Distal Tibia and Foot Involvement in a Patient With Waldenstrom's Macroglobulinemia

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ABSTRACT

Bone lesions are a rare presentation in Waldenstrom's macroglobulinemia patients. Although lytic bone lesions and generalized osteoporosis have been described variably in literature on Waldenstrom's macroglobulinemia patients, distal long bone and foot involvement has not been described to our knowledge. We report a patient with Waldenstrom's macroglobulinemia with IgM monoclonal spike, plasmacytic infiltration of bone marrow, and symptoms of foot pain, and found to have distal tibia and foot involvement. The symptoms of bone lesions in our patient were significantly improved with radiation treatment. The possibility of distal involvement of long bones in a clinically relevant presentation should be kept in mind in these patients.

INTRODUCTION

Waldenstrom's macroglobulinemia is a B cell neoplasm characterized by the plasmacytic lymphocyte infiltration and proliferation of bone marrow or lymphatic tissue and IgM monoclonal gammopathy.[1] Traditionally, it has been believed that Waldenstrom's macroglobulinemia is not associated with much osseous involvement. However, several case reports suggest the presence of lytic bone lesions and other bone lesion morphologies associated with Waldenstrom's macroglobulinemia, but the distal involvement of the long bones is not well described in the literature.

We report a patient with a longstanding diagnosis of Waldenstrom's macroglobulinemia who had received multiple therapies over the years, and then presented with biopsy-proven bilateral distal long bone involvement in the form of tibia and foot bones. This report and review of the literature is aimed at a better understanding of clinical and radiographic skeletal assessment in Waldenstrom's macroglobulinemia patients with relevant clinical presentation.

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CASE REPORT

An 80-year-old woman presented with complaints of pain along with swelling in her right ankle, toes, and dorsum of foot. She denied any history of preceding trauma. There was no associated fever, warmth, or redness of the foot or ankle. The swelling was not relieved by limb elevation or trial of furosemide. She had been diagnosed with Waldenstrom's macroglobulinemia 23 years prior. On bone marrow exam at presentation and subsequent exams, plasmacytoid lymphocytes and plasma cells were both increased at 19.1% (normal, <5%) and 7.6%. (normal, <5%) On flow cytometry of bone marrow aspirate, 25% lymphocytes were seen with the majority being B-cells having lambda light chain restriction (CD5 and CD10 negative). She had received multiple chemotherapeutic regimens at different times including chlorambucil, fludarabine, 2-chlorodeoxyadenosine, rituximab, dexamethasone, and bortezomib in varying combinations with variable responses since her diagnosis.

Upon examination, she had evidence of pes planus, limitation of the range of motion of the ankle, and absence of pain throughout the arc of motion. Ankle radiographs showed diffuse nonspecific swelling of the foot with osteopenic bones without any acute fractures (Figure 1). Bone scan was suggestive of significant hyperemia near the right ankle and the proximal foot and also along the lateral aspect of the left foot, consistent with an active inflammatory process (Figure 2). Magnetic resonance imaging (MRI) of the right lower extremity revealed multifocal lesions at the tibia, fibula, talus, calcaneus, medial navicular, 1st metatarsal base, and medial cuneiform. The most pronounced foci were seen at the distal tibia, talus, calcaneus, and medial navicular. There were regions of presumed small soft tissue extension and most likely represented extensive lymphomatous involvement of these osseous structures (Figure 3).

Subsequently, she underwent computed tomography-guided biopsy of prominent medial tibial lesion. Histopathology in conjunction with the flow cytometry was suggestive of low grade B cell lymphoma consistent with lymphoplasmacytic lymphoma with-

Figure 1. Ankle, Radiograph of Foot

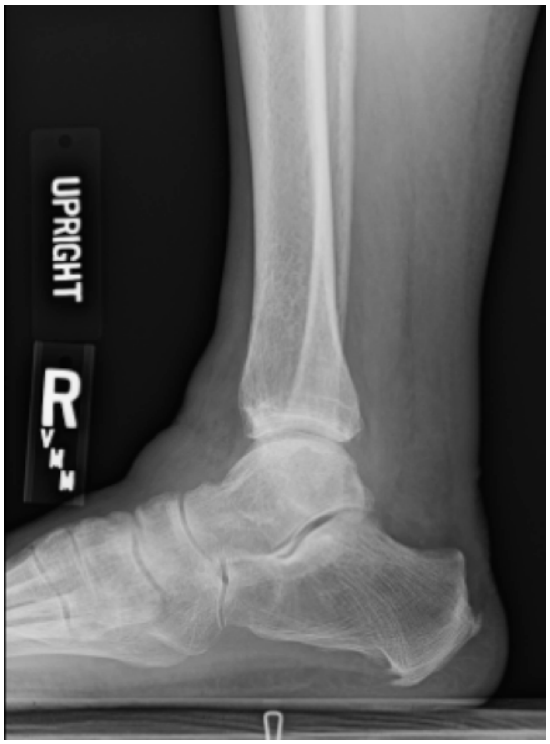
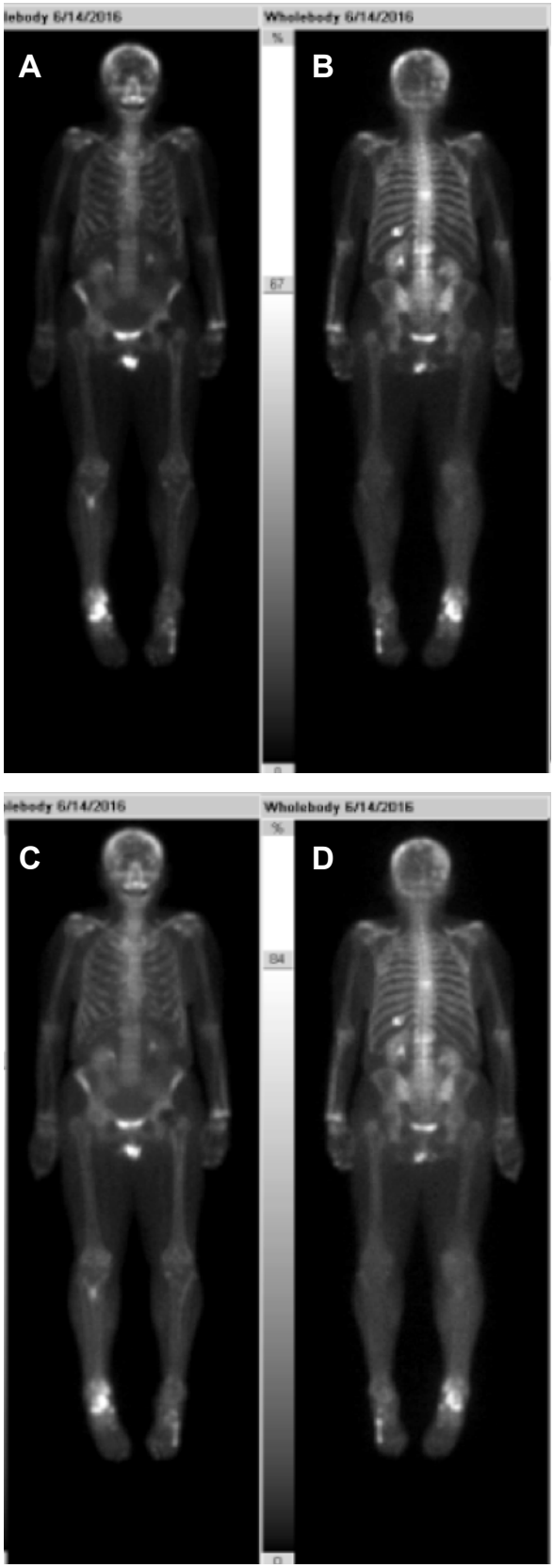


Figure 2 Increased Uptake in Right Distal Tibia and Foot Region on Bone Scan



out any evidence of large cell transformation. Immunoperoxidase staining of the tissue was CD20 positive (Focal) consistent with previous rituximab treatment, CD3 positive (normal T Cells), Kappa/Lambda chronogenic in situ hydridization non-contributory. After receiving local treatment to the right ankle and foot with radiation therapy, the patient achieved significant relief of her symptoms.

About 2 months later, she developed similar pain in her left foot and ankle. MRI revealed multiple osseous lesions within the left foot and ankle that were compatible with areas of lymphomatous involvement. Specifically, the 5th metatarsal shaft was the most pronounced, as the marrow was essentially replaced with presumed tumor. The patient then underwent radiation treatment for these lesions, which relieved her symptoms significantly.

DISCUSSION

Waldenstrom's macroglobulinemia is a B cell disorder characterized primarily by the bone marrow infiltration of lymphoplasmacytic cells and the presence of IgM monoclonal gammopathy. According to the Revised European-American Classification of Lymphoid Neoplasms and World Health Organization classifications, this condition is considered to be lymphoplasmacytic lymphoma.[1,2] As per international workshop criteria, Waldenstrom's macroglobulinemia is defined by IgM monoclonal gammopathy

Figure 3. Distal Tibia and Foot Bone Involvement, MRI Images

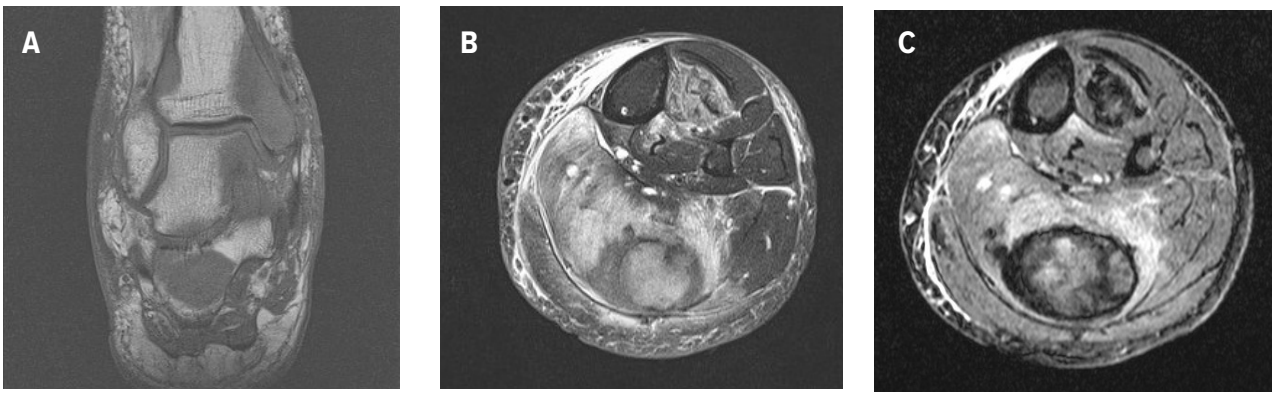


Table. Current Literature on Bony Involvement in Waldenstrom's Macroglobulinemia

Authors	Article Tye	No. of Cases	Lesion Distribution
Leb et al,[5] 1977	Case series	24	Osteolytic lesions with pathological fracture of proximal shaft of right humerus. Osteolytic lesions in skull, clavicles, scapulae, humeri, ribs, and femurs.
Vermess et al,[6] 1972	Case series	41	Lytic bone lesions in skull, vertebral bodies, pelvis, femur, humerus, clavicles, scapula, ribs. Extensive demineralization of bones with vertebral compression in 3 cases.
Ju et al,[7] 2001	Case report	1	Pathological compression fracture in T6-T7 with presence of posterior epidural mass.
Schlesinger et al,[8] 2000	Case report	1	Osteopenia along with pathological fractures of metacarpal bones and right tibia. Multiple lytic lesions found in appendicular skeleton.

of any concentration, bone marrow infiltration by small lymphocytes plasmacytic/plasma cells along with the diffuse, and interstitial or nodular pattern of bone marrow infiltration with $CD19^+$ and $CD20^+$, and surface IgM positivity with variable CD5, CD10, and CD23 positivity.[3]

None of the reports described in the literature have documented the distal involvement of long bones and feet by the Waldestrom's macroglobulinemia tumor like our patient had. The involvement in our case was biopsy proven and confirmed with immunophenotyping. The scarcity of reports on such presentation of Waldenstrom's macroglobulinemia prompted us to report this patient and review the available scientific literature on this topic (Table).

When Waldenstrom's macroglobulinemia was initially described by Waldenstrom in 1944, bony involvement was originally considered to be a differentiating criterion between Waldenstrom's macroglobulinemia and multiple myeloma.[4] Subsequently, Leb et al reported a series of 24 cases confirmed with immune electrophoresis and documented osteolytic lesions. These involved pathological fractures in the proximal shaft of the right humerus and osteolytic lesions in areas such as the skull, clavicles, scapulae, humeri, ribs, and femurs. In this series, the distribution of the bone lesions was mainly proximal.[5] Osteolytic lesions also were prevalent in a case series of 41 patients reported by Verness et al.[6] Of these patients, 19.5% had extensive lytic bone lesions in the skull, vertebral bodies, pelvis, femur, humerus, clavicles, scapula, and ribs. Extensive generalized demineralization in 7 patients, of which 3 had vertebral compression, also was noted. Only 4 patients in their series had lytic lesions involving proximal long bones (mainly femur and humerus) that were radiographically indistinguishable from the multiple myeloma lesions. Symmetric, cyst-like lesions in suprapubic portions of iliac bones also were seen in 3 patients. Notably, distal long bone involvement was not reported in this series.

Our patient also had back pain with subacute pathologic compression fracture of T8 on MRI but no sign of bony lytic lesions in the vertebrae. Ju et al reported a case of Waldenstrom's macroglobulinemia with pathological compression fracture in T6-T7 along with presence of posterior epidural mass in the same region.[7]

Our patient had evidence of osteopenia in the affected bones; Schlesinger et al similarly noted marked osteopenia in their patient. They also saw pathological fractures of the metacarpal bones and right tibia, along with multiple lytic lesions in the appendicular skeleton without any distal bony involvement.[8]

Limitations of the cases in the reported literature may be due to the difficulty in differentiating IgM myeloma from Waldenstrom's macroglobulinemia, especially with the cases diagnosed prior to immune phenotyping and cytogenetics. Recent advances in cyto-

genetics include presence of t (11, 14) in IgM myeloma and total absence in Waldenstrom's macroglobulinemia.[9] Similarly, 6q deletion was reported to be associated with Waldenstrom's macroglobulinemia in another study by Schop et al.[10] Cytogenetic analysis revealed our patient had 6q deletion as well. Other significant molecular markers for Waldenstrom's macroglobulinemia are the myeloid differentiation primary response 88 (MYD88), L265P mutation (seen in ~90% of cases) and CXCR4 (seen in ~30% of cases) since they are both almost exclusively present in MYD88-mutated Waldenstrom's macroglobulinemia.[11] Markers like these can be helpful in distinguishing between Waldenstrom's macroglobulinemia and multiple myeloma.

CONCLUSION

The diagnosis of Waldenstrom's macroglobulinemia should not deflect a clinician from the fact that the bone lesions may be present. Therefore, a bone survey and further investigations may be needed based on clinical presentation, even if symptoms involve distal long bones. The detection of such lesions is significant in view of their implications for symptomatic treatment and also by providing new insights into Waldenstorm's macroglobulinemia diverse clinical manifestations.

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