Review

Thromboangiitis Obliterans

Current Perspectives and Future Directions

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Originally described by von Winiwarter in 1879 and by Buerger in 1908, thromboangiitis obliterans became a focus of delayed controversy in the 1960s when its existence as a separate entity came into question. More recently, new information regarding the disease's pathogenesis, as well as a redefinition of its clinical and roentgenographic features, has given further credence to the theory that thromboangiitis obliterans is a distinct clinicopathologic and roentgenographic entity. By critically analyzing both old and new insights, this article assesses the current status and future directions of the disease. ***(Texas Heart Institute Journal 1990;17:112-7)***

In 1879, Felix von Winiwarter[1] described a patient with curious obliteration of the arteries and veins of the leg, which he attributed to "new growth of tissue from the intima." He proposed that this was a new entity and called it "endarteritis obliterans." Almost 30 years later, in 1908, Leo Buerger[2] observed a similar phenomenon in young Polish and Russian immigrant Jews living in New York City. He was impressed by its occurrence in a small number of young men from 20 to 35 years of age, who developed painful ulceration of the fingers and eventual gangrene of the upper and lower extremities after having typical symptoms of intermittent claudication. On the basis of histopathologic studies of 11 patients who required amputation, Buerger deduced that acute inflammation of the vascular wall led to the formation of thrombus, which later, during its organization, resulted in intimal hyperplasia. Therefore, he coined the term "thromboangiitis obliterans" (TAO), with which he proposed to replace such terms as "endarteritis obliterans" and "arteriosclerotic gangrene."

Thromboangiitis obliterans is a better name for this entity than the eponym "Buerger's disease," not only because it is descriptive, but because Buerger himself never had the disease, nor did he claim to be the first to describe it. "Von Winiwarter-Buerger syndrome" might be the fairest alternative, since it would acknowledge both of the men who painstakingly sorted out the details of the disease and alerted clinicians to it.

McKusick and colleagues[3] rightly credited von Winiwarter and Buerger when they argued that TAO is a distinct clinical and pathologic entity. Their argument was in response to earlier criticism by Wessler and coworkers,[4] who maintained that TAO is indistinguishable from atherosclerosis, systemic embolization, and peripheral thrombosis, either singly or in combination. While admitting that recurrent migratory superficial thrombophlebitis could occur in 30% to 40% of the patients with TAO, Wessler's group nevertheless felt that its presence alone would not justify TAO's being viewed as a distinct clinicopathologic entity; therefore, they recommended that the term thromboangiitis obliterans be discarded.

This controversy notwithstanding, many eminent physicians[5-8] and surgeons[9-11] have considered TAO to be a distinct clinical and pathologic entity different from atherosclerosis obliterans (ASO). This impression has been given further credence by the recent immunologic observation that HLA-A_9 and HLA-B_5 are more prevalent in TAO patients than in healthy control subjects or patients with ASO.[12] Moreover, TAO patients have been shown to have decreased cellular immunity against arterial antigen, as well as increased serum gamma globulin levels, specific humoral antiarterial antibodies, and immune complexes.[13] These findings further bolster the theory that TAO is a distinct inflammatory arterial and venous autoimmune disease.

This article synthesizes the various perspectives on TAO by critically analyzing both old and new insights into the disease.

Key words: *Thromboangiitis obliterans; atherosclerosis obliterans; Buerger's disease; peripheral vascular disease*

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Definition

Thromboangiitis obliterans is perhaps best described as an unusual occlusive peripheral vascular disease that is inflammatory and segmental; it occurs almost exclusively in young men who smoke tobacco. Recently, however, the disease has also been encountered in women between 20 and 35 years of age.[14] It affects both the upper and the lower extremities and is often (in 30% to 40% of cases) associated with recurrent migratory thrombophlebitis. A characteristic pattern of remission and exacerbation is related to the cessation and resumption of cigarette smoking. The degree of pain experienced by victims is much more intense than that suggested by the clinical findings. Diabetes mellitus, hyperlipidemia, and cardiac diseases that contribute to arterial thromboemboli are usually absent.

Prevalence

The previous impression that TAO is seen only in Russian and Polish Jewish immigrants is no longer tenable, because the disease has proved to be worldwide. Cases have been reported from Korea, Japan, and India, as well as from Eastern European countries.[3,10,13-17] In fact, all racial and ethnic groups appear to be susceptible. The recent decline in the incidence of TAO[14] has been more apparent than real and has most likely been related to initial over-diagnosis of the disease (based on recognition of its status as a distinct entity), followed by under-diagnosis (based on skepticism concerning its status). Patients with TAO constitute only 4% to 5% of all those with ischemic peripheral vascular disease.

Etiology

The cause of TAO remains unclear. Although the disease was thought initially to be infectious in origin, no evidence has been found to support this theory. As early as 1945, Silbert[11] wrote that TAO is caused by smoking in individuals who are constitutionally sensitive to tobacco. He observed that, in 100 patients who stopped smoking at the beginning of treatment and did not resume the habit, the disease remained in complete remission. The correlation between TAO and smoking remains strong and undisputed, and physicians should bear this in mind before making such a diagnosis in a nonsmoker.

The disease can also be familial: it has been reported among brothers, and in fathers and sons. A genetic predisposition to autoimmunity, in which nicotine is the culprit antigen that initiates and sustains the disease process, remains a distinct possibility (see Pathogenesis).

Pathology

Thromboangiitis obliterans is generally characterized by 2 phases: acute and chronic. Lesions occur in both the arterial and the venous circulation. In the acute phase, the architecture of the vascular wall is generally well preserved, but an inflammatory infiltrate consisting of polymorphonuclear leukocytes, plasma cells, and lymphocytes is present. At this stage, the lesion is characterized by a series of peculiar, usually multiple, microabscesses in a freshly organizing thrombus. These microabscesses consist of a central focus of polymorphonuclear leukocytes, surrounded by mononuclear epithelioid cells. Multinuclear giant cells are present in and around the abscesses. Appropriate stains fail to reveal microorganisms. Fibrinoid necrosis of the vascular wall, as seen in patients with polyarteritis nodosa or vasculitis, is rarely present.

In the chronic phase, the purulent microabscesses usually will have disappeared, but small epithelioid cell nodules remain, along with a few giant cells. Recanalization and organization of the thrombus at the intima are the hallmark of this stage. A chronic inflammatory infiltrate continues to be present in the vascular wall, but there is no scarring that would suggest the healing of necrosis. Periarterial fibrosis involving accompanying veins and nerves is common.

Pathogenesis

In 1974, Ohtawa and associates[15] reported an increased prevalence of HLA-A_9, HLA-BW_{10}, and a Japanese-specific antigen (J-1-1), together with an absence of HLA-A_{12}, in Japanese men with TAO. Similar observations were later reported from England,[12] indicating an increased incidence of HLA-A_9 and HLA-B_5 in TAO patients. Therefore, in genetically predisposed phenotypes with HLA-A_9, HLA-B_5, and HLA-BW_{10}, smoking may be the initiating factor in the pathogenesis of TAO.

Other findings in TAO patients include significant elevations of serum immunoglobulin levels (IgA, IgG, and IgM), increased consumption of CH50 and C3 (as evidenced by a reduced level in patient sera), and cryoglobulin containing polyclonal immunoglobulin and C3, all of which indicate the formation of immune complexes.[13] A decrease in cellular immunity against an arterial antigen and a prevalence of the specific humoral antiarterial antibody have also been observed.[13] Such immunologic abnormalities have been specifically sought,[16] and not found, in patients with ASO. The question remains whether these abnormalities represent the cause of TAO or one of its effects.

Whether thrombosis is the initiating factor that leads to vascular-wall inflammation or whether such inflammation leads to thrombosis remains unclear; both factors are invariably present by the time the pathologic process comes under study. Recurrent localized vasospasm may initiate thrombus formation,

which, in turn, causes inflammation in the vascular wall.

Diagnosis

Thromboangiitis obliterans usually presents in young men between 20 and 45 years of age. Women of similar age account for 1% to 2% of the patient population.[14]

Because of the undisputed relationship between cigarette smoking and the onset of the disease, the physician should hesitate to make a diagnosis of TAO in a nonsmoker. The signs, symptoms, and course of the disease are often ameliorated when the patient stops smoking.

In 60% to 75% of the cases, claudication pain is the 1st symptom.[8] Other symptoms, which may be present singly or in combination, include Raynaud's phenomenon, fatigue, recurrent migratory thrombophlebitis, and nonhealing ulcerations of the fingers and toes after trauma. The ulcerations are typically painful. Very rarely, TAO will manifest as an acute arterial occlusion.

The disease is heralded by no characteristic signs. The presence of migratory superficial thrombophlebitis in a patient with claudication and diminished distal small and medium-sized vessels, without the involvement of proximal large vessels, should alert the clinician to the possibility of TAO. Similarly, multiple amputations in the same extremity or in more than 1 extremity in a young person should arouse suspicion of the disease.

Unlike ASO, TAO is rarely accompanied by hyperlipidemia or hyperglycemia. A low total-serum-complement level and a high gamma-globulin level are often present in TAO patients, as are circulating immune complexes and antiarterial antigen antibody. Similarly, these patients have an increased prevalence of HLA-A_9, HLA-B_5, and HLA-BW_{10}. Plethysmography and Doppler ultrasound arterial evaluation often indicate an abnormality in a segmental, usually distal, distribution. A cardiac ultrasound study will fail to disclose left atrial or ventricular mural thrombi.

The most important laboratory tool for the confirmation of TAO is roentgenography. Calcification of the arterial wall is curiously absent, except in patients who have survived long enough for the damage of ASO to be superimposed on that of TAO. In early clinicopathologic descriptions of TAO, very little attention was paid to arteriography as a useful modality for differentiating TAO from ASO. More recently, in studying the peripheral arteriograms of 40 histologically confirmed TAO patients, Rivera[18] observed smooth arterial walls, narrow but uniform luminal caliber, abrupt segmental occlusions of the distal small and medium-sized arteries, and a "corkscrew" ("tree root" or "spider's leg") appearance of the collateral vessels (Fig. 1). These roentgenographic diagnostic criteria had been described earlier by McKusick and coauthors,[3] who also emphasized the striking bilateral similarity of these findings. Atherosclerosis obliterans—as manifested by an irregular lumen and intimal surface, calcification, and large secondary collaterals—is usually absent; sometimes, however, ASO can be superimposed on the above-mentioned roentgenographic features of TAO.[19] In studying 25 TAO patients by means of ascending venography, Chopra and associates[17] found that 60% of the venograms were abnormal, which indicated the presence of thrombi in superficial veins. This finding has not been observed in patients with ASO.

Differential Diagnosis. The 2 diseases that are often confused with TAO and that must be excluded before the diagnosis of TAO can be confirmed are polyarteritis nodosa and ASO.

Like TAO, polyarteritis nodosa is a segmental inflammatory disease of small and medium-sized vessels. Nevertheless, fibrinoid necrosis, the hallmark of polyarteritis nodosa, is usually absent from TAO, even in the acute stage. The course and prognosis of polyarteritis nodosa is not only different from that of TAO, but is not influenced as significantly by smoking.

On demographic, immunologic, and clinicopathologic grounds, TAO is quite distinct from ASO. Table I summarizes the most important differences in the 2 diseases. By using a multidisciplinary approach, the clinician should be able to make the correct diagnosis. It is only when one focuses on a single aspect, such as pathology, that confusion can arise.

Course and Prognosis

The earlier notion that TAO generally carries a less favorable prognosis than ASO was based on sparse data, yet many life insurance companies either declined to insure patients with TAO or assessed them at substandard rates. The prognosis of TAO patients differs markedly from that of patients with ASO: as shown in the following studies, some symptoms and consequences of TAO are more severe than those of ASO, but the survival rate is better. After studying 948 TAO patients, Horton[20] reported that approximately 70% had an amputation-free interval of 3 years after the onset of symptoms; this percentage decreased to 60% at 5 years and to 40% at 10 years. In a study of 268 patients (mean age, 45 years) with chronic occlusive peripheral vascular disease (149 with TAO and 119 with ASO), McPherson and associates[21] found that the TAO patients had a higher rate of subsequent gangrene and amputation than did those with ASO. During the 4-year study, none of the ASO patients had ulceration of the fingers or required amputation of an extremity. The TAO patients' survival rate compared favorably with that of normal

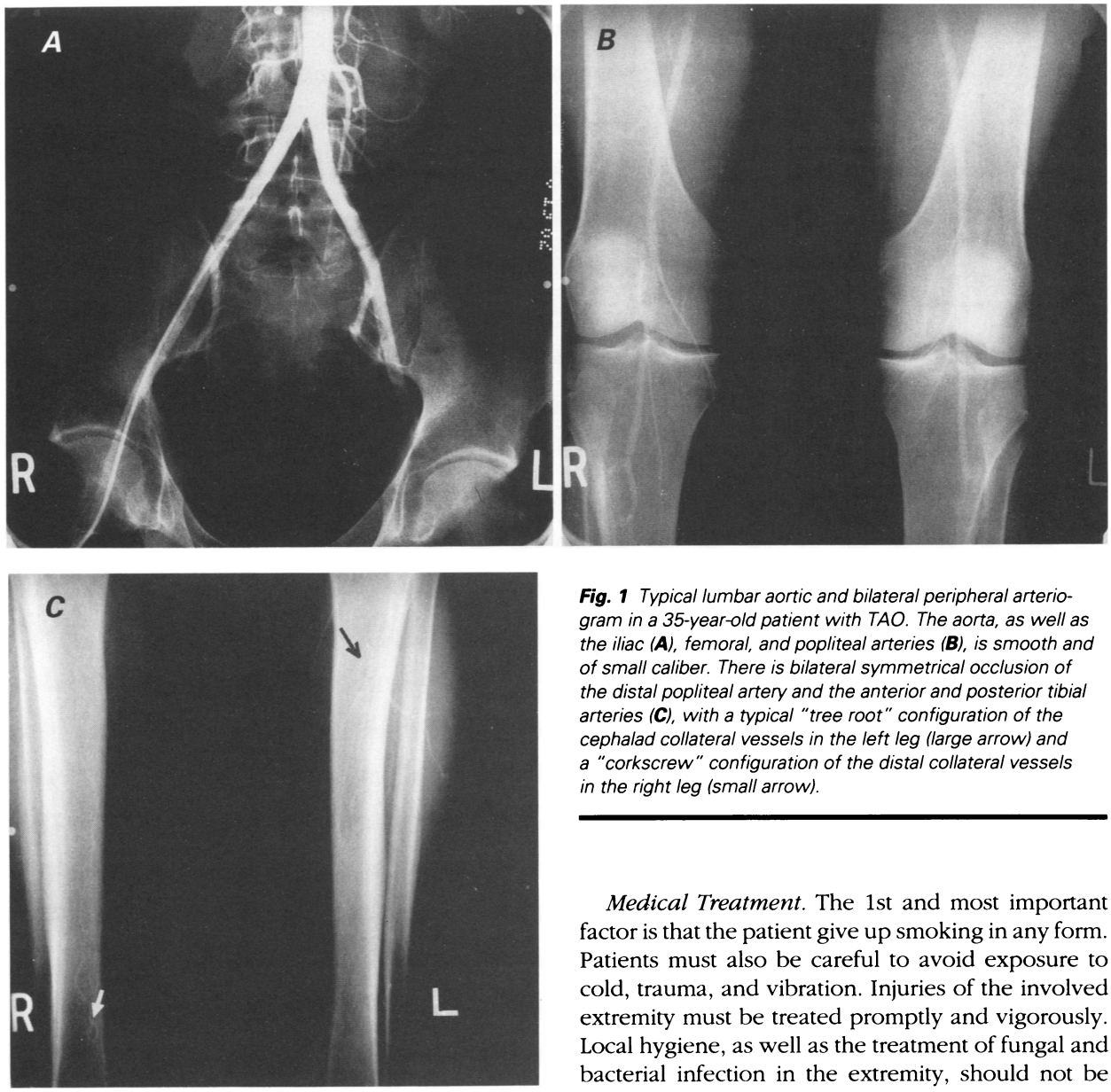

Fig. 1 *Typical lumbar aortic and bilateral peripheral arteriogram in a 35-year-old patient with TAO. The aorta, as well as the iliac (**A**), femoral, and popliteal arteries (**B**), is smooth and of small caliber. There is bilateral symmetrical occlusion of the distal popliteal artery and the anterior and posterior tibial arteries (**C**), with a typical "tree root" configuration of the cephalad collateral vessels in the left leg (large arrow) and a "corkscrew" configuration of the distal collateral vessels in the right leg (small arrow).*

control patients and was distinctly better than that of the ASO patients. The 10-year survival rate of TAO patients was 93.6% (the same as that of the normal population, whereas it was only 66% in the ASO patients. Curiously, the most common cause of death in both groups was coronary artery disease. Thus, patients with TAO clearly have a life expectancy equivalent to that of normal control subjects. Although TAO is associated with an increased amputation rate, this rate can be lowered significantly if the condition is diagnosed early and smoking is stopped.

Management

Because the etiology and pathogenesis of TAO remain unknown, management—whether medical or surgical—remains empirical.

Medical Treatment. The 1st and most important factor is that the patient give up smoking in any form. Patients must also be careful to avoid exposure to cold, trauma, and vibration. Injuries of the involved extremity must be treated promptly and vigorously. Local hygiene, as well as the treatment of fungal and bacterial infection in the extremity, should not be ignored.[22] The role of vasodilators such as pentoxifylline (Trental), and of thrombolytic agents, anticoagulants, and corticosteroids in the medical management of patients with TAO has not been carefully studied, but deserves attention. None of these measures, however, can substitute for the cessation of smoking.

Recently, a multicenter randomized control study comparing the use of iloprost (a chemically stable prostacyclin analogue) and aspirin in TAO patients was reported from France and West Germany.[23] One hundred fifty-two patients were randomly selected to receive either 1) oral aspirin, 100 mg/day, and a 6-hour daily placebo infusion or 2) a placebo tablet resembling aspirin and a 6-hour infusion of iloprost. For the 1st 3 days, the iloprost infusion was started at a rate of 0.5 ng/kg/min and was increased by 0.5 ng/kg/min at 30-minute intervals until it reached a maximum tolerated dose of 2.0 ng/kg/min, which was maintained for the rest of the 6-hour period. The

TABLE I. Differences between Thromboangiitis Obliterans and Atherosclerosis Obliterans

	Thromboangiitis Obliterans	Atherosclerosis Obliterans
Demographic Features		
Prevalence	Uncommon	Very common
Incidence	Apparently declining	Stable
Age	20 to 45 years	Over 45 years
Sex	Exclusively (98%) men (2% incidence in women)	Common in men (25% to 35% incidence in women)
Use of tobacco	Invariable	Common, but not invariable
Immunopathologic Features		
Incidence of HLA-A_9	Higher than in controls	Same as in controls
Incidence of HLA-B_5	Higher than in controls	Same as in controls
Antiarterial antibody	Present	Absent
Circulating immune complexes	Present	Absent
Hemolytic complement	Decreased	Normal
Gamma globulins (IgA, IgG, IgM)	Increased	Normal
Leukocyte migration index to arterial antigen	Low	Normal
Involved vessel size	Small and medium	Large and medium, rarely small
Extent of involvement	Segmental	Often diffuse
Clinical Features		
Migratory thrombophlebitis	Recurrent and common	Absent
Ischemic ulceration of hands	Common	Uncommon
Upper-extremity gangrene	Frequent	Rare
Lower-extremity gangrene	Frequent	Common
Improvement in symptoms and signs of ischemia with cessation of smoking	Very striking	Less striking
Hyperlipidemia	Absent	Present
Diabetes mellitus	Absent	Frequently present
Radiologic Features		
Arterial calcification	Usually absent	Often present
Arterial wall	Smooth	Irregular
Lumen	Generalized narrowing	Localized narrowing or stenosis
Occlusion	Abrupt	Gradual
Collaterals	Corkscrew, spider-leg, tree-root configuration of small vessels	Normal and often larger
Coexisting aneurysm	Rare	Common

maximum dose administered on day 3 was repeated on days 4 through 28 or until the symptoms and signs had completely resolved. The patients were then followed up for another 5 months.

Upon review, 19 of the patients did not fulfill the stringent entry criteria for TAO. Of the remaining 133 patients, 98 also had leg ulcers. After 21 to 28 days, 58 (85%) of the 68 iloprost-treated patients had ulcer healing or relief of ischemic pain, compared with 11 (17%) of the 65 in the aspirin-treated group. Forty-three (63%) of the iloprost-treated patients had complete relief of pain, compared with 18 (28%) of those taking aspirin. Of the 98 patients with leg ulcers, complete healing of ulcers was observed in 18 (35%) of the 52 who received iloprost, compared with 6 (13%) of the 46 who received aspirin. Six months after the start of the treatment, 45 (88%) of the 51 patients treated with iloprost had responded, compared with 12 (21%) of the 44 patients treated with aspirin.

For the 1st time, this multicenter trial has convincingly revealed the beneficial effects of prostanoids in the medical management of TAO. Side effects (head-

ache, flushing, nausea, and abdominal cramps) were minor and did not cause any patient to be withdrawn from the study. If these findings are subsequently confirmed, they will represent a substantial breakthrough in the management of TAO patients with intractable critical limb ischemia.

Surgical Treatment. Amputation of a limb or a segment of a limb must be postponed until after the patient has ceased smoking and gangrene has set in with clear demarcation. There is no medical evidence that a cervical or lumbar sympathectomy will improve survival or decrease the amputation rate; nevertheless, by improving collateral circulation and increasing superficial blood flow to the skin, such a procedure may help heal the ischemic ulceration and thus be beneficial in selected cases. Bypass grafting has been successful in cases involving a femoropopliteal segment.[24] Other previously-described treatments such as adrenalectomy,[25] repeated intravenous infusions of hypertonic salt solution,[26] and alternating pressure and suction are no longer considered effective and have been largely abandoned.

Conclusion

Thromboangiitis obliterans is an inflammatory, segmental, autoimmune peripheral vascular disease, involving small and medium-sized arteries and veins, that affects genetically-predisposed male cigarette smokers. Contrary to the beliefs of certain pathologists who ignored the disease's clinical component and were unaware of its immunologic nature, it is not a hodgepodge consisting of atherosclerosis and thromboembolic arterial disease; TAO is a distinct clinical entity and should be treated as such. Preliminary findings regarding the beneficial effects of prostanoids in TAO patients offer hope concerning the future medical treatment of this disease.

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