Current Topics of Buerger's Disease

Buerger Disease, Smoking, and Periodontitis

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Weak oral bacteria such as periodontal bacteria or *Chlamydia pneumoniae* have been observed in various arterial and venous lesions with epidemiological data reported prior to the discovery of bacterial invasion into vessels. Rich lymph vessels easily bring the bacteria from the mouth to the neck and the venous angle, which is directly open to the blood vessels. Periodontal bacteria travel within platelets and *Chlamydia pneumoniae* can be carried by monocytes. The transportation system of other weak oral bacteria have not been determined. Periodontal bacteria, especially *P. gingivalis* aggregate platelets and form thrombi. At the same time, secretions such as serotonin, various cytokines, and adhesion factors also appear in the blood. The characteristics of arterial lesions are dependent on the age of the patient and the condition of the endothelial cells. In young patients, infectious incidents occur due to embolic mechanisms in Buerger disease or adhesion to the superficial veins valves in varicose veins. In older patients, incidents result in adhesion in the proximal aorta, coronary arteries, or large arteries. The hypothesis here unifies the evidence on vessel lesion development and explains the possible discrepancy between vascular diseases.

Key words: weak oral bacteria, Buerger disease, *Treponema Denticola*, *Porphyromonas gingivalis*, platelet aggregation

INTRODUCTION

Since 1999, various weak oral bacteria have been identified in atherosclerotic lesions.¹⁾ Among these bacteria, *Chlamydia pneumoniae*, which resides in the mouth, pharynx, or bronchus, has been thoroughly investigated and confirmed to be transported to vessel walls by monocytes.²⁾ This mechanism of invasion appears to be a factor in the development of atherosclerosis. Additionally, cytomegalovirus can be absorbed from the oral cavity,

resulting in opportunistic infections. Recently, the so-called inflammatory abdominal aortic aneurysmal walls revealed the presence of cytomegalovirus.³⁾ However, further study of the virus has shown great difficulty compared with that of the bacteria. *Helicobacter pylori* is a well-known bacteria residing in the stomach and sometimes in the oral cavity. It also has been identified in vessel walls. In the 21st century, the periodontal bacteria group, which includes several species, has been demonstrated within vessel walls.⁴⁾

DETAILS OF BUERGER DISEASE INFECTION THEORY

Many investigators, including Leo Buerger, considered Buerger disease an infectious disease. In spite of studies of cases and animal experiments, no one was able to discover the pathogen. Reports were published by doctors such as Edgar Allen, Lauderdale, Rabinowitz, Goodman, Horton and Dorsey, Schmidt-Weyland, Barotolo, Roncon, Winternitz, and Haga. Buerger stated in his 1914 paper,

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“Thrombo-angiitis obliterans is an infectious disease in which a specific type of organism is at work; and although it has not yet been possible to demonstrate either bacteriologically or morphologically the presence of the offending agent, the pathological findings clearly indicate whither future studies should be directed in order that the causative factor may be discovered”.⁵⁾ In 1928, Professor Allen of the Mayo Clinic also had suspicions about oral bacteria as a cause and mentioned that 75% of 87 Buerger disease sufferers showed periodontal infection, and 80% showed tonsil enlargement or pus attachment.⁶⁾ Allen believed that Buerger disease was an infectious disease until his death in 1967. After his death, the molecular biological approach or immunological technique became popular enough to deviate from infection theory. Thereafter, no papers were written that discussed the infection theory. Finally, Buerger disease was classified as an inflammatory autoimmune disease.

PERIODONTAL BACTERIAL INVASION TO THE ARTERIAL WALL AND THROMBUS

Epidemiological evidence connecting periodontitis and vascular diseases with atherosclerotic changes was not widely reported prior to 2000. Periodontal bacteria are not detectable with the usual cultures, and they are extremely difficult to identify. These periodontal bacteria consist of anaerobic bacilli or spirochetes and include more than 300 species overall. Usually 6-7 species are examined as representative bacteria. When the bacteria are not expected to live in the vessel thrombi or plaques, methods for identification are extremely limited. Therefore, the established PCR (polymerase chain reaction) method of detecting the DNA of the oral bacteria became popular.⁷⁾ After their presence has been confirmed, immunofluorescence methods help to find the location of the bacteria in the vessel walls. PCR methods for oral bacteria are available as a sterile kit and have been used without contamination since 1980. Dr. Buerger and Professor Allen could not find the bacteria even though they both strongly suspected bacterial infection in Buerger disease.

Up to now, periodontal bacterial DNA has been detected from carotid arterial plaques, coronary arterial plaques, abdominal aortic aneurysmal walls (86% of patients), and intraluminal thrombi (88%), atherosclerotic vessel plaques (52%), occluded arteries of Buerger disease patients (93%), migrating phlebitis samples (2 cases, 100%), and primary varicose veins (48%).⁸⁻¹⁰⁾

HOW ARE BACTERIA TRANSPORTED TO THE VESSEL WALL ?

Our results using rats after continuous intravenous oral bacterial infusion showed newly formed thrombus in the small arteries of the extremities with 50% of the specimens having bacterial DNA.¹¹⁾ Other findings demonstrated reduced inflammatory response surrounding the occluded lesions, explained by the fact that the weak bacteremia caused thrombus formation, and the occlusions came from embolic episodes caused by the bacteria-including thrombus. Unexpectedly, the bacteria appeared on the arterial side without killing events carried out by white blood cells or organ phagocytic cells in the venous circulation.

In 2004, we began using platelet-rich plasma (PRP) to stimulate good wound healing. When we accidentally added periodontal bacteria (*P. gingivalis*) to the sample and saw the mixed fluid through stereoscopic microscope, we were able to find active movement. After examining the sample by electron microscope, we observed that periodontal bacteria (*P. gingivalis*) was engulfed by platelets, and no morphological change was observed in the bacteria for one hour. In addition, platelet aggregation was also observed. On the other hand, the bacteria captured by granulocytes were clearly killed within one hour. These observations confirmed that *P. gingivalis* bacteria aggregate strongly in the platelets, enter the platelets, and live without dying¹²⁾ (Figs. 1, 2). Another periodontal bacteria, *T. denticola*, showed relatively weak reactions with platelets.

P. gingivalis induced platelet aggregation that reached a maximum in a few minutes, and the mass became more than 20 microns greater than the size of the small artery. This suggested that the healthy small arteries of the rats could become embolized by platelet aggregation, as shown in animal experiments.¹²⁾ Moreover, clinically in Buerger disease, the healthy but spastic arterial lumen of the fingers or toes could be occluded through sudden onset.

Additionally, the aggregative reactions of periodontal bacteria with platelets are strong enough to secrete various cytokines, and products such as serotonin, E-selectin, ICAM-1, and VCAM-1. As periodontitis itself expresses inflammatory substances such as IL-6, and TNF- α , it should be considered a systemic disorder.¹³⁾

Fig. 1 Platelets may play a vital role in the transportation of oral bacteria. *P. gingivalis* is a round-shaped mass.

SERUM BACTERIAL ANTIBODY TITER CHANGES IN PERIODONTAL DISEASE AND BUEHRER DISEASE

The human body reacts to all bacteria with antibody production. The antibodies resist infection and should act to prevent pending infection. This immune style can prevent further periodontal disease development and progression. However, this theory remains controversial. It can be difficult for antibodies in the saliva and blood to protect the infection clinically, and the treatment of periodontal disease can also be challenging due to variations in the bacteria and pathogenesis of the disease. Chen et al. reported that the antibody titer for periodontal bacteria is significantly elevated in Buerger disease patients,¹⁴⁾ reconfirming that Buerger disease patients have a very poor periodontal environs⁹⁾ (**Fig. 3**). In Buerger disease the antibody titers may actually be changing related to the severity of periodontitis. Since the bacteria are actually weak and can be treated easily by antibiotics, the titer level decreases rapidly. However, this evidence should be discussed in more detail from the dental point of view.

Fig. 2 Schema of the reaction of oral bacteria and platelets.

The direct link between *Chlamydia pneumoniae* and atherosclerosis had been previously studied, and the effects of antibiotic treatment confirmed in animal experiments.¹⁵⁾ However, large clinical trials failed to show any significant differences with antibiotic regimens.¹⁶⁾ The fact that the bacteria are opportunistic, normally present, and weak, contains further problems in determining an-

Fig. 3 Oral conditions of Buerger disease patients (two recent cases. **A:** 34-year-old male; **B:** 55-year-old male, with no fingers and right below-knee amputation).

tibody titer changes, immune products, or advantages of intermittent antibiotic treatment. Further experiments are needed to resolve these issues.

DOES EVERYONE WITH SERIOUS PERIODONTITIS DEVELOP BUERGER DISEASE ?

When we hypothesize that all vascular lesions may be affected by oral bacterial infections, we can propose three factors that are strongly related: (1) Endothelial cells undergo age-dependent changes. The endothelial cell activity for a person aged 20–30 and one aged 50–60 is quite different in relation to adhesive factors, action against bacteria, and platelet or monocyte reactions. (2) Oral bacteria are affected by many internal and external factors such as smoking, diabetes, and pregnancy. The presence of these effects is important when considering the infectious progression. (3) Lesions may be influenced by genetic conditions. The influence seems to be reasonable, not dominant, as in cancer. Atherosclerosis runs in families, but Buerger disease does not. In the over 200 Buerger disease patients we have studied, we have not observed any parent-child connections, and only one set of identical twins.

However, recent studies on Buerger disease have shown a specific HLA locus and infection susceptibility for basilar bacteria, such as periodontal bacteria.¹⁷⁾ Varicose veins seem to occur in mothers and daughters. Interestingly, approximately 50% of varicose veins contain periodontal bacterial DNA suggesting that pregnancy may be linked to varicosity development when the woman suffers from periodontitis during pregnancy. It is apparent that varicose vein becomes evident after delivery in many women, and weak bacteria may be involved in the destruction of venous valves.

HYPOTHESIS AND FUTURE VIEWS OF BUERGER DISEASE DEVELOPMENT

We believe that the *Chlamydia pneumoniae* bacteria can be transported to the vessels containing monocytes, adhere to the damaged vascular regions, and then act as one of the factors in atherosclerosis. On the other hand, it is also possible that cytomegalovirus will appear in the aneurysmal wall along the same periodontal bacterial routes. *Helicobacter pylori* is not commonly associated with vascular lesions, but serum titers were high in our results of Buerger disease research. However, at the present time, the role of *H. pylori* is not well understood. Nevertheless, using recently reported evidence we have developed a hypothesis for Buerger disease.

Pathogens in Buerger disease are likely mainly periodontal bacteria, but pyloric bacteria may also be involved. Among periodontal bacteria, *T. denticola* and *P. gingivalis* are well known and may work together to form dental plaques. *P. gingivalis* is inevitably moved as an initiator of platelet aggregation, and from the venous angle of the neck, the bacteria group can enter the blood stream and stimulate platelet aggregation after uptake into platelets. It is suggested that aggregation reaches a maximum when platelet thrombi pass through the lung, after which the thrombi start to move in the arterial blood stream. When the arterial wall is young but spastic from cigarette smoking, the platelet thrombi containing the oral bacteria do not adhere to the arterial wall but make a small arterial embolism. It is suggested that the digital arterial obstruction in Buerger disease patient angiography may be initial findings. This change will grow to the proximal arterial regions owing to packing. Microorganisms that pass through capillaries can be caught at the venous valves, resulting in phlebitis migrans or deep

Fig. 4 Hypothesis of Buerger disease development.

vein thrombosis formation in the extremities. In Buerger disease, spastic changes of the small end arteries are a key finding. The literature shows small arterial changes are very common throughout the body, but are symptomatic only in the extremities (**Fig. 4**).

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