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Pathological Fracture Caused by Vascular Endothelial Cell Hemangioma-like Hyperplasia in POEMS Syndrome

POEMS syndrome is a rare paraneoplastic syndrome secondary to plasma cell dyscrasia.

Osteosclerotic bone lesion is a characteristic change seen in POEMS syndrome, whereas pathological fracture is rare. Monoclonal λ plasmacytoma may be the main pathological change responsible for bone lesions in patients with POEMS syndrome.[1] In this study, we describe a patient who presented with a pathological fracture. Bone pathology indicated hemangioma-like vascular endothelial cell hyperplasia. To the best of our knowledge, this is the second report of pathological fracture caused by POEMS syndrome and the first report of pathological fracture caused by hemangioendothelioma-like changes in a patient with POEMS syndrome.

A 55-year-old woman was hospitalized in August 2013 for severe pain in her left leg. An x-ray revealed a pathological fracture with an osteolytic lesion on the distal left femur and a sclerotic lesion on the proximal right femur (Figure 1A). Splenomegaly, ascites, skin hyperpigmentation and hemangiomas, multiple enlarged lymph nodes and elevated serum creatinine (228 μmol/L, normal range, 70–110 μmol/L) were found. Serum immunoglobulin assay yielded the following results: immunoglobulin A (IgA), 2.23 g/L (normal range, 0.82–4.53 g/L); IgG, 9.63 g/L (normal range, 7.51–15.6 g/L) and IgM, 1.37 g/L (normal range, 0.4–2.74 g/L). The monoclonal M-protein (IgA, λ) was detected on serum immunofixation, but not through serum electrophoresis and urine immunofixation. Endocrine investigations revealed an increase in thyroid-stimulating hormone (11.9 mIU/L, normal range, 0.34–5.6 mIU/L) and a decrease in free triiodothyronine (3.38 pmol/L, normal range, 4.36–6.23 pmol/L). Bone marrow biopsy and aspiration were negative for plasma cells. The patient exhibited no symptoms of peripheral neuropathy, but electromyography examination showed symmetric peripheral nerve defects in both lower extremities. Pathology of lymph nodes indicated hyaline-vascular type Castleman's disease (CD). Biopsy of the distal left femur revealed dramatic glomeruloid-like vascular endothelial cell hyperplasia, which was similar to the pathological changes observed in hemangiomas (Figure 1; panels B1, B2 and B3). No plasmacyte infiltration was found. Immunohistochemical findings were positive for the presence of human soluble adhesion molecules (SMA), CD34 and negative for CD38 and CD138. Kidney pathology showed diffuse mesangial cell and capillary proliferation in the glomerulus, with eosinophilic material deposits. Plasma vascular endothelial growth factor (VEGF) was higher than normal (898 pg/mL, normal level <145 pg/mL). POEMS syndrome was diagnosed. Interlocking intramedullary nail internal fixation of the fracture was performed and chemotherapy was given (lenalidomide, 15 mg/d, days 1–21; dexamethasone, 40 mg, once weekly in a 28-day

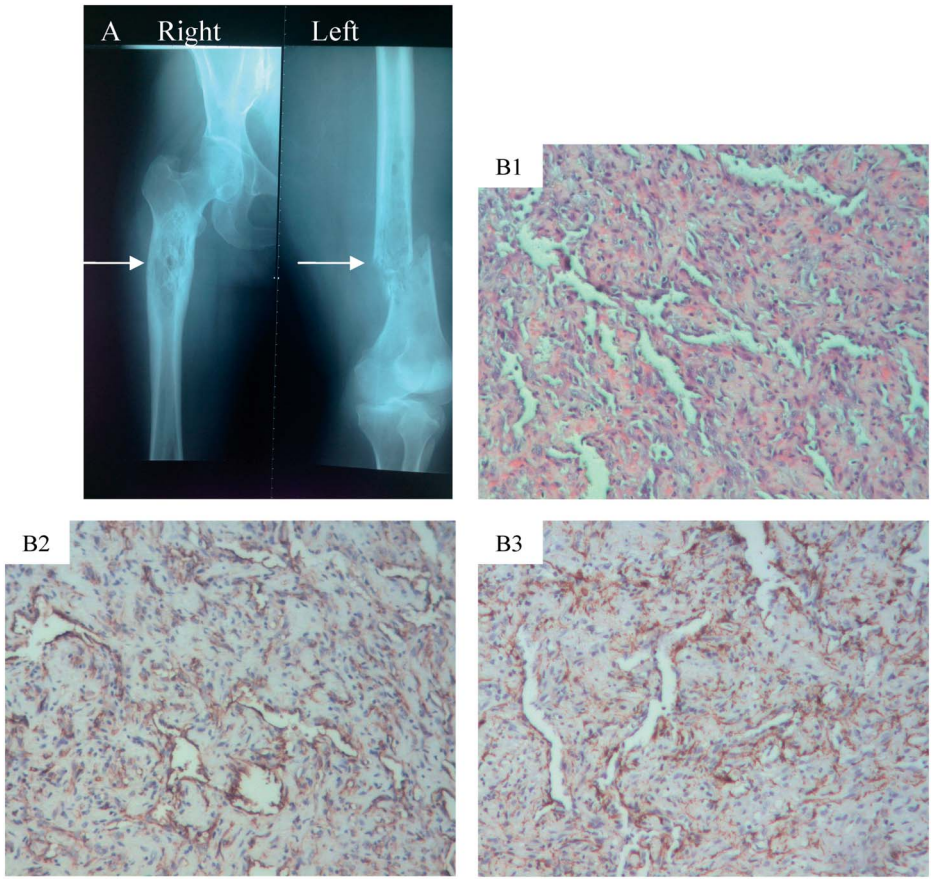

FIGURE 1. Imaging and pathology. (A) X-ray of the bilateral femurs revealed a pathological fracture with an osteolytic lesion on the distal left femur and a sclerotic lesion on the proximal right femur (arrowhead). (B1) Dramatic endothelial cell proliferation with labyrinth-like vessel lumen formation was revealed in this biopsy of the distal left femur, which showed similar characteristics to glomeruloid hemangioma (hematoxylin and eosin staining, ×200). Immunohistochemical study demonstrated positive expression of CD34 (B2, ×200) and SMA (B3, ×200).

cycle). The patient also received radiation treatment (4000 cGy). At the 14-month follow-up, the patient had no signs of pain or ascites.

The great diversity of POEMS syndrome clinical features can easily lead to misdiagnosis.

Although bone lesions, which are characterized by sclerotic or osteolysis damage with a sclerotic edge, are seen in more than 90% of patients with POEMS syndrome, most patients do not have symptoms of bone pain and fracture is rare.[2] Livingston et al[3] reported the first case of pathological fracture caused by POEMS syndrome. To the best of our knowledge, our present report is only the second description of pathological fracture in a patient with POEMS syndrome.

Pathological fracture is a rare complication in POEMS syndrome. Plasmacytoma may be the major pathological change responsible for bone lesions in POEMS syndrome, as studies of bone lesion pathology show that more than 95% of patients with POEMS syndrome have monoclonal λ plasmacytoma.[4] In this case, the patient exhibited a pathological fracture caused by hyperplastic vascular endothelium, similar to the pathologic changes observed in hemangioendothelioma. Although the M-protein might be a driving factor in POEMS syndrome pathogenesis, VEGF also reportedly plays important etiological roles.[2,5] VEGF is the dominant cytokine in the regulation of endothelial cell proliferation, migration and permeability. Elevated VEGF is considered to be responsible for several characteristic symptoms of POEMS syndrome, including extravascular volume overload, hemangioma and papilledema.[2] Higher VEGF levels may stimulate vascular endothelial cell proliferation in the bone to form a labyrinth-like vessel lumen, causing bone destruction or pathological fracture. It is currently unknown whether bone lesions occur due to plasmacytoma or whether they occur secondary to the elevated VEGF level.

In this case, the biopsy showed only hyperplastic vascular endothelium, with no evidence of plasma infiltration, suggesting that the hemangioendothelioma-like change may have been the major cause of the bone lesion. To the best of our knowledge, this is the first report of pathological fracture caused by a hemangioendothelioma-like change in POEMS syndrome. The patient also displayed capillary proliferation in the affected lymph nodes and kidney. Similar pathological changes have been reported in biopsies of patients with POEMS syndrome combined with CD.[2] It is possible that capillary proliferation is a pathological change common among all affected organs in patients with POEMS syndrome combined with CD; however, confirmation of this hypothesis requires additional investigation. To better understand the pathology of bone lesions in POEMS syndrome, further pathogenetic and histopathological analyses are needed.

The treatment for POEMS syndrome is based on the extent of the plasma cell infiltration and the number of bone lesions.[1] For patients with solitary or limited bone lesions (≤3 bone lesions) without diffuse plasma cell lesions, radiation is the first-line therapy.[6] In cases with disseminated bone marrow involvement, systemic therapy is indicated.[4] There are no standard recommended therapy protocols for the treatment of POEMS syndrome. Recent studies indicated that lenalidomide was a promising drug for its direct antimyeloma, anti-VEGF effects and much lower risk for peripheral neuropathy.[7] Considering that the patient's tumor was massive and that there was multiple organ involvement, local irradiation was performed in combination with chemotherapy. Although evaluation of the long-term outcome for this patient will need an extended observation period, an excellent short-term result was achieved.

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The authors have no conflicts of interest to disclose.

Supported in part by funds from the Bureau of Health of Hebei Province, China, to Jinqiao Zhang (Grant no. 20130225).

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