

Pathogenic Mechanism of the Artery and the Vein in Buerger Disease: Our Hypothesis

Takehisa Iwai^{1*}, Makoto Umeda², Yoshinori Inoue³ and Tokyo Medical and Dental University Buerger Disease Research Group

¹Tsukuba Vascular Center, NPO Buerger Disease Research Institute, Japan

²Department Periodontology, Osaka Dental University, Japan

³Vascular Surgery Service, Tokyo Medical and Dental University, Japan

*Corresponding author: Takehisa Iwai, Tsukuba Vascular Center, NPO Buerger Disease Research Institute, 980-1, Tatsuzawa, Moriya city, Ibaraki prefecture, 302-4541, Japan, Tel +81297479955, Fax +81-298-45-4541; E-mail: iwai@keiyu.or.jp

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Abstract

Our hypothesis started from the discovery of the periodontal bacteria DNA in occluded arteries and phlebitis veins of Buerger disease. It was accelerated by the observation of platelets and bacterial coexistence showing aggregation of platelets. Using our hypothesis, we would like to explain the characteristic points of Buerger disease that have already been reported in various documents. Our hypothesis of Buerger disease is able to explain the signs and symptoms pretty easily. More investigations are necessary to understand the full story of the disease. The infection of the thrombus is the core of the disease. Angiitis is a secondary reaction of the intimal area.

Keywords: Buerger disease; Periodontal bacteria; Platelets aggregation; Bacterial emboli; Phlebitis migrans

Introduction

A new hypothesis about Buerger disease can be drawn from our investigations, mainly, and from others' studies. The hypothesis started with the discovery of periodontal bacteria DNA in occluded arteries and phlebitic veins of Buerger disease [1,2]. It was accelerated by the observation of platelets and bacterial coexistence showing aggregation of platelets [3].

Using our hypothesis, we would like to explain the characteristic points of Buerger disease that have already been reported in various documents. Of course, it requires a bit of imagination and clinical common sense.

In animal experiment using rats, intravenous infusion of periodontal bacteria showed thrombus formation and the bacteria are re-isolated from the vessel parts of the rats [4]. Another rat model experiment showed similar pathological findings of Buerger disease.

Hypothesis

Here we would like to summarize it as part of the story of how we developed the hypothesis.

Smoking worsens the teeth and leads to periodontitis [5]. Periodontitis includes plenty of bacteria, which are mostly anaerobic and reside in the gingival deep pockets around the teeth.

Some of the bacteria invade or drain into the lymph vessels around the gingiva. The bacteria are transported to the venous angle in the neck by the movement of the lymph vessel.

The bacteria move into the venous stream and, firstly, react with the blood. At least, one of the well-known periodontal bacteria, *Porphyromonas gingivalis* (Pg) react with platelets and that protects

the life of the Pg for a while, keeping the bacteria inside (Figure 1) [3]. Other oral bacteria may be transported with monocytes or unknown granulocytes. This study will be our next step. Some bacteria may be transported directly without any protection.

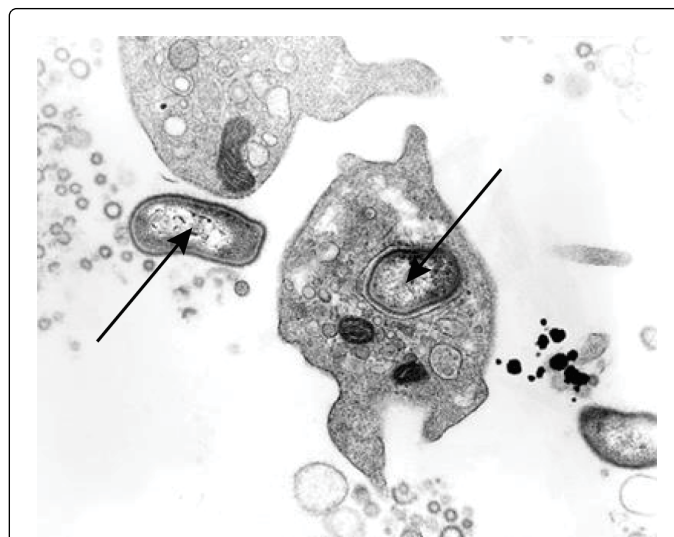


Figure1: Pg react with platelets and platelet keeps the bacteria inside. From the literature (3). Arrows indicate Pg

Platelets aggregate promptly after stimulation of Pg invasion or engulfment [3]. During this reaction, serotonin, or many cytokines will be released. The aggregation size may reach over 80 μm (Figure 2). Platelet thrombus that includes bacteria will be an embolic source to all of the regions of the body, especially to the extremities that are weak zones for phagocytosis.

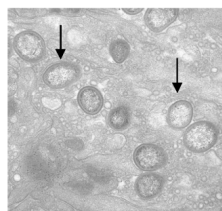
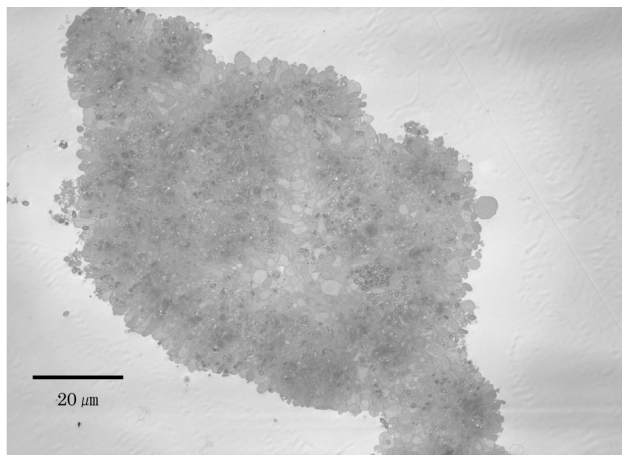


Figure 2: The platelet aggregation size, including oral bacteria, reaches over 80μm. From the literature [3]. Arrows indicate Pg.

The platelet thrombus plays a main role in the development of Buerger disease. The fingers and toes are the targets for the small thrombus emboli. It is easy to see that the most cases start with the sudden onset of toe or finger necrosis (Figure 3) [6].



Figure 3: Typical case of Buerger disease started with the sudden onset of big toe necrosis

The thrombus gradually blocks the proximal area of the artery. The middle area may be opened by thrombolysis or recanalization. This phenomenon is strongly related to a normal intimal surface, which is completely different from an atherosclerotic damaged intimal surface found in the elderly. Only a spastic condition or allergic reaction will present in the artery as the effect of nicotine from tobacco [7].

The bacteria may enter the vaso vasorum, which leads to adventitial inflammation and sympathetic nerve damage. Just as above, the recanalized thrombus vessels may be invaded by bacteria, which may show some diffuse infiltration of the infection.

Adventitial infiltration via vaso vasorum may change the sympathetic nerve. We observed the degeneration of the sympathetic nerve with an electron microscope (Figure 4). Another study suggested that, in Buerger disease, there is reproduction of the nerve fibers in the re-vascularized thrombus.

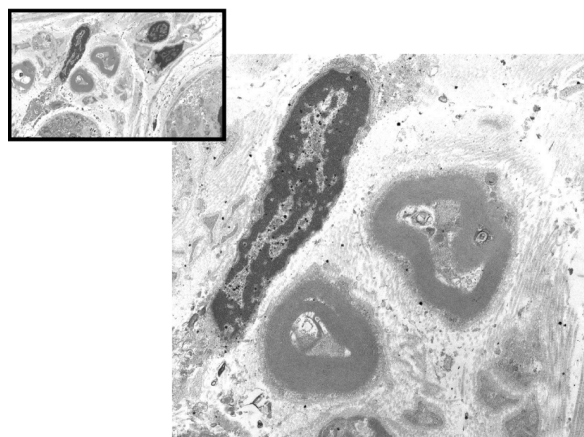


Figure 4: The degeneration of the sympathetic nerve fiber and sheath which adhered to vessels. An electron-microscopic view

After passing through the small vessels, or capillary network, the bacteria will reach the small vein. The valve of the small vein functions as a good net to catch the bacteria. Phlebitis will occur [2]. The bacteria will move up to the proximal portion of the superficial vein; this is called migrating phlebitis. On the other hand, bacterial thrombi in the deep veins destroy the vein valve and cause the deep vein thrombosis or reflux. Usually, the velocity is higher in the deep veins than in the superficial ones, which explains why deep vein thrombosis is not so common in Buerger disease [2].

These phenomena will occur in other organs or arteries too. In our hypothesis, systemic arterial attacks should occur. However terminal arteries with poor phagocytic areas will suffer from the occlusion of the vessels. These are possibly the digital, coronary, or gastric arteries. The brain, lung, liver, kidney, spleen, and sexual organs seem to be safe from the bacterial small thrombi invasion. We experienced three gastric arterial occlusions (Figure 5) [8]. The literature shows coronary occlusions and cerebral artery occlusions have already been reported as well [9,10].

Dental care clearly lowers the incidence of Buerger disease development. The decrease started in the USA 60 years ago and in Japan, 40 years ago. So, adequate oral care is one factor, but genetic influence is another; not all heavy smokers will be a candidates for Buerger disease [11]. The schema of our hypothesis is shown in Figure 6.

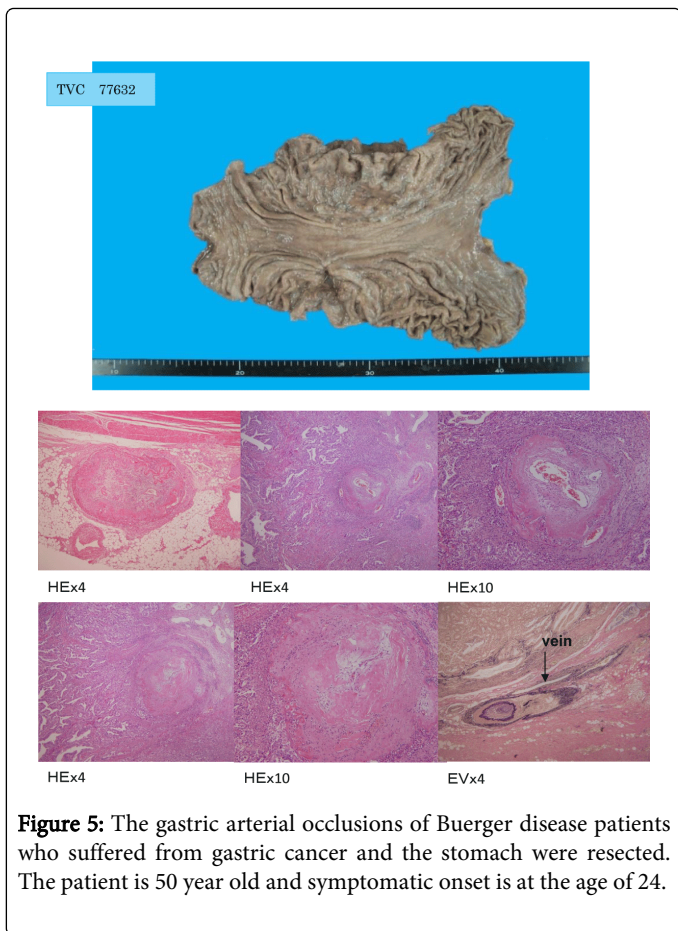


Figure 5: The gastric arterial occlusions of Buerger disease patients who suffered from gastric cancer and the stomach were resected. The patient is 50 year old and symptomatic onset is at the age of 24.

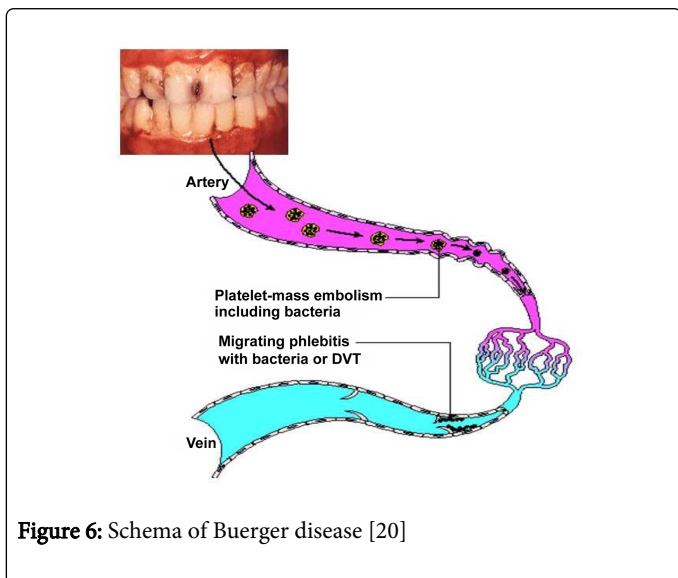


Figure 6: Schema of Buerger disease [20]

Discussion

A small epidemiological study (n=14) shows that Buerger disease patients suffer from periodontal disease in moderate to severe or dental-loss stages [1]. A global study is desirable. The relationship between periodontal disease and cigarette smoking is being studied

and the correlation is clear [5]. The main factor is the nicotine in the tobacco.

The fact that there is a lymphatic pathway from the oral region to the venous angle is well established. Why anaerobic bacteria Pg enter the platelets and reside is not well known. However, the inside of the platelets are anaerobic and Pg like to feed on iron, which the platelets contain. We need to conduct more surveys about other targets from blood components such as monocytes, in which Chlamydia pneumonia is known to reside and be transported to the peripheral vessels [12].

About the lung circulation of the periodontal bacteria, we know that oral bacterial endocarditis or peripheral infectious arterial aneurysms have occurred pretty often after a tooth extraction when we antibiotics were not used. It is also well known that after brushing, after extraction of the teeth, or after periodontitis treatment, oral bacteria appear in the venous or blood stream quite often. These phenomena explain that the bacteria follow a route from the dental region to-the neck, then to-the lung and then to- the heart. And this means that circulating bacteria is common in humans and it shows that lung filtration is not so tight and not so complicated. So, we can guess that bacteria including platelets easily pass through the lung. Our experiment revealed that it takes more than 10 seconds to make a large platelet mass, which seems to be enough time to make a large thrombus after leaving the heart.

Since Buerger disease is recognized as an independent disease in general, a lot of blood chemistry data were examined looking for characteristics and diagnostic factor. CRP, ANCA and anti-cardiolipin antibodies were not specific [13,14]. Finally it was concluded that no specific blood test could identify Buerger disease.

The angiographic finding is relatively characteristic [15]. Distal digital arterial occlusion is often observed. In our hypothesis, this is the likely story. Continuous thrombi emboli make a long distance occlusion from the toe or finger to below the knee usually, but a segmental opening is explained easily by movement of the soft thrombi to the branch by melting. In our hypothesis, in the limited acute phase, fever or malaise will be demonstrated with positive CRP tentatively. After the acute phase, we believe the antibody will work to kill the bacteria in the blood. Our investigation revealed a hyper antiperiodontal immunoglobulin level in the most of the cases [16].Cork-screw type collateral will appear in the chronic phase.

The liver, lung, spleen, brain and lymph node have a strong phagocytic activity; they ingest the oral bacterial mass. In contrast to the above-mentioned organs, fingers or toes, the lower or upper extremities lack such a system. So, we called it a weak phagocytic zone in our hypothesis [5].

One Japanese vascular surgeon says the phlebitis migrans has an acute infectious-like appearance [17]. From these reports, it is apparent that Buerger disease is different from general vasculitis. The phlebitis site includes giant cells and granulocyte invasion as shown in the occluded artery site. In the chronic phase, pathological changes of the vessels are minimal and the steroid therapy is not effective and was abandoned.

Antibiotics might be necessary for recovery from the acute phase [18]. It is well known that periodontal bacteria are easily killed by antibiotics. Especially, azithromycin is effective at keeping the periodontal bacteria count to nearly zero for more than three months.

Dr. Hachisuga showed sympathetic re-growth in the occluded arteries [19]. He proposed the Leriche hypothesis: a sympathectomy is very effective at repressing the sympathetic activity through blocking it. Actually, most Buerger disease patients are happy with a sympathectomy, usually of the lumbar type. Some of our patients enjoy skiing after a lumbar sympathectomy because they no longer feel the cold.

Modern life, including modern dental care, is decreasing the incidence of Buerger disease. However, the numbers are still high in southern and west Asia, Africa and even in northern China. We hope to continue to raise awareness all over the world.

The major difference between Buerger disease and atherosclerotic disease is that Buerger disease is infectious. Mainly, the infection originates in the thrombus, so we can say the thrombitis is a true characteristic. On the other hand atherosclerotic disease is a degenerative disease. It originates from the changes in the internal and medial layer deposition of the fat, cells or sometimes, from bacteria. Oral periodontal bacteria may be one of the large components.

Conclusion

Our hypothesis of Buerger disease is able to explain the signs and symptoms pretty easily. More investigations are necessary to understand the full story of the disease. The infection of the thrombus is the core of the disease. Angiitis is a secondary reaction of the intimal area.

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