Does adaptive T cell immunity have any role in the pathophysiology and histopathology of Buerger's disease?

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Received; 25/03/2020 Revised; 12/05/2020 Accepted; 6/06/2020

Abstract

Buerger's disease is a clot forming vasculitis which can lead to severe complications such as amputation of extremities. It is more prevalent in young male smokers and has a higher occurrence in eastern regions of the globe. The risk factors which raise the susceptibility to this condition include infection, tobacco consumption, and genetic factors. It is also hypothesized that the LPS of oral commensal bacteria can lead to various immune reactions that are seen in this disease. Several pathways have been proposed to be responsible for this disease, and the main pathways are through the innate and adaptive immune systems. One of the controversial aspects of the pathophysiology of this disease is its relation to the T cell immunity; histopathology findings have shown T cell infiltration in the arterial wall. In this literature review, our aim was to review the articles published in relation to Buerger's disease, and the conclusion was that the T cell adaptive immunity might have a fundamental role in the disease pathophysiology, however, further investigation is needed.

Keywords: Buerger`s disease, Thromboangiitis obliterans, T cells

Introduction

Buerger's disease or Thromboangiitis Obliterans (TAO) is a non-sclerotic obliterative disorder of the small and medium-sized arteries and veins of the superior and inferior limbs (1). It leads to clot formation and recurrent and progressive inflammation of the vessels (2). Painful ulcers on the tip of phalanges and intermittent phalangeal pain are the main two signs of TAO (3). Several risk factors have been known to be associated with this condition; these include smoking and any other kind of tobacco consumption, however, the exact cause of the disease is still unknown (4). Buerger's disease is more prevalent in men than women, but it is showing a rising incidence in women too. This could be attributed to the increasing smoking trend in women (4).

Although the incidence of TAO is decreasing in North America and Western Europe, it's shown a rising pattern in the eastern and Mediterranean parts of the world (4-6). TAO usually leads to severe complications such as organ amputation; the only way to stop the progression of the disease is to quit smoking and any other kind of tobacco consumption (7, 8). Although the role of cigarette smoking

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in the disease pathogenesis is prominent, the etiology of the disease remains controversial (9). Other proposed etiologies of the disease are drug abuse, bacterial and viral infections, environmental factors, and genetic predispositions (10, 11).
The cellular immune response is among the proposed causes of this disease (12, 13). In this study, we aim to review the articles that discussed the role of the immune system, especially cellular immunity, in the pathogenesis of the disease.

Buerger's Disease

Several clinical reports from the 19th century described patients with signs resembling that of TAO, but most of them lack pathologic certifications or could be attributed to arteriosclerosis (14). In 1879, Felix von Winiwarter described histopathological findings of TAO in the autopsy of a person suffered from chronic calf ischemia (15). In 1908, Leo Buerger reported detailed pathological features of 11 amputated limbs, proposing the hallmark of the disease as a pre-senile auto-amputation (7). He also reported the phenotype of TAO patients being a young male between 20 to 40 years old suffering from cold extremities, pallor, and pain. Trophic disorders leading to gangrene formation in the extremities and major amputations of the limbs are common in TAO patients. Other clinical findings in Buerger's disease are perivascular inflammation and fibrosis-adhesion of the terminal nerves and the veins of the lower extremities (8).

Demographic Features and Epidemiology of Buerger's Disease

TAO has been reported globally, but its incidence rate is variable (16). Between 8 and 12.6 per 100,000 people in North America suffer from TAO. It is rare among the European nations; the highest incidence of TOA is in India, Japan, South Korea, Sri Lanka, and amongst the Ashkenazi Jews (4, 16, 17). The distribution of TAO incidence could be related to the specific methods of tobacco consumption in the prevalent regions, such as homegrown Kawung cigarettes in Indonesia or Bidi cigarettes in Sri Lanka and Bangladesh (18).

Genetic Predisposition

TAO incidence is high in Israel, India, and Japan (4, 19, 20). These epidemiologic findings suggest that major histocompatibility complex (MHC) molecules have an effect on the pathogenesis of the disease.
Mc Loughlin et al. reported that HLA-A9 and HLA-B5 are more common in TAO patients (9). Furthermore, a study conducted by Otawa et al. shows that the prevalence of HLA-A1 and HLA-BW is higher in Japanese males who suffer from TAO (21). Several other HLA types are related to TAO, including HLA-DR4 and HLA-B8 (9, 22). HLAB12 may have a protective effect on the disease (10).

Clinical Manifestations

Differential diagnosis of the TAO includes all conditions that have the potential to cause terminal ischemia of the extremities. The signs of TAO include pain at rest, ulceration, and gangrene formation (4, 18, 23). Despite the arteriosclerosis in this group of patients, intermittent claudication is one of the rare manifestations. If intermittent claudication is present, it would be a sign of calf artery's involvement. The most common signs of TAO are pain at rest due to ischemia and ulcers of the fore-foot. Unlike arteriosclerosis, the involvement of the superior part of the limb is common. Around 50% of the patients have isolated lower extremity involvement, in 30 to 40% of the cases, both lower and upper extremities are involved, and in 10% of the cases, only the upper extremity is affected (17). Unlike

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atherosclerosis, TAO presents with Raynaud phenomenon or Frank digital ischemia, due to the involvement of the upper extremities. Thrombophlebitis is present in 40 to 50% of TOA cases (17). Histopathological findings suggest the involvement of aortic, iliac, cerebral, coronary, mesenteric, pulmonary, and even the spermatic artery (24-26). Unlike the other necrotizing autoimmune arteritis, around 90% of TAO patients have involvement of lower extremities (16).

Due to the need for major limb amputation, the prognosis of TAO is worse than arteriosclerosis and other types of arteritis (16, 27). A review reported that 19% of TAO cases need Hallux amputation, amputation of the forefoot, and 6.3% will have finger amputation (16). There is a greater number of amputation cases reported in North America and Europe than in Japan. Tobacco consumption makes TAO patients more prone to amputation, but the process of the disease seems benign in those TAO patients who cease tobacco consumption. In a study conducted by Olin et al., amputation was not needed in 94% of patients who quit cigarette smoking, but 43% of TAO patients who continued smoking had at least one amputation procedure (4, 28). Life expectancy in TAO patients is the same as the healthy general population. It has a 97% five-year survival and 94% ten-year survival rate (16).

Pathogenesis

Allen and Brown were the first who hypothesized that the etiology of TAO disease might be linked to a pathogenic microbe or virus (29, 30). In 1923, a gram-negative bacillus was successfully cultured from the blood samples of TAO patients, and in 1925, various organisms, such as staphylococcus and gram-negative bacilli, were cultured from the tissues of the affected organs (30). Only in one case, the inoculation of the disease was reported, which was in a limb amputation surgery of a TAO patient, and arteriography supported the assumption about the infectious nature of the disease (31). Leo Buerger prepared a mixture of the arteries from the TAO patients' amputated organs and inoculated a series of volunteers, who were in the silent phase of the disease, with the mixture. After ten years, the collected data could not support the hypothesis of the disease being infectious (32). In 2005, Iwai et al. found oral bacteria-like *Porphyromonas* in an arterial thrombosis (33). A gram-negative commensal bacteria-like *Porphyromonas gingivalis* can commonly induce IL23 expression in macrophages, through the adenosine triphosphate pathway (ATP) (34). IL23 triggers the differentiation of naïve T cells into Th17 or increases the stability of Th17. Th17 plays a key role in inflammatory autoimmune diseases (35, 36).

Lipopolysaccharides (LPSs) of oral commensal bacteria like *P. gingivalis* can lead to platelet aggregation and reduce the risk of endothelial thrombomodulin, however, they cause arterial thrombosis and inflammation (37). LPS of aggressive bacteria like *P.gingivalis* activates endothelial cells through TLR4 and leads to increased production of proinflammatory molecules such as IL1β, IL6, IL8, MCP-1, ICAM-1, VCAM-1, and E-selectin (33, 37-40). This, in turn, can affect monocytes, induces TNF-α, IL1β, and IL6 production, and increases monocyte adhesion to the endothelium (41, 42). TLR4 is a member of the Toll-like receptor family and plays a crucial role in the innate immune response to the microbial components. TLR4 can recognize the LPS of gram-negative bacteria through a receptor of LPS called CD14 (39, 40). Overexpression of CD14 molecules can cause progressive tissue degradation (43).

Neutrophilic elastase and reactive oxygen intermediates (ROIs) can cause tissue degradation (42). Cigarette smoking

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produces ROIs. Neutrophilic elastase increases IL8 through TLR4 (43). In the presence of LPS, TLR4 can induce immune responses of Th1 and Th17 (44). In the early stages of the inflammatory response to *P.gingivalis*, LPS can trigger inflammatory reactions through monocyte/macrophage activity (45). Inflammatory cells release vasoactive mediators, histamine, bradykinin, prostaglandins, ROIs, and chemokines like IL8 and MCP-1, causing vasodilation or constriction (44, 45). In addition to the detection of microbial components, TLR-4 recognizes exogenous free oxidative radicals in cigarette smokers (46).

LPS can also inhibit Prostaglandin I2 (*PGI2*) synthetase. Prostaglandin H2 (PGH2) accumulates in the cells and causes smooth muscle contraction. Therefore, PGH2 should be converted to Prostaglandin E2 (PGE2), which is an inducer of P-selectin (47). LPS can modify platelet function, and aggregation can cause more thrombotic events through increasing platelets (48, 49). Figure 1 summarizes the role of LPS in TAO pathogenesis.

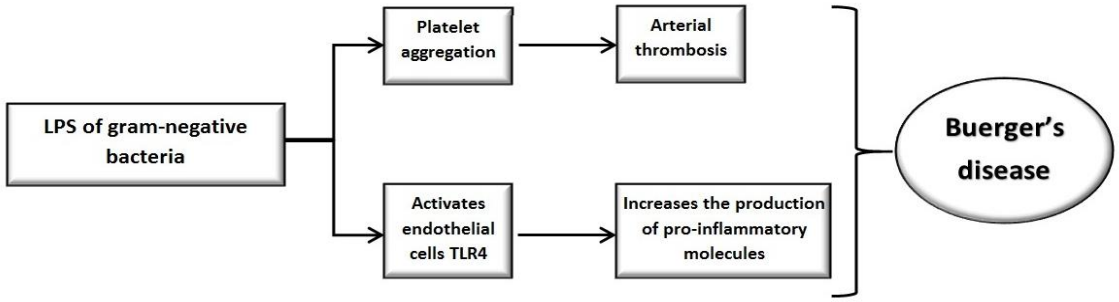


Figure 1. Schematic that illustrates the role of gram-negative bacteria lipopolysaccharide.

The Role of the Notch Signaling Pathway

The Notch signaling pathway plays an important role in differentiation, survival, angiogenesis, and cell proliferation (11-13, 50). In endothelial cells, the Notch pathway aids VEGF in the regulation of VEGFR-1 and VEGFR-2 receptors, this, in turn, will control the activity of the endothelial cells and leads to the production of new blood vessels through angiogenesis (13, 50-53). Although recent studies proposed the important role of the Notch signaling pathway in angiogenesis (54, 55), limited data exist about the association of TAO and the Notch signaling pathway (56).

Literature Review of Humoral Immune System and Buerger's Disease

Kobayashi et al. did a study on the TAO patient's arterial walls, and they showed that the cells' infiltration mainly occurs in thrombus and intima. The number of infiltrated T cells (CD3+) was much higher than B cells (CD20+). In acute and sub-acute phases of the disease, macrophages (CD68+) and dendritic cells (S-100+) are present in the intima of the vessels. Furthermore, IgG, IgM, IgA, and complement factors such as 3d and 4c were precipitated out in the internal elastic lamina (57).

In an immunological study which was conducted on 10 TAO patients by Gulati et al., adaptive immunity by T cells, in response to arterial antigens, led to increased serum immunoglobulins and anti-arterial antibody formation, and immune complexes were observed. Therefore, immunological factors could be a plausible explanation (22).

A study conducted on the immunological causes of autoimmune diseases, such as TAO, showed that there is a link between tobacco consumption and a decrease in the level of IFN, the activity of antigen-

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presenting cells, and the level of circulating immunoglobulins; this will result in the suppression of adaptive immune system. In addition, cigarette smoking can increase free oxidative radicals, release intracellular antigens, and increase the activity of B cells and circulatory level of T cells, causing allergies, inflammatory, and autoimmune diseases (58).

The Zheng et al. study showed that Gamma globulins, immune complex, and IgG levels rise during the disease, and the T cell immunity is dampened. Light microscopy provided evidence of infiltration of lymphocytes, neutrophils, and monocytes in all layers of the vessel. Electron microscopy showed immune complex precipitation in the involved vessels. They, therefore, proposed that TAO is an autoimmune disease that correlates well with the Ab-Ag complex (59). Li et al. and Roncon de Albuquerque et al. proposed that immune complex precipitation in blood vessels is a main histopathological finding in this disease (60, 61).

Papa et al. concluded that TAO patients who smoke show the same degree of cell-mediated response to tobacco glycoprotein (TGP), compared to smokers who are not suffering from TAO; however, there was not any T cell-mediated response in non-smokers (62).

A study in 2012 showed that there is an increase in cytokine production in TAO patients, which correlates with the inflammatory response in patient's blood vessels. Besides, increased circulatory IL-17 and IL-23 suggested the presence of an autoimmune cause (63).

Conclusion

The current literature examining the association between T cell immunity and TAO disease supports the presence of an immunological basis of the TAO disease as an autoimmune condition. In some studies, it is concluded that infectious particles act as a trigger for the disease, through the release of cytokines such as IL23 which will induce the formation of Th17; this plays a key role in the pathogenesis of autoimmune diseases such as TAO. One of the known bacteria that causes IL23 secretion is *Porphyromonas gingivalis.* A voluntary inoculation of the silent patients with tissues of the TAO patients did not support the infectious nature of the disease; therefore, the association of the infectious disease with TAO remains controversial.

Several histopathological studies discussed the role of the T cell-mediated immunity in the pathophysiology of the disease on the basis of T cells presence in the arterial tissue. Furthermore, the immune complex and complement precipitate in vascular tissue, which does support the immunological hypothesis of TAO. Despite the fact that several studies validated the role of T cell immunity in the pathogenesis of the disease, studies conducted on the immunological basis of the TAO showed suppression of T cell immunity during the course of the disease. In addition, another study showed no difference in cell-mediated immune response between TAO patients who smoke and smokers who do not have TAO. To conclude, studies that investigated the effect of T cell-mediated immunity could not come to a conclusion with a robust result, and this link remains controversial. Since the treatment of medical conditions is mainly based upon their pathophysiology, it is advisable for researchers to analyze the hypothesis behind this condition, especially the T cell-mediated pathways. Furthermore, even though we know that tobacco consumption might initiate an immunologic response, such as T cell response, further investigations are required to prove the role of smoking in this mechanism.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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