periodontal disease by altering the host immune response to periodontal pathogens (15).

When patients stopped smoking at the initial stage, the disease did not progress. Thus, it was suggested that TAO is a process of self-aggression triggered by substances in tobacco. The initial injuries are immune reactions associated with activation of lymphocytes, macrophages and dendritic cells in the arterial wall, followed by deposition of antiendothelial cell antibodies (16-20). Genetic influences are suggested by different prevalences in certain ethnic groups (TAO occurs frequently in Israelis, some Indian groups, the Japanese, Southeast Asians and Middle Eastern groups, and rarely in African-Americans) and an association with major histocompatibility complex haplotypes (21-23). Mutations in prothrombin 20210 G-A have also been the object of research (24,25).

Moreover, Barlas et al (26) described a study in a group of patients with TAO (2468 total; 94.5% men and 5.5% women) who were treated between 1975 and 1992 at the Thoracic and Cardiovascular Surgery Department, Istanbul Medical Faculty, Istanbul University (Istanbul, Turkey). Mean ($\pm$ SD) age was 43 ± 10 years (range 23 to 80 years) at the time of diagnosis. In 1975, only 8% of the patients were older than 40 years of age, which increased to 44% in 1992, of which 35% were men and 65% were women. At the time of admission, 78.2% had rest pain, 58% had intermittent claudication, 17.6% had superficial thrombophlebitis, 10.5% had Raynaud's phenomenon and 68.9% had ischemic ulcers. The study was divided into early (1975 to 1983) and late (1984 to 1992) periods. In the late period, an increase in the upper extremity involvement rate (47.5%) and in the large artery involvement rate of the leg (40.1%) was noted. In both periods, the majority (58%) of the patients with large artery involvement were older than 40 years of age. In addition, sympathectomy, amputation, revascularization and medical therapy were proven to be mostly ineffective in these patients. Of the patients who stopped smoking, 5.7% had subsequent amputations, whereas 46% of patients who continued to smoke had single or multiple amputations. The authors demonstrated that TAO is no longer a sole pathology of small- and medium-sized arteries affecting young male smokers' lower extremities (26).

Clinically, TAO manifests as migratory thrombophlebitis or signs of arterial insufficiency in the extremities. Vascular insufficiency caused by TAO tends to be accompanied by intense pain, even at rest, possibly related to nerve involvement and inflammatory mediators. Other associations are Raynaud's phenomenon and muscle cramps, usually in the legs and arches of the feet, but rarely in the hands, arms or thighs. The patients remain in generally good condition, without any manifestation of systemic disease. Later, with the worsening of symptoms, gradual evolution of ischemia results in gangrene of the extremities (27,28).

Studies have shown a possible relationship of TAO with hypercoagulable states, although its details are presently unknown. There are cases associated with protein S and

protein C deficiencies (29,30), antiphospholipid antibodies (31) and hyperhomocysteinemia (32,33). A recently published study showed that high concentrations of anticardiolipin antibodies were correlated with an early and more severe form of disease, including higher rates of amputation (15,34).

In other publications, high concentrations of plasma catecholamines were found in TAO patients, likely because there is a possible change of relaxation due to endothelial dysfunction, which could be attributed to the adrenergic effect of tobacco (35). Regarding possible peripheral adrenergic system involvement, some authors have proposed that cocaine abuse may be the underlying cause in many cases of TAO (36). Other studies have not confirmed the relationship between the sympathetic system and TAO, suggesting that a local vascular disruption is the responsible mechanism (37).

THE IMMUNE SYSTEM AND INFLAMMATORY COMPONENTS IN THE DEVELOPMENT OF TAO

The physiological function of the immune system to provide defenses against infectious organisms, as well as noninfectious foreign substances, can trigger an immune response. Moreover, the mechanisms that normally protect people from infection and remove foreign substances are capable of causing tissue damage and diseases in some situations. Different molecules, glycoproteins, cells and lymphoid tissues directly act together to guarantee the body defense system. Moreover, the spectrum of events observed during inflammation varies according to the tissue and the type of injury involved. The most important characteristics are the changes in diameter and permeability of blood vessels, and the local expression of molecules on the endothelial surface of these vessels. However, a response may also involve influx of specific types of white blood cells, occurrence of fever, activation of the clotting system, release of immune and complementary kinins, and many other phenomena (38,39).

The immune system seems to play a critical role in the etiology of TAO. However, knowledge about immunological aspects involved in the progression of vascular tissue inflammation, and consequently the evolution of this disease, is still limited. There are several studies that suggest the involvement of genetic factors associated with major histocompatibility complex (major susceptibility gene haplotypes in HLA-A9, HLA-B5, HLA-DR 4 and HLA-DRB1*1501 in Japanese patients; less frequent in patients with HLA-DRW6) and environmental factors (immunogenic nicotine stimulation) (21,40-42).

Results have shown increased levels of antiendothelial cell antibodies in patients with active disease. Vasodilation is impaired in patients with TAO. TAO may actually be an autoimmune disorder, likely initiated by an unknown antigen in the vascular endothelium, possibly a component of nicotine. (11,43,44) The presence of different antibodies, such as antinuclear, antielastin, anticollagen I and III, and antinicotinic antibodies, as well as identification of deposits of immunoglobulin (Ig) G, IgC3 and IgC4 in the blood vessels of patients, provided evidence to the theory of the immune character of TAO (45). Accordingly, the formation of immune complexes, activation of cell-mediated phagocytosis and the release of toxins stimulated by nicotine are the main agents responsible for vascular damage. Another factor of vascular injury is

changes in the balance of prostacyclin I₂ and thromboxane A₂, which can further accelerate platelet aggregation causing spasms of the arterioles (15,46). Maslowski et al (16) suggested that anticardiolipin antibodies are important for the pathogenesis of TAO. However, patients with generalized periodontitis had significantly greater titres of IgG or IgM anticardiolipin antibodies, and these levels were significantly higher in smokers than in nonsmokers (47).

In addition, elevated titres of IgG against periodontal pathogens are related to development of TAO (48). Slavov et al (18) reported that in TAO patients with persistent immune inflammation, production of culture supernatant and serum interleukin (IL)-6, IL-12 and IL-10 was altered, and apoptosis in cultures of polymorphonuclear leukocytes was increased. High levels of circulating immune complexes (IgG, IgM and IgA) were also reported. An increase in plasma levels of endothelin-1 was associated with clinical exacerbation of symptoms of TAO (18). Some molecules, such as the P-, E- and L-selectins, play an important role in the vascular endothelium and have increased expression in these patients. Prostaglandin E₁ could be an alternate treatment for repair of the vascular wall (endothelium). Simultaneously, it can produce an improvement in tissue perfusion, thus promoting a reduction in expression of selectins, which hamper the inflammatory response and leukocyte aggregation in the vascular endothelium (42,46,49). Halacheva et al (50) showed that endothelial cells were activated in TAO. Vascular lesions may trigger the secretion of TNF- α by inflammatory cells and express intercellular adhesion molecule 1-, vascular cell adhesion molecule-1- and E-selectin-favouring leukocyte adherence. The presence of lymphocytes (T and B) and macrophages was observed in biopsies of muscle fibres affected by TAO, suggesting that immunogenic factors can be found along these elastic fibres (51-54).

Recently, a case of TAO involving multiple large vessels was described (20). Using immunohistochemistry, CD3(+) T cells were revealed around the recanalization sites within the abdominal aorta. CD4(+) T cells were almost equal in number to CD8(+) T cells. These findings indicate inflammation and immunological processes in TAO with multiorgan involvement.

Brodmann et al (55) reported that nitric oxide is synthesized by nitric oxide synthase (NOS), and plays a key role in the adaptation of endothelial function, such as vasodilation and reduction of free radicals caused by smoking. In smokers, a genetic defect of endothelial NOS could result in impairment of endothelial function. However, this study did not investigate the association of a genetic defect of the common variant of endothelial NOS (Glu 298→Asp) in patients with TAO, probably due to the limited number of patients, which is a general problem when evaluating patients with TAO.

DIAGNOSTIC CRITERIA

Several different diagnostic criteria have been offered for the diagnosis of TAO. The traditional diagnosis of TAO is based on the five criteria of Shionoya (7,56,57), which are smoking history, onset before 50 years of age, infrapopliteal arterial occlusive disease, either upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other

than smoking; or based on the Olin criteria (58), which are onset before 45 years of age, current tobacco use, distal extremity ischemia (infrapopliteal and/or infrabrachial) such as claudication, rest pain, ischemic ulcers or gangrene documented with noninvasive testing, laboratory tests to exclude autoimmune or connective tissue diseases and diabetes mellitus, exclusion of a proximal source of emboli with echocardiography and arteriography, and demonstration of consistent arteriographic findings in the involved and clinically noninvolved limbs. A biopsy is rarely needed to make the diagnosis unless the patient presents with an unusual characteristic, such as large artery involvement or age older than 45 years. The acute lesion is considered diagnostic (59). The artery or vein is modestly swollen, and there is a moderate infiltrate of the adventitia and media. The lumen is occluded by a highly cellular, unique thrombus, with characteristic microabscesses. Lymphocytes exceed neutrophils, and occasional giant cells, and some eosinophils may be seen. In the subacute phase, cellularity of the vessel wall and thrombus decreases, microabscesses disappear and recanalization begins.

Several misconceptions in the past led to either overdiagnosis of TAO or refusal to accept its existence as a specific disorder (60,61). However, this mistaken belief regarding Buerger's disease is no longer considered, and there is no doubt today that it is a pathological entity quite distinct from atherosclerosis. Sometimes this pathology may be presented in asymptomatic patients as occlusive lesions, and has been demonstrated in angiograms in the small arteries of the foot or hand and may remain unnoticed until the involvement of arteries in the calf or forearm. As the disease progresses distally and extends proximally, Fontaine's classification is not appropriate for determining its severity. Surprisingly, gangrene precedes claudication, which is not frequent, and when present, is usually confined to the foot (62). There are two important distinctions between TAO and other arteritides – the absence of positive serological markers of inflammation and the nonexistence of autoantibodies. Preservation of the internal elastic lamina distinguishes it from the true necrotizing forms of arteritis. Because there are no specific laboratory tests for TAO, a definite diagnosis should be based on clinical data and the investigation should exclude other disorders that may mimic the disease, as described in Table 1 (7).

The angiographic findings in patients with TAO, although considered by some investigators to be pathognomonic, are not adequate to make a diagnosis, and their sensitivity and specificity are not high enough to be considered the gold standard. The most important arteriographic features of the disease include segmental occlusive lesions of small- or medium-sized vessels (tibial, peroneal, plantar, palmar or digital arteries) interspersed with healthy-appearing segments; abundant collaterals described as 'corkscrew,' 'spider legs' or 'tree roots'; and normal proximal arteries free of atherosclerosis, aneurysms or other sources of emboli (5,63,64). Corkscrew collaterals are not pathognomonic and may be present in any connective tissue disease, such as scleroderma, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia (CREST) syndrome, lupus, or any other small-vessel obstructive disorder such as diabetes or repetitive

TABLE 1
Suggested diagnostic investigation for Buerger's disease

Blood count
Liver function
Renal function
Fasting blood sugar
Erythrocyte sedimentation rate
C-reactive protein
Antinuclear antibodies
Rheumatoid factor
Complementary measurements
Anticentromere antibodies (for CREST)
Anti-Scl-70 antibodies (for scleroderma)
Antiphospholipid antibodies
Lipid profile
Urinalysis
Toxicology screen for cocaine and cannabis
Cryoproteins
Segmental arterial Doppler pressures
Arteriography
Echocardiography (to exclude source of emboli)
Computed tomography (to exclude potential source of emboli)
Biopsy (of questionable value)
Complete thrombophilia screen: Proteins G and S, antithrombin III, factor V Leiden, prothrombin 20210, homocysteinemia
Hand radiographs (to exclude calcinosis)
<i>CREST Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia. Adapted from reference 7</i>

embolization. Cocaine and cannabis abuse can also mimic TAO arteriographic findings (64-66).

Furthermore, angiography alone or in combination with biopsy (or a revascularization procedure) in patients undergoing amputation of limbs can also provide important findings. Angiographic findings are considered relevant in patients older than 40 years of age, and young female or male passive or active smokers. The absence of gangrenous limbs or end-stage ischemic ulcers, and previous sympathectomy (chest, bilateral lumbar, thoracic and lumbar, lumbar and unilateral) may also be important in the clinical diagnosis of TAO (26).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TAO is usually not difficult in the presence of a typical clinicopathological picture. The most important diseases to exclude are atherosclerosis, emboli and autoimmune diseases. There are situations in which diagnosis can be difficult, such as early onset arteriosclerosis in young male smokers, and collagen and autoimmune diseases in young people associated with digital cyanosis, pain and gangrene. The literature has demonstrated that ischemia induced by cocaine and cannabis ingestion can mimic TAO (66,67). Cannabis arteritis resembles Buerger's disease or it may, in fact, be a precipitating factor in addition to tobacco use. Occlusive disease of the digits is a frequent vascular manifestation of hematological disorders.

Diagnoses that can mimic TAO

Atherosclerosis, emboli, systemic lupus erythematosus, rheumatoid arteritis, CREST or scleroderma, antiphospholipid antibody syndrome, Takayasu's arteritis, thrombophilic disorders, ergotamine use (abuse), cannabis arteritis and calciphylaxis

can all mimic TAO. A careful history with laboratory tests to exclude connective tissue disease and hypercoagulable states, image studies (computed tomography, magnetic resonance imaging or echocardiography) to exclude emboli, and arteriographic findings can confirm the diagnosis of TAO. Clinically, it manifests as migratory thrombophlebitis or signs of arterial insufficiency in the extremities.

TREATMENT

There are various therapies available for treatment of TAO, but the major and most indispensable measure is smoking cessation. It has been demonstrated in case reports and series that complete abstinence from tobacco is a reliable way to halt the progression of Buerger's disease and avoid future amputations (68). Some researchers suggest that it is difficult to get patients with TAO to discontinue smoking (69). Psychological help may be useful in certain cases (69,70), but patients should be reassured that if they manage to give up smoking completely, the disease will go into remission and amputation can be avoided. Selective cannabinoid receptor antagonists, such as rimonabant, promise to be a treatment option for helping patients to stop smoking and reveal an interesting perspective on treatment of tobacco-related diseases (71).

The management of patients with TAO should be initially clinical. Patients with claudication should be encouraged to walk, whereas patients with 'critical' ischemia should be admitted to a hospital for bed rest (72).

Local care is another important component of therapeutic management (73). Foot care, including lubrication of skin with moisturizer, lamb's wool between the toes and avoidance of trauma, is a fundamental step to maintaining a patient's quality of life.

A dihydropyridine calcium channel blocker, such as amlodipine or nifedipine, seems to be effective if vasospasm is present (74). Cilostazol has been used in attempts to heal ischemic ulcers (75). Hussein and el Dorri (76) used selective low-dose intra-arterial streptokinase (a 10,000 U bolus followed by 5000 U/h) in 11 patients with longstanding Buerger's disease who had gangrene or pre-gangrenous lesions of the toes or feet. They reported an overall success rate (defined as avoidance or alteration in the level of amputation) of 58%. There is no new evidence of the efficiency of thrombolytic therapy for Buerger's disease.

Surgical revascularization is rarely possible for patients with Buerger's disease due to the diffuse vascular damage and the distal nature of the disease. Sasajima et al (77) reported a five-year rate of primary patency of 49% and a secondary patency rate of 62% in 61 patients following infrainguinal bypass. The patency rates were 67% in those who discontinued smoking, and 35% in those who continued to smoke. In situ bypass should be considered in patients with severe ischemia who have target vessels (78). Chemical sympathectomy may be used to alleviate symptoms of rest pain and as an adjunct to other treatments of ulcers (79). Spinal cord stimulation has been used in patients with rest pain or trophic lesions (80), but the value of this therapy remains to be demonstrated.

Fiessinger and Schafer (81) performed a prospective, randomized, double-blind trial comparing the effects of a 6 h daily infusion of iloprost (a prostaglandin analogue) with the

effects of acetylsalicylic acid. Iloprost was superior to acetylsalicylic acid at 28 days, with total relief of pain at rest and complete healing of all trophic changes. At six months, 88% of the patients receiving iloprost had a response to therapy, compared with 21% of the acetylsalicylic acid group. Only 6% of the iloprost group required amputation, compared with 18% of the acetylsalicylic acid group. Iloprost helps patients with critical limb ischemia get through the period when they first discontinue cigarette smoking. The results of an European study that compared two doses of oral iloprost with a placebo were less impressive (82). Low-dose iloprost was significantly more effective than placebo for relieving pain at rest without the need for an analgesic at the end of follow-up. High-dose iloprost was not significantly more effective than placebo.

Neovascularization by autologous bone marrow mononuclear cell transplantation is being examined as an alternative therapeutic option. Kamihata et al (83) and Shintani et al (84) have shown that bone marrow mononuclear cells contain not

only endothelial progenitor cells but also angiogenic factors and cytokines, and that implantation of bone marrow mononuclear cells into ischemic tissues augments collateral vessel formation. Various studies have concluded that transplantation of bone marrow mononuclear cells could contribute to a safe and effective strategy for achievement of therapeutic angiogenesis and hence prevention of amputation (85). Kajiguchi et al (86) demonstrated that therapeutic angiogenesis using cell transplantation improves critical limb ischemia, using objective findings such as the extent of ulceration, ankle-brachial pressure index, transcutaneous oxygen pressure, thermography and angiography. Motukuru et al (87), in a study of Buerger's disease patients, used bone marrow-derived progenitor cell transplantation into ischemic limbs; no demonstrable side effects were detected at six months. These study data support conducting controlled, multicentre trials to evaluate the efficacy of this therapy in preventing amputation in selected patients with Buerger's disease who have critical limb ischemia.

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