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LITERATURE REVIEW

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

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Abstract

Buerger's disease or thromboangiitis obliterans [TAO] is a progressive inflammatory disease that is non atherosclerotic and segmental. Small and medium arteries in the upper and lower extremities are most commonly affected. Despite the etiology and pathophysiology of TAO being still unclear, smoking plays a vital role in the emergence and development of the disease. Diagnosis of TAO can be established through anamnesis, physical examination, and supporting examinations. Definitive and 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 maximum blood flow and preventing complications such as amputation and secondary infections.

Keywords

Buerger's disease, Thromboangiitis obliterans, Smoking, Chronic limb ischemia, Rare disease

Introduction

Buerger's disease or thromboangiitis obliterans [TAO] is a progressive inflammatory disease that is nonatherosclerotic, segmental, and most often affects small and medium arteries in the upper and lower extremities [1,2]. Inflammation that occurs in TAO due to occlusion in the periphery causes patients with TAO to usually complain of claudication or pain at rest in the arms, hands, legs, and feet. Patient perceives it as pain arising from joint or neuromuscular disorders. This condition is known as Raynaud's phenomenon [3,4].

Von Winiwarter, who was an Austrian-Belgian surgeon, was the first to introduce the thromboangiitis obliterans disease in 1879. Developments regarding TAO disease continued after Leo Buerger, in 1908, was able to describe this disease based on evaluation and pathological findings of the extremities of an amputated TAO patient [5,6]. Thromboangiitis obliterans are found all over the world, but this disease is more prevalent in Eastern Europe, South East Asia, and South America [7]. Thromboangiitis obliterans have a varying prevalence of disease, the lowest prevalence is found in Western Europe with 0.5 to 5.6%, while the highest is found in India with 45 to 63% in India [8]. Male are more often affected by TAO than female, ratio of the disease between male and female is three to one. However, among women there is also a trend of increasing cases associated with smoking trends in women [9].

Although etiology of TAO is still unclear, TAO, which attacks the peripheral blood vessels, has a strong relationship with smoking. Thromboangiitis obliterans are mostly found in young to middle-aged male patients (21-45 years) with a smoking history. Both directly and indirectly, cigarette exposure is associated with disease progression [6]. Based on studies from Fazeli, et al. [10], showed that 108 patients who were diagnosed with TOA through Shionoya criteria have an average smoking age of 21 years with an average number of cigarettes smoked about one pack or around twenty cigarettes per day. Multivariate analysis of the study showed that smoking duration was significantly associated with an adverse outcome, namely major amputation of the affected extremity [10].

Despite the large number of smokers in the world, only a few patients have become TAO. The small amount of literature on TAO and its relationship to smoking as well as research discussing smoking and its effect on TAO made the authors raise the topic of TAO and its relation to smoking.

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Clinical Feature

Patients with TAO are more often found in men younger than 50 years and have a smoking history [11]. Classic symptom of TAO is Raynaud's phenomenon or livedo reticularis which the patient feels pain in the hands, feet, and fingers at rest. These symptoms indicate the occurrence of ischemic processes in the vascular in the periphery. Initially, TAO affects the distal extremity vessels, but as the disease progresses, TAO can affect the proximal vessels [9]. The study was conducted by Sasaki, et al. [12], with 825 research subjects (749 male and 76 female) and an average age of 50.8 ± 0.4 years. Based on the study results obtained, 42 patients (5.1%) showed involvement of the arteries of the upper extremities, 616 patients (74.7%) were confined to the lower extremities, whereas 167 patients (20.2%) showed involvement of both extremities. Anterior tibial artery (41.4%) and posterior tibial artery (40.4%) were most commonly affected in the lower extremities, while the ulnar artery (11.5%) was most commonly affected in the upper extremities [12].

Etiology

Thromboangiitis obliterans which is an autoimmune vasculitic disease that affects medium and large sized vessels has an unclear etiology, but smoking exposure is considered as the initiation of disease emergence and disease progression [13]. Smoking exposure is thought to cause immunological dysfunction and hypersensitivity correlated with increased type-1 and type-3 collagen, impaired vasorelaxation in the endothelium, and increased anti- endothelial cell antibody titers. Apart from exposure to cigarettes, there are other etiologies that may be related to the occurrence of this disease, such as genetic factors due to increased amount of human leukocyte antigens (HLA-54, HLA-A9, and HLA-B5), hypercoagulability, infection, and immunological mechanisms, although this is still limited [14,15].

Pathophysiology of Smoking Induce Buerger's Disease

Pathophysiology of TAO is still unclear, but infection, thrombosis, and the presence of some autoantibodies are thought to play a role in the occurrence of the disease. [16]. Liew, et al. [15], showed that there are currently four hypotheses about the pathogenesis of TAO, including variant of immunologic arteritis, atherosclerosis, hyperhomocysteinemia, and dental bacterial thrombosis [17]. Based on histopathology, there are three phases of TAO, including acute, subacute, and chronic. Acute phase, the main characteristic of the acute phase is the occurrence of minimal inflammation in the vessel walls of the affected vessels. In the acute phase, the main features of the acute phase are minimal inflammation of the affected vessel wall, polymorphonuclear leukocytes (PMN) predominate and microabscess formation within the thrombus. Subacute phase, also called granulomatous inflammation, surrounds the PMN cells in the microabscess, and has the potential to cause organization and recanalization of the thrombus. Chronic phase, where there is thrombus and vascular fibrosis that occludes blood vessels, is the end stage of the disease [9].

From several existing pathophysiology, smoking has been found to play a central role in the pathophysiology and incidence of TAO [18]. Smoking can cause an inflammatory response through increased levels of neutrophil elastase (NE) and reactive oxygen intermediates (ROIs) which cause tissue damage [19]. Neutrophil elastase is a proteolytic enzyme found in PMN primary granules that acts on collagen by degrading collagen and elastin fibers as a result of the neutrophil antimicrobial response [20]. Iwai, et al. [21], 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 cause chronic gingivitis thereby stimulating the proliferation of Porphyromonas gingivalis in the cavity and has the potential to cause bacteria to be engulfed by platelets, resulting in the formation of an infective thrombus that crosses the bloodstream and causes thrombosis of blood vessels [18]. These findings are also consistent with Allen and Brown's hypothesis which states that the etiology of TAO may be related to pathogenic microbes or viruses [22]. These gram-negative bacteria can act as intermediaries to induce an immune response from Th1 and Th17 through the TLR4 receptor due to increased cytokine interleukin-8 (IL-8) and NE levels. As a result of this series of events, inflammatory cells release vasoactive mediators, histamine, bradykinin, prostaglandins [19]. The inflammatory response by neutrophils causes granulomatous formation and results in the occlusion of blood vessels by an inflammatory thrombus [9].

Smoking can also damage vascular walls, resulting in impaired prostacyclin production and increased interactions between blood vessel walls and platelets [23]. Composition of cigarettes that cause microvascular damage are not characterized by certainty, carbon monoxide and nicotine are thought to mediate damage to blood vessels [23,24]. Damage to the vessel wall can potentially cause injury to the vascular endothelium, triggering an inflammatory response and affecting disease progression [25]. Endothelial cells can initiate and promote the development of vasculitic lesions, thereby causing impaired endothelium-dependent vasorelaxation [18,26]. Exposure to cigarette smoke also triggers the release of inflammatory cytokines that activate cellular signaling pathways through adhesion of immunocytes and endothelial cells, thereby causing intravascular thrombosis and vasculitis [23]. Several molecules such as cell-to-cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-

1) play important roles in mediating cell-to-cell adhesion [27,28]. Both molecules are present in excess in affected blood vessels, indicating a role in the disease process [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. Sasaki, et al. [11], in a study of the 850 patients (771 male and 79 female), most of the patients had a history of smoking (93.2%). Patients who failed to quit smoking significantly increase the risk of ulcer formation (odds ratio 51.71, 95%CI 51.19-2.47; P50.004) and amputation (odds ratio 52.73, 95% CI 51.86-4.01; P < 0.0001) [11]. Another study conducted by Fazeli, et al. [10], of 108 (103 male and 5 female) patients diagnosed with TAO using the Shionoya criteria based on multivariate analysis, showed that the duration of smoking had a significant relationship with the occurrence of complications in the form of major amputation (P = 0.004), however, the multivariate analysis performed could not show the effect of the number cigarettes smoked per day, age of disease onset, sex in, and limb salvage from amputation [10]. Joncour, et al. [30], in a retrospective study of 224 patients (173 male and 51 female) confirmed that patients who quit smoking have a lower risk of amputation than those who still smoke (P = 0.001). Based on 48 patients who had their first amputation, 5 (10.4%) were former smokers and 43 (89.6%) were active smokers. In subsequent amputations, there were 34 patients, 8 (23.5%) were former smokers and 26 (76%) were patients who continued to smoke. Based on these results, it supports that smoking cessation can improve amputation-free survival in TAO patients. Further studies are needed regarding 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. When taking anamnesis, a smoking history is usually obtained as well as a feeling of claudication in the fingers, feet and hands. Most patients diagnosed with TAO are usually smokers. Thromboangiitis obliterans can also occur in individuals with a history of consuming other forms of tobacco, such as chewing tobacco. Individuals who consume one and a half packs of cigarettes or more daily are very likely to develop TAO [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. Allen's test is performed to test the extent of the initial disease and assess the vascularity of the hand region. 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 with the aim of obstructing blood flow to the hand [34]. The interpretation is that TAO patients are usually negative or have slowing of blood flow to the hands [5].

There are several criteria that help establish the diagnosis of TAO, including the criteria of Shionoya, Olin, and Papa [35-37]. Shionoya criteria consist of five criteria: Smoking history; onset of disease before age of 50 years; infrapopliteal artery occlusion; upper extremity involvement or phlebitis migrans; and no risk factors for atherosclerosis other than smoking [35]. Olin's criteria consist of onset under 45 years; history of tobacco use; 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 [36]. Papa's criteria include the criteria that are in the previous criteria, but have a lower age of onset, namely under 30-40 years plus Raynaud's syndrome; intermittent foot claudication; single limb involvement (negative criterion); and female gender (negative variation) [37]. From some of the criteria previously mentioned, one of the most used and generally accepted worldwide is the Shionoya clinical criteria [16].

Supporting examinations for TAO disease investigations are angiogram, vascular biopsy, and histopathological examination. Although several supporting examinations have been mentioned previously, no specific investigations can be used to diagnose TAO [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 [38]. Martorell's sign is not a pathognomonic sign of TAO, as it can be found in systemic lupus erythematosus (SLE), scleroderma, and other small vessel occlusive diseases [39]. Biopsy is used in atypical patients, for example elderly patients or patients with large artery disease. Histopathological examination usually reveals thrombus infiltration and polymorphonuclear leukocytes (PMN) and the presence of multinuclear giant cells (MN) in the associated vessels [6].

Treatment

Until now, there is still no cure for TAO. Definitive and effective method of TAO management is smoking cessation. Use of smokeless tobacco (chewing tobacco or using nicotine-containing patches) can influence disease development [6,40,41]. Educating patients regarding the impact of exposure to cigarettes or tobacco products on the development of TAO is critical [41,42]. Besides smoking cessation, supportive therapies can be carried out to maintain maximum blood flow and avoid secondary infection if there are ulcers on the extremities [15]. Pharmacological therapy that can be given is by administering drugs class of platelet inhibitors, vasodilators, anticoagulants, anti-inflammatories, thrombolytics, and prostacyclin analogues. Vasodilators that are often used and effective in TAO are calcium channel blockers and prostaglandin E1. Meanwhile, the most effective inhibitor of platelet aggregation is ticlopidine [43]. The use of anti-inflammatory steroids has not shown a significant effect [15,43]. Prostacyclin analogue drugs, namely iloprost and intra-arterial thrombolytic with streptokinase have a good effect on controlling pain that occurs at rest and reducing the risk of amputation [43]. Non-pharmacological therapy for TOA disease from spinal cord stimulation, sympathectomy, vascular endothelial growth factor gene therapy, and amputation [15,44,45].

Prognosis

Because TAO deaths are unusual, data on mortality is rare or difficult to come by. According to the US Centers for Disease Control and Prevention (CDC), between 1999 and 2007, TAO disease was the cause of 117 deaths in the United States [9]. The risk of long- term amputation from TAO disease is 25% per 5 years, 38% per 10 years, and 46% per 20 years [40]. Furthermore, in another study, the prevalence of amputation was 26% and 34% at 10 years and 15 years later [30]. Smoking cessation has a protective effect because it is associated with minimizing the occurrence of amputation, and surgery is rarely necessary if the patient is able to stop smoking [6,32].

Conclusion

Thromboangiitis obliterans is an inflammatory disease with no identifiable cause and is closely related to smoking and use of tobacco products. This disease is characterized by symptoms of ischemia due to occlusion of the distal vessels in the form of intermittent claudication and can develop into persistent ischemic pain at rest. Smoking and using smokeless tobacco can influence the development of the disease. Smoking cessation has a protective effect because it is associated with minimizing the occurrence of amputation and surgery.

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