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Angiomyomatous Hamartoma of Popliteal Lymph Nodes Occurring in Association with Diffuse Pigmented Villonodular Synovitis of Knee

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We report the first case of an angiomyomatous hamartoma (AH) of the popliteal lymph nodes (LNs) occurring in association with diffuse pigmented villonodular synovitis (PVNS) of the knee. AH is a rare benign vascular disease with a predisposition for the LNs of the inguinal region. Twenty-five cases of AH have been reported to date; however, the precise pathogenesis is still undetermined. In the present case, an open synovectomy revealed two of three popliteal LNs in close proximity to the extra-articular component of diffuse PVNS. These LNs demonstrated irregularly distributed thick-walled blood vessels in the hilum. These vessels extended into the medulla and cortex and were associated with haphazardly arranged smooth muscle cells in the sclerotic stroma. These findings are compatible with an AH. Our observations raise the possibility that AH of the popliteal LNs may represent an abnormal proliferative reaction against the inflammatory process caused by PVNS of the knee.

Key Words: Angiomyoma; Hamartoma; Popliteal; Lymph nodes; Synovitis, pigmented villonodular

Angiomyomatous hamartoma (AH) of the lymph nodes is a rare benign vascular disease of unknown etiology. It was first described by Chan *et al.*[1] in 1992. It typically affects lymph nodes in the inguinal region;[2-5] however, cases involving cervical or femoral lymph nodes have also been described.[6,7] AH is characterized by replacement of the nodal parenchyma by haphazardly arranged smooth muscle cells and fibrous tissue, as well as a proliferation of abnormal blood vessels. Although 25 cases of AH have been reported to date, the precise pathogenesis is still undetermined. There has been only one report of AH in a single popliteal lymph node.[8] In this report, we present a case of AH occurring in the popliteal lymph nodes in association with diffuse extra-articular and intra-articular pigmented villonodular synovitis (PVNS) of the knee. To the best of our knowledge, the present case report is the first to describe AH in association with another disease.

CASE REPORT

A 37-year-old woman initially presented with a three-day history of swelling and pain in the right knee. Muscle weakness of the lower extremities was not apparent. Laboratory data and plain radiography showed no remarkable changes. Magnetic resonance imaging demonstrated a diffuse synovial hypertrophy with low signal intensity on T2-weighted images due to hemosiderin deposition. The disease involved the entire synovium and the popliteal fossa (Fig. 1A) consistent with diffuse PVNS. Arthroscopic (Fig. 1B) and open synovectomies were performed for the intra-articular and extra-articular components, respectively. During open synovectomy, three popliteal lymph nodes were detected in close proximity to the PVNS lesion. These lymph nodes were biopsied and submitted for histopathological examination.

The synovectomy specimen showed a grossly hypertrophied and thickened synovium with bunched up masses of villi and nodules. There were areas of yellow brown pigmentation. Microscopically, the lesion showed a proliferation of foamy histiocytes, fibroblasts, multinucleated giant cells, and hemosiderin-laden macrophages with a chronic inflammatory infiltrate and hemorrhagic foci, compatible with PVNS (Fig. 1C). The popliteal lymph nodes measured 0.7×0.5×0.5 cm in the largest di-

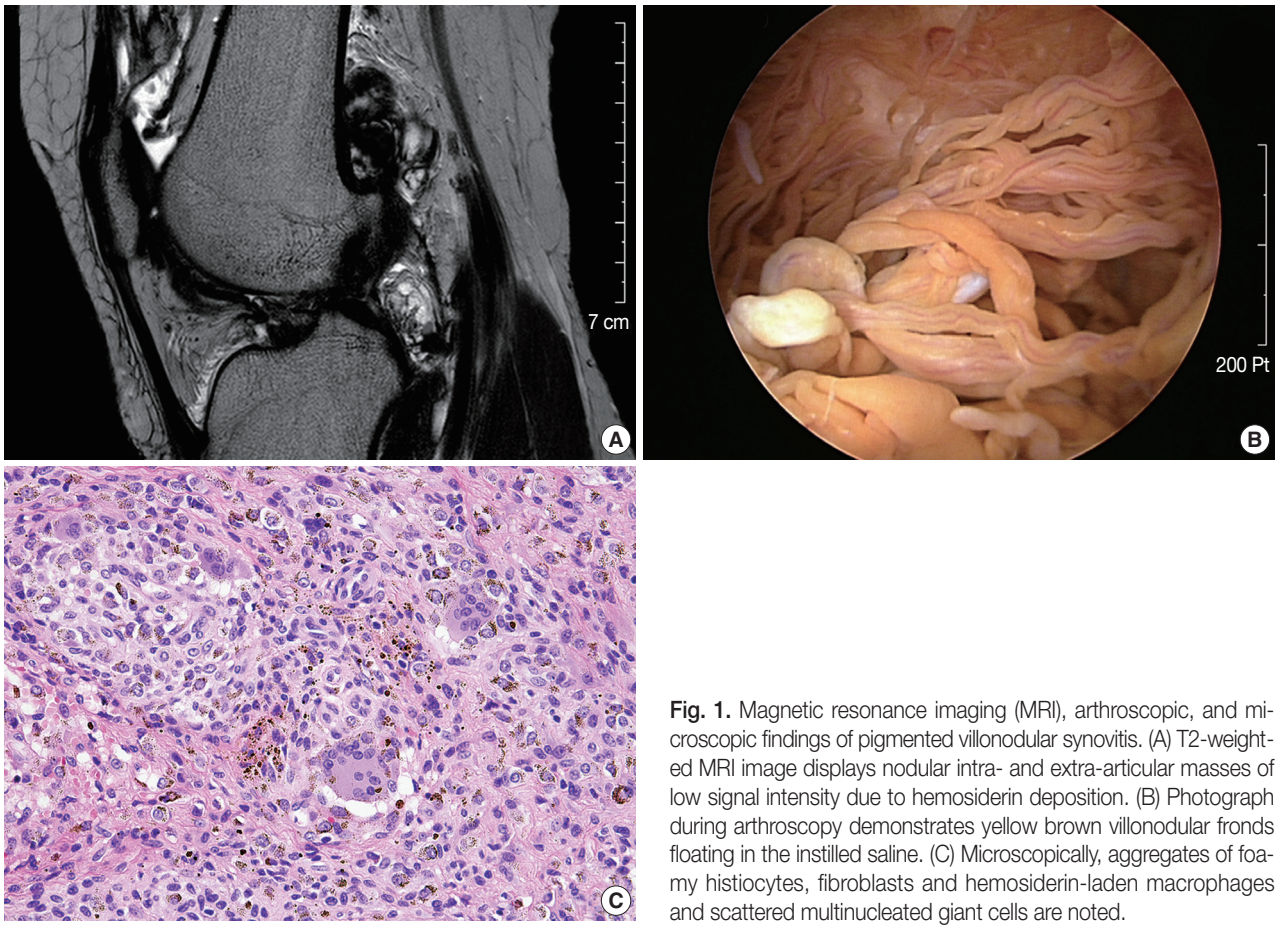

Fig. 1. Magnetic resonance imaging (MRI), arthroscopic, and microscopic findings of pigmented villonodular synovitis. (A) T2-weighted MRI image displays nodular intra- and extra-articular masses of low signal intensity due to hemosiderin deposition. (B) Photograph during arthroscopy demonstrates yellow brown villonodular fronds floating in the instilled saline. (C) Microscopically, aggregates of foamy histiocytes, fibroblasts and hemosiderin-laden macrophages and scattered multinucleated giant cells are noted.

mension and had a pink-white oval cut surface with small scattered spots of blood. Microscopically, two of the three lymph nodes demonstrated irregularly distributed thick-walled blood vessels in the hilum. These vessels were associated with haphazardly arranged smooth muscle cells in the sclerotic stroma. These changes gradually extended from the hilum to the convex surface of the lymph node, leaving a peripheral rim of cortical lymphoid tissue (Fig. 2A, B). There were scattered groups of fat lobules in the cortex, medulla, and hilum. These histopathological findings were typical of AH. The remaining lymph node also showed adipose metaplasia with mild expansion of the medullary sinuses. Immunohistochemically, CD31 (1:500, clone JC/70A, Labvision, Fremont, CA, USA) was found on the vascular endothelial cells and highlighted the rich vascularity of the lesion (Fig. 2C). The abundant smooth muscle in the blood vessel wall and intervening spaces was identified by the presence of smooth muscle actin (1:4,000, clone 1A4, DakoCytomation, Glostrup, Denmark), as presented in Fig. 2D. The patient was followed in the outpatient clinic for seven months after surgery. There was no evidence of recurrence during this follow-up period.

DISCUSSION

The precise pathogenesis of AH remains unclear. This is likely because most cases of AH occur without an associated disease or causative condition. Some cases of AH of the inguinal lymph nodes have been reported to be associated with lymphedema of the ipsilateral limb.[1-4] However, lymphedema appears to be caused by impaired lymphatic flow due to AH, rather than being a cause of AH. Bourgeois *et al.*[2] suggested that the destruction of nodal sinuses by vascular and stromal alterations may represent impairment of the lymphatic flow across the affected lymph node and may contribute to the clinical expression of lymphedema in the extremities. No lymphedema was noted in our patient. In our case, AH was associated with diffuse PVNS, which had an extensive extra-articular component. Chan *et al.*[1] have reported that AH may result from an abnormal reaction to previous nodal inflammation. Channer and Davies[9] have also reported that

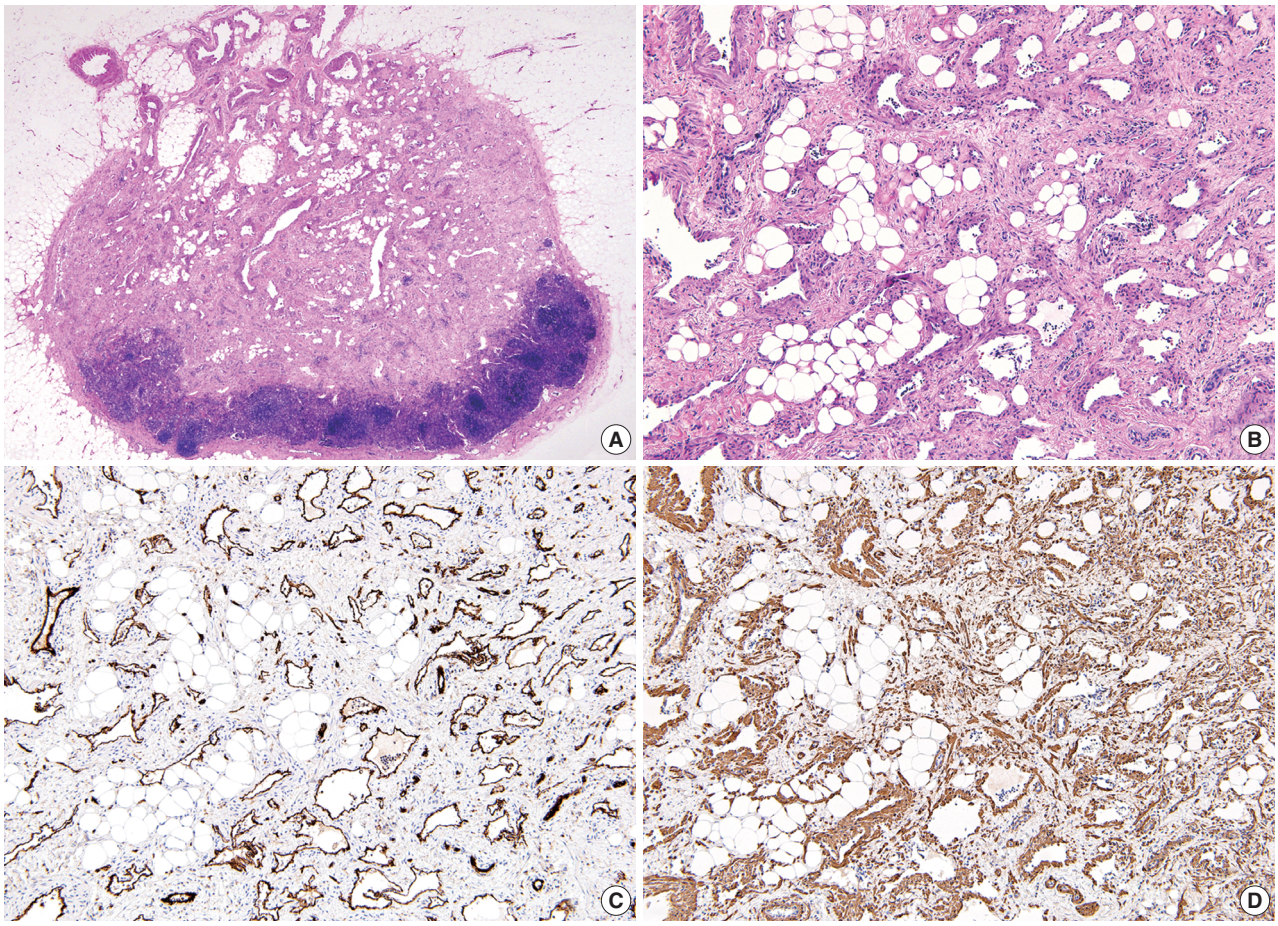

Fig. 2. Microscopic and immunohistochemical findings of angiomyomatous hamartoma. (A) The nodal parenchyma is almost totally replaced by fibrous tissue with numerous vascular spaces and scattered adipose tissue, leaving a peripheral rim of cortical lymphoid tissue. Abnormal thick walled blood vessels in the hilum extend into the medulla. (B) The blood vessels have a smooth muscle wall of variable thickness and are intermingled with haphazardly arranged smooth muscle cells and fat lobules. (C) CD31 immunostaining decorates the vascular endothelial cells and highlights the rich vascularity of the lesion. (D) Smooth muscle actin immunostaining reveals the presence of numerous smooth muscles in the blood vessel wall and intervening spaces.

a haphazard smooth muscle component within the hilum results from the reparative reaction to inflammation. Our observation of the close proximity between the affected lymph nodes and the PVNS lesion raises the possibility that an immune reaction caused by PVNS may be involved in the pathogenesis of AH. During the inflammation process, various types of cells, growth factors, and cytokines are produce at the affected site and transported to the draining lymph node. They can induce changes in the lymph node that lead to increased blood flow and enhanced vascular proliferation. The presence of macrophages and inflammatory cytokines, such as tumor necrosis factor alpha, interleukin (IL)-1 beta, and IL-6 have been described in PVNS.[10,11] These molecules, together with macrophage-derived growth factors, such as vascular endothelial growth factor and basic fibroblast growth factor, are involved in angiogenesis and smooth muscle proliferation.[12,13] In addition, PVNS tissues have been shown to produce matrix metalloproteinase (MMP)-1 and MMP-9.[11,14] These promote angiogenesis by stimulating endothelial cell growth and by releasing vascular endothelial growth factor. Based on these facts, we postulate that macrophages and related cytokines and growth factors are removed from the PVNS lesion to the adjacent popliteal lymph nodes through the draining lymphatics. Once in the lymph nodes, these could enhance angiogenesis and vascular smooth muscle proliferation in the nodal parenchyma.

Also of interest in the present case was the presence of adipose tissue within the AH. Some authors have stated that, although mature adipose tissue confined to the hilar portion of AH represents entrapped fat, the adipose tissue in the cortex may be an additional component of hamartomatous lesions.[7]

However, we observed that groups of fat lobules were randomly scattered in the cortical and medullary portions of one popliteal lymph node without AH, as well as in two lymph nodes with AH. We cannot rule out that adipose metaplasia occurred in the cortex. Therefore, adipose tissue within AH should not be seen as an additional hamartomatous component simply because it is located in the cortex.

Considering the clinical course and histopathological findings, the present case of AH associated with diffuse PVNS provides insight into the pathogenic process. Although the precise pathogenesis of AH remains unclear, we postulate that AH of the popliteal lymph nodes may represent an abnormal proliferative reaction against an inflammatory process caused by diffuse PVNS of the knee.

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