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Morphologic Change of the Internal Elastic Lamina in Buerger's Disease

Morphologic features and pathogenesis of arterial changes occurring in Buerger's disease (thromboangiitis obliterans) are still controversial. This study describes histopathologic features of medium sized arteries from patients with Buerger's disease, particularly of the internal elastic lamina in relation to the immunologic mechanism of the injury. Seventeen segments of occluded arteries (femoral or popliteal arteries) from 17 patients with Buerger's disease were analyzed by histopathological and immunohistochemical methods. The most characteristic features were total luminal obliteration, together with a varying degree of recanalization and deposition of hemosiderin pigments. Detailed analysis, however, showed marked undulation and multiplication of the internal elastic lamina (100%) associated with basophilic degeneration and delicate linear calcification (47%). Lymphocytic infiltration along the internal elastic lamina was seen in 71% and was associated with localized edema. Lymphocytes along the lamina were consistently positive for T cell marker. Mild to moderate fibrosis was present at the media in 24%. Adventitial changes included mild, nonspecific and irregular fibrosis seen in 53%. Immunologic injury to the internal elastic lamina associated with T-lymphocytic infiltration might be the initial morphogenetic mechanism of the thrombotic occlusion and organization of medium-sized arteries in Buerger's disease.

Key Words: *Thromboangiitis Obliterans; Internal Elastic Lamina; T-Lymphocytes*

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INTRODUCTION

Buerger's disease (thromboangiitis obliterans) is a non-arteriosclerotic, segmental, occlusive inflammatory disease of small- and medium-sized arteries and veins of unknown cause (1). Smoking is claimed to be the most consistent clinical risk factor (2, 3) but the exact morphogenetic features are still to be elucidated (4). Several studies have suggested the possible involvement of cell-mediated sensitivity to collagen (5, 6), vasoconstriction induced by disturbances in catecholamine metabolism (7), hypercoagulability leading to thrombosis (8) or genetic predisposition (6). Recent investigations of the pathogenesis involved have revealed several immunologic mechanisms, including an association with certain HLA types (9), serum anti-elastin antibodies (10), and IgE and anti-collagen antibody activity (5, 11), circulating immune complex (12, 13), and antiendothelial cell antibodies (14). Immunohistochemical study showed that the immune complex is localized at the vasa vasorum, intima, and internal elastic lamina (15).

The morphological changes in diseased arteries occurring in Buerger's disease were reviewed by Williams (16) and Shionoya (17). They focused on the morphologic changes in the small arteries, which showed thrombosis associated with transmural neutrophilic inflammation but media and internal elastic lamina were well preserved (16, 17). Though changes in the medium-sized femoral or popliteal arteries have more clinical significance if surgical treatment is considered, they have not been thoroughly studied.

We studied histopathologic changes in 17 medium-sized arteries resected from 17 patients with Buerger's disease. Particular emphasis was given to the pertinent morphologic features observed in the medium-sized occluded arteries, amenable to the surgical treatment, and the immunologic mechanism of the vascular injury.

MATERIALS AND METHODS

A histopathological study was performed on the oc-

cluded arterial segments from 17 cases of Buerger's disease occurring between 1986 and 1997. Every patient was a heavy smoker, and the clinical diagnosis was made on the basis of clinical criteria (18); smoking history, onset before the age of 50, infrapopliteal arterial occlusive lesions, either upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other than smoking. The clinical profiles of these cases are summarized in Table 1. In 14 cases, short segments of occluded arteries were resected for diagnostic pathological study during the arterial bypass procedure and in three cases, diseased vessels were dissected from amputated specimens. The Institutional Review Board for Ethics of the Seoul National University College of Medicine confirmed that there was no violation of the standard surgical procedure for the treatment of Buerger's disease. Two additional muscular arteries, occluded due to organized bland thrombus in which no inflammatory infiltrates were seen, were used as controls.

Cross and longitudinal sections were obtained from paraffin blocks. Hematoxylin and eosin, Masson's trichrome or elastic stains were used in each section. For those with lymphocytic infiltration, immunohistochemical staining was also performed using antibodies against L26 and UCHL-1 in order to reveal B and T cell subsets.

RESULTS

Total luminal obliteration with a varying degree of recanalization was the most characteristic feature of 13 cases. Dense collagenous tissue and a small number of fibroblasts were seen, though infiltration of inflammatory cells was rare. Recanalizing capillaries were scattered evenly within the fibrous tissue plug, and deposition of hemosiderin pigments at the fibrous luminal plug was seen in 11 cases (65%). A focal edematous area was present, but in no case was a foam cell collection or cholesterol cleft seen, thus excluding the possibility of atherosclerotic lesion. One case showed focal calcification in the thrombus. In three cases luminal contents were relatively early thrombus, showing aggregates of red cells, neutrophils and fibrin surrounded by a layer of granulation tissue. One of these three cases contained a multinucleated giant cell, one of typical feature in acute lesion (19), at the thrombus-vascular lumen interface. Lymphocytic aggregates were present along the elastic lamina. In 14 cases (82%), artifactual splitting of arterial wall had occurred between the intima and media, suggesting shrinkage of the luminal content.

Cross-sectionally, all 17 cases showed marked undulation and multiplication of internal elastic lamina (Fig. 1).

Table 1. Clinicopathologic summary of cases

Case No.	Sex/Age	Chief complaint	Biopsy site	Operation method*
1	M/32	Necrosis, left foot	Popliteal a.	Popliteal - peroneal, vein bypass
2	M/41	Delayed wound healing, left foot	Femoral/Popliteal a.	Femoral - tibial, vein bypass
3	M/33	Pain, left toe	Popliteal a.	Popliteal - peroneal, vein bypass, followed by amputation
4	M/36	Ulcer, left foot	Popliteal a.	Femoral - peroneal, vein bypass, followed by amputation
5	M/29	Claudication, right leg	Femoral/Popliteal a.	Femoral - tibial, vein bypass
6	M/23	Pain, left calf	Femoral/Popliteal a.	Femoral - peroneal, vein bypass
7	M/31	Pain at rest, right foot	Femoral/Popliteal a.	Femoral - peroneal, vein bypass
8	M/55	Pain, right lower leg	Femoral a.	Ileo - femoral, PTFE bypass
9	M/29	Necrosis, right toe	Femoral/Popliteal a.	Femoral - tibial, vein bypass
10	M/41	Gangrene, left foot	Femoral a.	Femoral - popliteal, vein bypass
11	M/43	Pain, left foot	Femoral/Popliteal a.	Femoral - tibial, vein bypass
12	M/45	Swelling, right leg	Femoral/Popliteal a.	Femoral - tibial, vein bypass
13	M/38	Gangrene & pain, right foot	Iliac/Femoral a.	Ileo - popliteal, composite bypass, followed by amputation
14	M/33	Pain, right foot	Femoral/Popliteal a.	Femoral - tibial, PTFE bypass
15	M/45	Ulcer, left toe	Popliteal a.	Femoral - tibial, vein bypass
16	M/28	Pain & ulcer, right leg	Popliteal a.	Popliteal - popliteal, PTFE interposition
17	M/40	Pain, right lower leg	Popliteal a.	Femoral - tibial, vein bypass

*PTFE, polytetrafluoroethylene tube graft

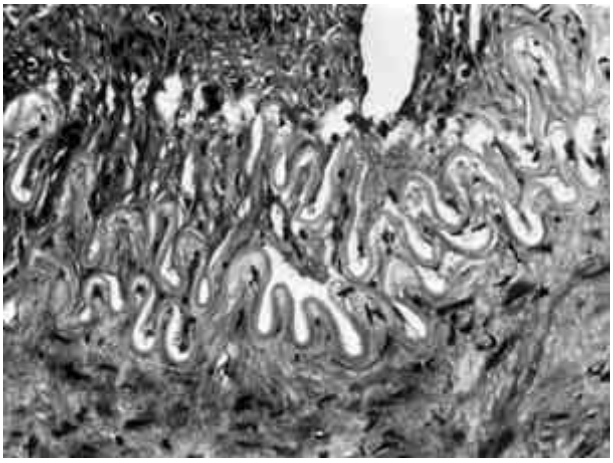

Fig. 1. The typical morphology of internal elastic lamina, seen in every case. Histological sections show marked undulation of the lamina, which show multiplication and artifactual splitting (H&E stain, ×200).

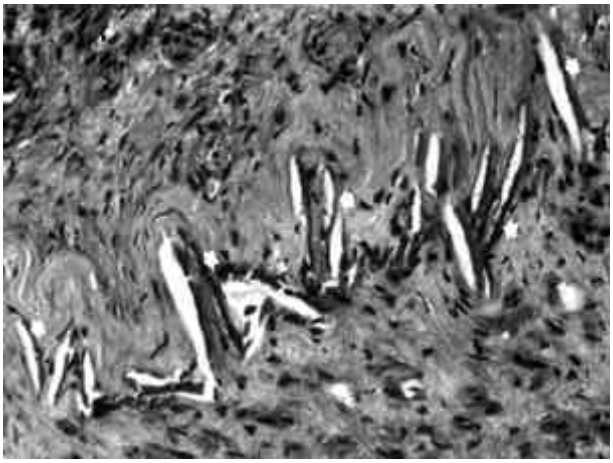

Fig. 2. Delicate linear spicules of calcification are seen along the internal elastic lamina (H&E stain, ×200).

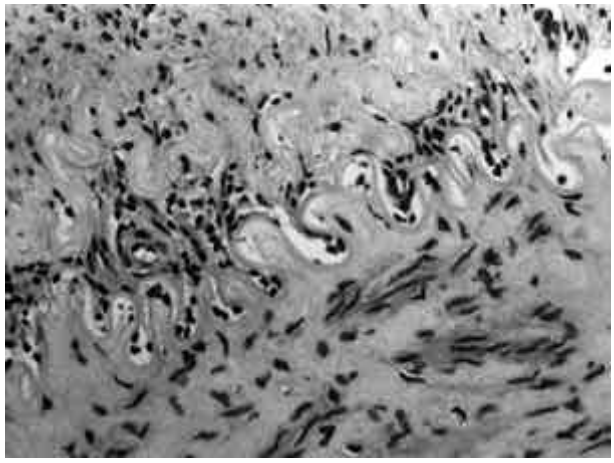

Fig. 3. Dense linear collection of T lymphocytes along the internal elastic lamina is associated with localized edema (H&E stain, ×200).

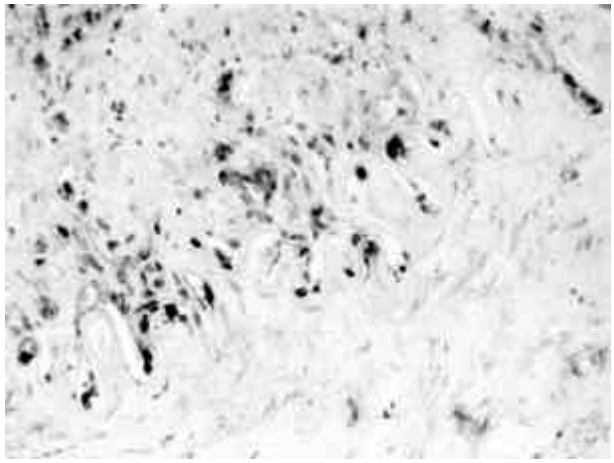

Fig. 4. Darkly stained UCHL-1 positive cells are noted along the internal elastic lamina (UCHL-1 stain, ×200).

Layers of lamina were of different thickness and some showed basophilic degeneration. Delicate linear calcification of the lamina was present in eight cases (47%, Fig. 2) and in three (18%) a dense patchy collection of lymphocytes was seen (Fig. 3). Two of these three cases (66%) showed non-recanalized early thrombi, nine other cases (53%) showed a few lymphocytes scattered along the internal elastic lamina; seven cases (41%) had localized edema.

In 11 cases, minimal to mild fibrosis was present at the media, but in others, the muscular layer was completely normal. In four cases (24%), mild focal lymphocytic infiltration was present at the media. One case showed microabscess formation. Mild, nonspecific and irregular fibrosis was present at the adventitia in nine cases (53%), and mild lymphocytic infiltration in four (24%); one of these showed perivascular inflammation.

Lymphocytes along the internal elastic laminae (Fig. 4) were consistently positive for UCHL-1, and two cases with fresh luminal thrombus showed dense collections of T-lymphocytes along the lamina. Lymphocytes scattered in the thrombus, however, showed a mixed population of B and T cells. In one case, a neutrophilic microabscess was focused at the internal elastic lamina. Localized collections of lymphocytes were seen at the adventitia in five cases (29%), and at the media in four (24%). In those areas, there were mixed populations of B and T lymphocytes.

The morphology of two cases in the control group showed organized thrombotic occlusion of medium-sized muscular artery. Hyalinized collagen bundles occluded the lumen and recanalizing channels and some inflammatory cells were present only in the thrombus. The internal elastic lamina was intact, without any focus of

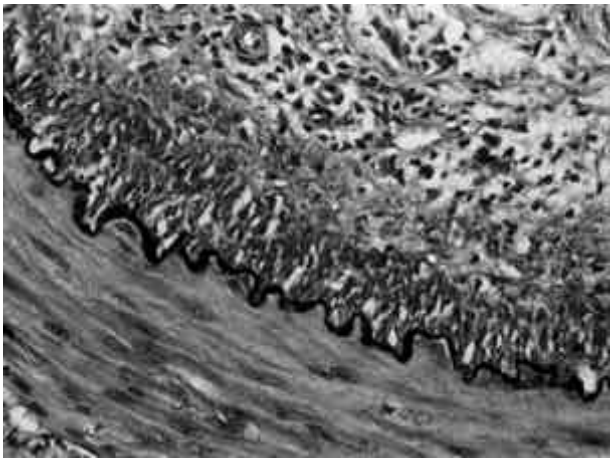

Fig. 5. Control artery with organized thrombotic occlusion shows a single layer of intact internal elastic lamina (Verhoeff's elastic stain, ×200).

splitting, duplication or calcification (Fig. 5).

DISCUSSION

Buerger's disease (thromboangiitis obliterans) is morphologically characterized by segmental involvement of acute and chronic thrombosing inflammatory disease affecting intermediate or small arteries and veins of the extremities (19, 20). Luminal obliteration is an early event in this disease but unlike in atherosclerotic narrowing, initial morphological change takes the form of thrombosis rather than intimal thickening and foam cell collection. The intimal thrombus seen in early lesion contains dense aggregates of polymorphonuclear leukocytes and this lesion persists as a microabscess (16, 17, 19). Inflammatory reaction of the vasa vasorum with intense infiltration of lymphocytes is also present in early lesion, and this progresses to perivascular fibrosis (16). Vasculitis has been described as panarteritis (6) but the medial muscle layer is well preserved without necrosis (16, 17). The elastic lamina showed few abnormalities (16, 17) and intimal occlusive lesion was sharply demarcated by this lamina from well-preserved media (4).

In general, our result endorses the current understanding of the pathologic features of this disease; however, it emphasizes that certain findings were neglected or underevaluated in previous studies. The most prominent finding in our cases was morphological change in the internal elastic lamina. As previously noted, earlier studies described the elastic lamina as normal (16, 17), though very recently, their fragmentation has been described (4). In early thrombus, there was a dense linear accumulation of T cells along the internal elastic lamina, and this latter showed some features of acute injury, such as edema and splitting. In the late stage we found consistent changes; fragmentation, degeneration and calcification of the internal elastic lamina. We also noted linear infiltration of immunoreactive T-lymphocytes as a conspicuous feature. The pathogenetic role of the morphological change in elastic lamina has yet to be elucidated, though the results of certain studies support our conclusion. Immunohistochemical study showed deposits of IgG and IgA at the internal elastic lamina and at the vasa vasorum (15). Anti-elastin antibody was demonstrated in serum (10, 21).

We are also doubtful of the role of the vasculitis of vasa vasorum in this disease. Previous studies noted intense inflammation around these vessels (16, 17). The classic example of vasculitis of vasa vasorum is seen in cases with vasculitides of large vessels and syphilitic aortitis, and under those conditions, vasculitis of the vasa vasorum leads to occlusion of these nutrient vessels. In those diseases, patchy fibrosis and weakening of the medial layer of the artery are the final outcome (22, 23). In contrast to those situations, the media in patients with Buerger's disease is characteristically well preserved, as shown in previous studies and ours (17, 21). The adventitia may show an intense inflammatory response at the initial stage, resulting in perivascular fibrosis and adhesion. Vasa vasorum, however, did not show fibrous obliteration and there was no evidence that this caused ischemic change of the vascular media.

Our data were based on the medium-sized arteries at the terminal occluded phase and samples from small arteries and at the early stage were not included. Our results, therefore, are applicable to those cases with occlusion of medium-sized femoral or popliteal arteries. At the late stage of this disease, as far as we have studied, morphological abnormality of the internal elastic lamina is the most prominent feature and the fibrotic changes in the media and vasa vasorum are not conspicuous. Our study did not demonstrate direct evidence of damage to the internal elastic lamina, but the initial event may be the immunologic injury of this lamina by T lymphocytes. Subsequent hypercontraction of medial smooth muscle and damage to the intima led to endothelial injury, luminal platelet aggregation and thrombotic occlusion. Multiplication of elastic fibers and calcification are diagnostic features in the late stage of Buerger's disease.

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