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Review

Thromboangiitis obliterans (Buerger's disease)

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HIGHLIGHTS

- Current concepts on the pathophysiology and diagnosis of Thromboangiitis Obliterans.
- Importance of complete abstinence of tobacco.
- Actual Treatments of Thromboangiitis Obliterans.

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ABSTRACT

Thromboangiitis Obliterans is a non-atherosclerotic inflammatory disease of unknown etiology, which has a strong association with tobacco. We present current concepts on the pathophysiology and diagnosis, as well as a review in treatments.

Contents

1. Introduction

Thromboangiitis Obliterans (TAO), also known as Buerger's disease, was described in 1908 when Buerger published his classic paper and later his book in 1924 [1]. It is a nonatherosclerotic inflammatory disorder of unknown etiology that affects small and

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medium-sized vessels of the extremities and has a strong association with smoking [2,3].

This panarteritis affects men ages between 25 and 35 years and can involved arteries, veins and nerves of arm and legs [1]. Extraordinary manifestations of TAO can involve the gastrointestinal, cerebrovascular, coronary and renal arteries [4,5].

2. Epidemiology

Although Buerger's disease has a worldwide distribution, it is more prevalent in the Middle East and Far East than in North America and Western Europe.

The prevalence of the disease among all patients with peripheral arterial disease varies from as low as 0.5 to 5.6% in Western Europe to as high as 45 to 63% in India, 16 to 66% in Korea and Japan, and 80% in Israel among Jews of Ashkenazi ancestry [6].

Several studies have reported an increase in the prevalence of the disease in women ranging from 11% to 23% [7].

3. Pathophysiology

The pathological features accompanying TAO are categorized in three phases including acute, subacute and chronic, according to the thrombus pattern and the nature of the inflammatory cells. In contrast to other forms of vasculitis, the normal structure of the affected vessel, and particularly the internal elastic lamina, remains intact in all three phases of TAO [8].

The main characteristic of the acute phase is a hypercellular and inflammatory thrombus with minimal inflammation in the vascular wall of the affected vessel. In this phase, the polymorphonuclear (PMN) leukocytes are predominant cells at the site of inflammation, which may form microabscesses within the thrombus. However, in the subacute phase, PMNs in the microabscesses are surrounded by a granulomatous inflammation, which may lead to organization and recanalization of the thrombus. Finally, the mature thrombus with vascular fibrosis is observed in the end-stage phase [9].

Although smoking is considered to be the most important risk factor of TAO, the essence of this relationship remains unclear until now. Endothelial cells play a key role in initiation and perpetuation of the inflammatory response and endothelial dysfunction in turn is reflected by impaired endothelium-dependent vasorelaxation, observed in studies on forearm blood flow [10,11].

4. Diagnosis

The diagnostic criteria of TAO still vary, despite the fact that the need for strict criteria was postulated 30 years ago. Some criteria are: Shionoya, Mills and Japanese Ministry of Health and Welfare, but the most used are Shionoya Criteria (Table 1) [4].

The exclusion of arteriosclerosis or risk factors of other occlusive vasculopathies is the most crucial criterion. Vascular disease to be ruled out: arteriosclerosis obliterans, traumatic arterial thrombosis, popliteal arterial entrapping syndrome, occlusive vasculopathy due to systemic lupus erythematosus or scleroderma diffusum, Behcet's disease [4].

Table 1
Shionoya clinical criteria.

Clinical criteria
1. Smoking history
2. Onset before the age of 50 years
3. Infrapopliteal arterial occlusions
4. Either upper limb involvement or phlebitis migrans
5. Absence of atherosclerotic risk factors other than smoking.

Typical arteriographic lesions are described as corkscrew-shaped collaterals, known as Martorell's sign, which may represent compensatory changes in vasa vasorum, in the presence of segmental lesions, or in occlusions in the distal extremity [7].

Unfortunately, corkscrew collaterals are not pathognomonic of Buerger's disease as they may be seen in diseases such as systemic lupus erythromatosis, mixed connective tissue disease, scleroderma, CREST (calcinosis, Raynaud's syndrome, oesophageal dysmotility, sclerodactyly and telangiectasia) syndrome or any other small vessel occlusive disease or in patients with cocaine, amphetamine, or cannabis ingestion [12].

Arteriographic abnormalities in the unaffected contralateral hand are also typical, because the disease is usually not limited to a single limb [13].

Vessel biopsy is rarely indicated, unless the patient presents atypically, such as at an older age or with large-sized artery involvement. The typical histopathologic findings include a highly inflammatory thrombus infiltrated with polymorphonuclear leukocytes and multinucleated giant cells, affecting both arteries and veins [14].

5. Prognosis

Amputation risk of the long-term results of TAO management are 25% per 5 years, 38% per 10 years and 46% per 20 years [15].

Fazeli et al. described 108 patients with Shionoya's criteria. The mean age of starting cigarette smoking was about 21 years old and the mean number of cigarettes smoked was about one pack of twenty cigarettes per day. The multivariate analysis demonstrated that the duration of smoking has a significant relationship with adverse outcome, namely major amputation and could not demonstrate an influence of number of cigarettes smoked per day, the age of disease onset or gender on limb salvage from amputation. Smoking cessation had a highly protective effect with respect to avoiding amputations, while decreasing the number of cigarettes per day did not have any effect on the outcome of the disease [16].

6. Therapy

1. Cessation of smoking:

Results in dramatic improvement. Complete abstinence from the use of all tobacco, including cigarettes, cigars, and smokeless tobacco, is advisable in these patients [17]. Substituting cigarette smoking with smokeless (chewing) tobacco does not appear to decrease the risk of TAO. Nicotine-containing patches can also keep the disease active [18].

2. Surgical revascularization

Surgical revascularization is often ineffective because the distal target vessels are often involved in this diffuse segmental disease [19].

3. Endovascular Therapy

This treatment may be technically challenging because of the prevalent location of lesions in distal vessels, with frequent compromised runoff at the foot level; thus, to extend the intervention until the foot, reconstitution of more distal arteries dorsalis pedis, plantar, and foot arch has been made mandatory to achieve the high technical success rates. Graziani et al. achieved technical success in 95%. No mortality or complication related to the procedure and sustained clinical improvement was achieved in 16 of the

19 limbs (84.2%) successfully treated, resulting in a 100% limb salvage rate [20].

Also two cases had been reported using endovascular atherectomy devices in the treatment of TAO with popliteal occlusions, this treatment was effective and free of significant complications [21].

4. Prostacyclin

Prostacyclin (PGI2) or its analogues (iloprost, beraprost, treprostinil sodium) are used to managed TAO [22]. Iloprost, is considered as the most effective treatment [23].

A randomized trail comparing intravenous Iloprost versus lumbar sympathectomy, demonstrated: the complete healing rate in the Iloprost group was 61,9% versus 41% in the other group at the 4th week ($P = 0.012$); respective values for the 24th week were 85,3% and 52,3% ($P < 0.001$). The size of the ulcer decrease more in the Iloprost group [24].

Another study demonstrate Iloprost was significantly more effective than placebo for relief of rest pain without need of, but Iloprost showed no significant effects versus placebo on total healing of lesions [25].

De Haro et al. used Bosentan a dual Endothelin-1 receptor antagonist, administered orally, which is approved in the European Union to treat pulmonary arterial hypertension in systemic sclerosis patients and to prevent the occurrence of new digital ulcers in systemic sclerosis patients with ongoing digital ulcers. Treatment with Bosentan may result in an improvement of clinical, angiographic and endothelial function outcomes, but larger studies are required to confirm these results [22,26].

Subcutaneous treprostinil therapy could be clinically useful in TAO that does not improve with smoking cessation, particularly in the presence of critical limb ischemia (CLI) where other therapeutic options have failed [27].

5. Growth Factors

Administration of growth factors to patients with peripheral arterial disease increases the concentration of angiogenic factors in the lower ischemic limb, aiming to improve endothelial cell proliferation, migration, and blood vessel formation in the ischemic limb. Diverse methods were reported for angiogenic therapies over the last 2 decades [28].

Saito et al. made autologous implantation of bone marrow-mononuclear cells to 7 patients with ischemic limbs because of peripheral arterial disease. Although the extent of the improvement was not consistent among the 7 cases, all of the patients experienced some improvement in their symptoms; a combined use of autologous bone marrow transplantation and hyperbaric oxygen therapy may be safe and effective for achievement of therapeutic angiogenesis [29].

Boda et al. made a study with 5 patients (4 with TAO and 1 with arteriosclerosis obliterans) with rest pain and nonhealing ulcer, autologous bone marrow–derived stem cell therapy was used and significant improvement of pain and walking distance was observed in all patients. Nonhealing ulcers disappeared in 3 patients and became smaller and thinner in 1 patient [30].

Heo et al. retrospectively analyzed the data of 58 limbs of 37 patients with Buerger's disease with critical limb ischemia who were treated with autologous whole bone marrow stem cell transplantation. At 6 months, patients demonstrated significant improvements in Rutherford category, pain score and toe brachial pressure index. A total of 76.5% ischemic wounds achieved complete or improved healing, the mean follow-up duration was 11.9 ± 7.2 months [31].

Unfortunately, such studies involve small numbers of patients. Randomized, multicentric, controlled clinical trials are required to confirm these results and further research is needed to identify the contribution of the distinct cell types and to explore the mechanisms contributing to these effects. However, this may not be feasible except in the very largest centres in areas where Buerger's disease is commonest.

6. Sympathectomy

Sympathectomy, particularly lumbar, has been used in patients with nonhealing ischemic lesions, but the results are unclear [32]. However, studies have shown that patients with an ankle/brachial index of less than 0.3 have a poor response to sympathectomy [33].

In patients with severe ischemia of upper limb extremities thoracoscopic sympathectomy permits symptomatic control and maximum tissue salvage. The procedure is minimally invasive, safe, and associated with a low rate of complications [34].

However, the usefulness of surgical sympathectomy seems to be dependent on smoking cessation [35,36], and its role in Buerger's remains controversial because there are no long term data to affirm its benefits [37].

7. Spinal Cord Stimulation

Electrical stimulation of the posterior column, Spinal Cord Stimulation (SCS) was first introduced in the late 1960s. It is thought to be based on the “gate-control” theory of pain described in 1965 by Melzack and Wall. It is generally used for the treatment of pain and is currently an established treatment of neurogenic pain [38,39].

Since 1976, multiple articles have been published on the alleged success of SCS in severe peripheral vascular obstructive disease and was reported to improve limb survival in nonoperable CLI. SCS involves implantation of a pacemaker with epidural lead activation of the dorsal columns of the spinal cord. Stimulation at T10-L1 level induces paraesthesia in the lower extremity, alleviating ischemic pain. Reduction in sympathetic tone and increase in nutritional blood flow have been postulated [40,41].

Despite extensive research in the area, the mechanisms of action are still only partially understood [42].

As compared with the large total number of publications on SCS for non-reconstructable CLI, only a few randomized studies have been performed. There is evidence that SCS is better than conservative treatment alone in order to achieve amputation risk reduction, pain relief, and improvement of the clinical situation in patients with non-reconstructable chronic stable CLI. The benefits of SCS must be considered against the possible harm of relatively mild complications and the costs [43].

In patients with TAO, trans-cutaneous oxygen pressure tension (tcpO2) increased at 3 months staying stable for up to 4 years, and claudication and rest pain almost disappeared under SCS in cases of reduced (less than three cigarettes per day) tobacco consumption [44].

7. Conclusion

Buerger's Disease is a medical condition of unknown cause, inextricably linked to tobacco abuse. Surgical revascularization is usually not possible, making other therapies important although there are few randomized clinical trials examining their effectiveness. Currently, complete abstinence from the use of all tobacco is the corner stone of management.

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Author contribution

Dr. Ignacio Rivera-Chavarría: writing the paper, final approval.
Dr. José D. Brenes-Gutiérrez: writing the paper, final approval.

Conflicts of interest

Dr. Ignacio Rivera-Chavarría and Dr. José D. Brenes-Gutiérrez have no conflict of interest.

Guarantor

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