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Buerger's Disease (Thromboangiitis Obliterans) among Smokers: A Literature Review

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ABSTRACT

Thromboangiitis obliterans (TAO) also referred to as Buerger's disease is a segmental, non-atherosclerotic, and progressive inflammatory vascular disease. The most frequently impacted arteries are the small and medium arteries in the upper and lower extremities. Smoking plays a significant role in the emergence and progression of TAO, despite the fact that its etiology and pathophysiology are uncertain. Anamnesis, physical examination, and supporting examination can all be used to confirm the diagnosis of TAO. The effective method of TAO management is smoking cessation. Besides smoking cessation, there are supportive therapies both pharmacological and non-pharmacological that can be carried out to maintain the maximum blood flow and prevent complications such as amputation and secondary infections.

Keywords: Buerger's disease; thromboangiitis obliterans; smoking; chronic limb ischemia; rare disease

INTRODUCTION

Thromboangiitis obliterans (TAO), often known as Buerger's disease, is a segmental, nonatherosclerotic, progressive inflammatory vascular disease that most frequently affects small and medium arteries in the upper and lower extremities (1,2). Inflammation that occurs in TAO due to peripheral vascular occlusion causes the patients to usually complain of claudication or pain at rest in the arms, hands, legs, and feet. The patients perceive it as pain arising from joint or neuromuscular disorders. The term for this condition is Raynaud's phenomenon (3,4).

The term "thromboangiitis obliterans" was first used in 1879 by Von Winiwarter, an Austrian-Belgian surgeon. Leo Buerger was able to describe TAO disease in 1908 based on the pathological findings of the amputated extremities of a TAO patient. Since then, there have been further developments about TAO disease (5,6). Although there are cases of thromboangiitis obliterans worldwide, they are more prevalent in Eastern Europe, South-East Asia, and South America (7). The prevalence of thromboangiitis obliterans varies worldwide. Western Europe has the lowest prevalence, ranging from 0.5% to 5.6%. Eastern Europe, South-East Asia, and South America are the regions where this disease is more prevalent (7). India has the highest prevalence, with 45 to 63% of the population (8). TAO affects males three times more frequently than females, with the ratio being about three to one. However, there is also an increasing trend of cases among women, which is associated with smoking trends (9).

TAO has a strong relationship with smoking despite the fact that the etiology is still uncertain. Thromboangiitis obliterans is mostly found in young to middle-aged males (21-45 years) with a smoking history.

Direct and indirect exposure to cigarette smoke is associated with the progression of disease (6). According to research by Fazeli et al. (2012), 108 patients who were diagnosed with TOA based on Shionoya criteria have an average smoking age of 21 years and smoked an average of one pack or around twenty cigarettes per day. Based on the multivariate analysis of the study, smoking duration was significantly associated with an adverse outcome, which is the amputation of the affected extremity (10).

Only a small percentage of smokers worldwide eventually become TAO. Due to limited publication and research on TAO and smoking behavior, the authors decided to write about TAO and its relation to smoking.

CLINICAL FEATURE

Males with a history of smoking and who are younger than 50 years old are more likely to have TAO (11). The classic symptom of TAO is Raynaud's phenomenon, also known as livedo reticularis, in which the patient experiences pain in their hands, feet, and fingers at rest. These symptoms indicate the ischemic processes of the peripheral vascular. Initially, TAO affects the distal extremity blood vessels, but as the disease progresses, it can also affect the proximal vessels (9). According to research by Sasaki et al. (2000), 74.7% of cases were confined to the lower extremities, whereas 20.2% involved both extremities. The most frequently affected vessels of the lower extremities were anterior tibial artery (41.4%) and posterior tibial artery (40.4%), while the ulnar artery (11.5%) was the most frequently affected in the upper extremities (12).

ETIOLOGY

The etiology of thromboangiitis obliterans, an autoimmune vasculitis disease that affects medium and large-sized vessels, remains unknown.

Cigarette smoke exposure is considered the initial step in the emergence and progression of diseases (13). Moreover, it is thought to lead to immunological dysfunction and hypersensitivity, which are associated with increased levels of type-1 and type-3 collagen, impaired endothelial vasodilatation, and increased anti-endothelial cell antibody (AECA) titers. In addition to exposure to cigarette smoke, there are several possible etiologies for the occurrence of this disease, including genetic factors due to an increased amount of human leukocyte antigens (HLA-54, HLA-A9, and HLA-B5), hypercoagulability, infection, and immunological mechanisms (14,15).

PATHOPHYSIOLOGY OF SMOKING-INDUCED BUERGER'S DISEASE

Although the pathophysiology of TAO is still unclear, it is believed that thrombosis, infection, and the presence of some autoantibodies may contribute to the occurrence of the disease. (16). According to Liew et al. (2015), there were four hypotheses about the pathogenesis of TAO, including variants of immunologic arteritis, atherosclerosis, hyperhomocysteinemia, and dental bacterial thrombosis (17). Based on histopathological findings, TAO was classified into three phases, including acute, subacute, and chronic. The occurrence of minimal inflammation in the vessel walls of the affected vessels is the main characteristic of the acute phase, polymorphonuclear leukocytes (PMN) predominate and microabscess formation within the thrombus. In the subacute phase, which is also called granulomatous inflammation, the PMN cells surround the microabscess and have the potential to organize and recanalize the thrombus. At a chronic phase, which is the end stage of the disease, the thrombus and vascular fibrosis occlude the blood vessels (9).

From several existing pathophysiology, smoking has been discovered to have a significant part in the pathophysiology and incidence of TAO (18). Increased levels of neutrophil elastase (NE) and reactive oxygen intermediates (ROIs) in smoking may trigger an inflammatory response that damages tissue (19). As a result of the neutrophil antimicrobial response, neutrophil elastase, which is a proteolytic enzyme degrades collagen and elastin fibers in the PMN primary granules (20). Furthermore, Iwai et al. (2005) found bacteria from the genus *Porphyromonas* in arterial thrombosis, which are gram-negative bacteria and originate from the mouth (21). This finding is in line with the postulate that smoking can lead to chronic gingivitis, which in turn stimulates the proliferation of *Porphyromonas gingivalis* in the cavity and may eventually lead to the bacteria being engulfed by platelets, resulting in the formation of an infective thrombus in which it crosses the bloodstream and causes thrombosis of blood vessels (18). These findings are also consistent with Allen and Brown's hypothesis, which stated that the etiology of TAO may be related to pathogenic microbes or viruses (22). These gram-negative bacteria can induce an immune response from Th1 and Th17 through the TLR4 receptor due to increased levels of cytokines interleukin-8 (IL-8) and NE. This series of events causes inflammatory cells to release vasoactive mediators, including histamine, bradykinin, and prostaglandins (19). An inflammatory thrombus occludes blood vessels as a result of neutrophils' inflammatory response, which also result in granulomatous formation (9).

Smoking can also damage vascular walls, in which affects the formation of prostacyclin and increases interactions between blood vessel walls and platelets (23). It is presumed that carbon monoxide and nicotine both damage blood vessels (23,24). The vascular endothelium may get injured as a result of this damage to the vessel wall resulting in an inflammatory response and affecting the progression of the disease. (25).

Endothelial cells have the ability to initiate and enhance the development of vasculitic lesions, which impairs endothelium-dependent vasodilation (26,18). In addition, exposure to cigarette smoke triggers the release of inflammatory cytokines that activate cellular signaling pathways through the adhesion of immunocytes and endothelial cells, leading to intravascular thrombosis and vasculitis (23). Several molecules serve significant roles in mediating cell-to-cell adhesion, including cell-to-cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (27,28). The presence of both molecules in excess in blood vessels that are affected suggests that they play a part in the development of the disease (29).

RELATIONSHIP BETWEEN SMOKING AND BUERGER'S DISEASE

Smoking has become a risk factor for the occurrence of TAO, several existing diagnostic criteria include smoking or smoking history as one of the points in assisting the diagnosis of TAO. Research on the relationship or effect of smoking on TAO is still very limited. Moreover, the majority of the patients in Sasaki et al. (2000) study, which included 850 patients (771 males and 79 females), had a history of smoking (93.2%). Patients who failed to quit smoking had a much higher chance of developing ulcer (odds ratio 51.71, 95%CI51.19–2.47; P50.004) and having an amputation (odds ratio 52.73, 95% CI51.86–4.01; P<0.0001) (11). Another study conducted by Fazeli et al. (2012), found that the duration of smoking had a significant relationship with the complications in the form of major amputation (P=0.004) in 108 (103 males and 5 females) patients diagnosed with TAO using the Shionoya criteria based on multivariate analysis. However, the results of multivariate analysis could not demonstrate the effect of daily cigarette consumption, age of disease onset, sex, and limb salvage from amputation (10). Furthermore, in a retrospective study of 224 patients (173 males and 51 females), Joncour et al. (2018), discovered that patients who quit smoking have a lower risk of amputation than those who continued to smoke (P=0.001). Based on 48 patients who underwent their first amputation, 5 (10.4%) were former smokers, and 43 (89.6%) were active smokers. Meanwhile, a total of 34 patients had undergone subsequent amputations; 8 (23.5%) were former smokers, and 26 (76%) were patients who continued to smoke. These findings suggest that smoking cessation can improve amputation-free survival in TAO patients. Further research is needed to fully understand the effects of smoking and its relationship to the extremities (30).

DIAGNOSIS

The diagnosis of TAO can be established through anamnesis, physical examination, and supporting examinations. A smoking history is usually obtained during anamnesis, along with information on any claudication in the fingers, feet, or hands. Most patients diagnosed with TAO are usually smokers. Thromboangiitis obliterans can also occur to those who have previously consumed chewing tobacco or tobacco products. TAO is very likely to occur for those who smoke at least one and a half packs per day (31,32).

Physical examination in TAO patients usually shows Raynaud's phenomenon, namely changes in skin color to become paler when in a cold environment (33). Raynaud's phenomenon occurs in about 40% of patients with Buerger's disease (15). Allen's test is performed to test the extent of the initial disease and assess the vascularity of the hand region (9). The procedure for Allen's test is that the patient is asked to clench his hand and the examiner presses on the patient's wrist intending to obstruct blood flow to the hand. TAO patients usually negative or have slowing of blood flow to the hands (5,34).

There are several criteria that can be used to diagnose TAO, including Shionoya, Olin, and Papa (36,37,38). First, there are five Shionoya criteria listed as follows: smoking history; onset of disease before the age of 50; infrapopliteal artery occlusion; upper extremity involvement or phlebitis migrans; and no additional risk factors for atherosclerosis besides smoking (36). Next, there are Olin's criteria, which include the following: onset under 45 years; a history of tobacco use; the presence of distal limb ischemia with indications for claudication, rest pain, ischemic ulceration or gangrene, and documented by non-invasive vascular testing; excluding autoimmune diseases, hypercoagulability, and diabetes mellitus; excluding emboli originating proximally using echocardiography or arteriography; and findings confirmed using arteriography of clinically associated and unrelated extremities (37). The last set of criteria is Papa's criteria, which have the same criteria as the previous ones but a lower age of onset, specifically between 30-40 years, as well as Raynaud's syndrome, which is characterized by intermittent foot claudication, single limb involvement (a negative criterion), and female gender (a negative variation) (38). Among the aforementioned criteria, the Shionoya clinical criteria are one of the most widely utilized and acknowledge worldwide (16).

Supporting examinations for TAO disease investigations are angiogram, vascular biopsy, and histopathological examination. Despite the fact that a number of supporting examinations have already been mentioned, TAO cannot be diagnosed by any particular investigations (9,32). Angiographic findings in TAO patients are corkscrew-shaped collaterals or Martorell's sign, indicating compensatory changes in the vasa vasorum due to segmental lesions or due to occlusion of the distal extremities (39). Martorell's sign can be detected in systemic lupus erythematosus (SLE), scleroderma, and other small vessel occlusive diseases, hence it is not a pathognomonic sign of TAO (40). A biopsy is used in atypical patients, such as elderly patients or patients with large artery disease. A histopathological examination typically indicates thrombus infiltration, polymorphonuclear leukocytes (PMN), and the presence of multinuclear giant cells (MN) in the associated vessels (6).

TREATMENT

There is currently no cure for TAO. The most effective method of TAO management is smoking cessation. The use of smokeless tobacco, such as chewing tobacco or applying nicotine patches, can affect the development of disease (6,42). It is essential to educate about how exposure to cigarettes or tobacco products affects the development of TAO (42,43). In addition to smoking cessation, supportive therapies can be used if there are ulcers on the extremities to maintain maximum blood flow and prevent secondary infection (15). Platelet inhibitors, vasodilators, anticoagulants, anti-inflammatories, thrombolytics, and prostacyclin analogues are a few examples of the medications that can be used to provide pharmacological therapy. Calcium channel blockers and prostaglandin E1 are vasodilators that are commonly utilized and effective in TAO. Meanwhile, the most effective inhibitor of platelet aggregation is ticlopidine (44). The use of anti-inflammatory steroids has not demonstrated a significant effect (15,44). Prostacyclin analogs, such as iloprost and intra-arterial thrombolytics with streptokinase, are effective at managing pain that occurs at rest and reducing the risk of amputation (44). Furthermore, spinal cord stimulation, sympathectomy, vascular endothelial growth factor gene therapy, and amputation are examples of non-pharmacological therapy for TOA disease (15,45,46).

PROGNOSIS

Data on mortality of TAO is few or difficult to find because TAO deaths are uncommon.

The US CDC, reported that 117 deaths in the United States were caused by TAO disease between 1999 and 2007 (9). The risk of long-term amputation due to TAO disease is 25% every 5 years, 38% every 10 years, and 46% every 20 years (41). Furthermore, in another study, the prevalence of amputation was 26% and 34% at 10 years and 15 years later, respectively (30). Smoking cessation has a preventive effect since it is associated with reducing the risk of amputation. Moreover, if the patient is able to quit smoking, surgery is also less likely to be required (6,32).

CONCLUSIONS

Thromboangiitis obliterans is an inflammatory vascular disease with no identifiable cause and is closely associated with smoking and the use of tobacco products. This disease is characterized by ischemia due to occlusion of the distal vessels in the form of intermittent claudication, which can progress to persistent ischemic pain at rest. The development of the disease may be influenced by smoking and using smokeless tobacco. Smoking cessation has a preventive effect since it is associated with reducing the risk of amputation and surgery.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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