CASE REPORT

Clinical Case Reports Open Access WILEY

Management of lytic bone disease in lymphoplasmacytic lymphoma: A case report and review of the literature

Mizba Baksh[1] | Liuyan Jiang[2] | Unnati Bhatia[1] | Victoria Alegria[1] |
Taimur Sher[1] | Vivek Roy[1] | Asher Chanan-Khan[1,3,4] | Sikander Ailawadhi[1,3] |
Ricardo D. Parrondo[1]

[1]Division of Hematology-Oncology, Mayo Clinic, Jacksonville, Florida, USA

[2]Department of Pathology, Mayo Clinic, Jacksonville, Florida, USA

[3]Department of Cancer Biology, Mayo Clinic, Jacksonville, Florida, USA

[4]Hematology-Oncology, St. Vincent's Riverside, Jacksonville, Florida, USA

Correspondence
Sikander Ailawadhi, Division of Hematology-Oncology, Mayo Clinic, 4500 San Pablo Road S, Mangurian Building, 3rd Floor, Jacksonville, FL 32224, USA.
Email: ailawadhi.sikander@mayo.edu

Abstract

Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) is often differentiated from myeloma based on the presence of lytic bone lesions (LBL). However, WM/LPL can present with LBL, and management is poorly understood. We describe a case of an 81-year-old woman with LPL who presented with LBL and was successfully treated with chemoimmunotherapy.

KEYWORDS

IgM myeloma, lymphoplasmacytic lymphoma, lytic bone lesions, multiple myeloma, non-Hodgkin's lymphoma, Waldenström macroglobulinemia

1 | INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare, indolent, lymphoproliferative disorder that represents 1%–2% of all non-Hodgkin lymphomas (NHL).[1] It is pathologically defined as lymphoplasmacytic lymphoma (LPL) by the World Health Organization and is characterized by bone marrow infiltration with clonal lymphoplasmacytic cells and IgM monoclonal gammopathy, although non-IgM secreting lymphoplasmacytic lymphomas have also been described.[2,3] Lytic bone lesions are rare in WM/LPL

and are often used as a differentiating clinical feature between WM/LPL and multiple myeloma (MM), particularly IgM myeloma. Schuster et al. used strict defining criteria for IgM myeloma to make a clear distinction from WM/LPL since the approach to their treatment and prognosis vary significantly.[4-7]Table 1 Rothschild et al[8] documented in their clinical case study that WM/LPL has a combination of features of other hematologic malignancies such as myeloma and leukemia on both macroscopic and radiologic examination of osteolytic lesions. Papanikolaou et al[9] substantiated this rather unusual presentation in WM/LPL

on imaging studies such as PET-CT (positron emission tomography-computed tomography) or MRI (magnetic resonance imaging), while some other studies even reported improvement of lytic lesions with treatment.[10,11,12,28,29]

There is a paucity in the literature as to whether patients with WM/LPL and lytic bone lesions should be treated with chemoimmunotherapy or novel agents and whether bone-strengthening agents should be used. A consensus panel from the 10th International Workshop on WM has updated both first-line and salvage treatment recommendations. The preferred primary therapy options for symptomatic patients with WM include chemoimmunotherapeutic combination regimens of rituximab with alkylating agents (ie, bendamustine, cyclophosphamide) and proteasome inhibitors (ie, bortezomib) or with Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib. Treatment options need to be customized according to the individual patient's clinical presentation and genomic features.[13-16] Studies for anti-resorptive agents in WM/LPL are lacking. Herein, we describe a case of LPL with lytic bone lesions who was treated with rituximab, cyclophosphamide, and dexamethasone and had achieved a CR with complete resolution of lytic bone lesions on PET-CT.

2 | CASE

An 81-year-old woman with progressively deteriorating Parkinson's disease despite ongoing medical treatment for more than 5 years and osteoporosis (on denosumab every 6 months) presented to our institution's spine center for worsening back pain and frequent falls. She was initially diagnosed with a mild degenerative disc disease of her cervical, thoracic, and lumbar spine without myelopathy and severe facet arthrosis in the lumbar spine from L2-3 to L5-S1 as demonstrated on MRI images. Due to progressive pain and the possibility of compression fractures from her recurrent falls, a PET-CT was performed which reported several foci of marked hypermetabolism including a dominant lesion in the right humeral head, SUV max 9.9, and additional hypermetabolic lesions were seen in the bilateral scapulae, clavicles, right hemi-sacrum, right iliac wing, left acetabulum anterior column, left superior pubic ramus, and right femoral head (Figure 1A). The images were suggestive of MM-associated lytic lesions and a subsequent serum protein electrophoresis and immunofixation revealed small monoclonal IgA lambda immunoglobulins on immunofixation only, no m-spike was present. Complete blood cell count, quantitative serum-free light chains, β2-microglobulin, albumin, LDH, and creatinine were all within normal ranges. The patient have mild hypercalcemia with a calcium level of 10.3 mg/dl. A subsequent bone biopsy from the left anterior acetabulum was obtained, which revealed diffuse proliferation of small B-lymphocytes with an interstitial and paratrabecular pattern (Figure 2A). Immunohistochemistry (IHC) studies showed that the lymphocytes were positive for CD20 and PAX5 (Figure 2B, C), which proved the B-cell

TABLE 1 Comparison of key distinguishing characteristics of IgM Myeloma vs. Waldenstrom macroglobulinemia

Characteristic	IgM myeloma	Waldenstrom's Macroglobulinemia
MYD88 and CXCR4 Mutations	−	+
Hypercalcemia, renal failure, anemia, lytic bone lesions (CRAB)	+	−*
Lymphadenopathy, splenomegaly	−	+
CD20 Expression	−	+
Flow cytometry profile [45,46]	CD38$^+$, CD138$^+$ CD20$^-$, CD19$^-$, CD79a$^+$, CD56, Cyclin D1$^+$, CD117$^-$	CD138$^-$, CD19$^+$, CD20$^+$, CD22$^+$, CD23$^-$, CD5$^-$, CD10$^-$
Presence of t(11;14)	+	−
Response to anti-CD20 monoclonal antibody therapy	−	+
Early autologous hematopoietic stem cell transplant (HSCT)	Yes	No, only for refractory/relapsed disease
Clinical course and prognosis	Aggressive	More indolent than MM
Overall survival [4]	Shorter (~30 months)	Longer (in years)
High expression of IL-1 (Osteoclast-activating factor) [4]	+	−
Association with immunological phenomenon [47,48]	No	Yes, with cold agglutinin disease, cryoglobulinemia, Raynaud's syndrome, peripheral neuropathy

Note: WM/LPL can present with lytic bone lesions. Lytic bone lesions associated with non-Hodgkin's lymphomas such as CLL and WM/LPL are well reported in the literature.

lineage of the lymphoma. The neoplastic lymphocytes were negative for MUM1 and cyclin D1. Moreover, CD138 highlighted scattered plasma cells that were positive for IgA and lambda-light chain-restricted (Figure 2D-F). A

MYD88 L265P alteration was detected via amplification of DNA using allele-specific polymerase chain reaction with an allele-specific primer. A bone marrow biopsy was done and showed a plasma cell proliferative disorder

FIGURE 1 (A) Positron emission tomography-computed tomography at diagnosis showing evidence of lytic lesions in right humeral head (red arrow), right femoral head (orange arrows) and left acetabulum (green arrow). (B) PET-CT showing resolution of lytic lesions after six cycles of rituximab-cyclophosphamide-dexamethasone
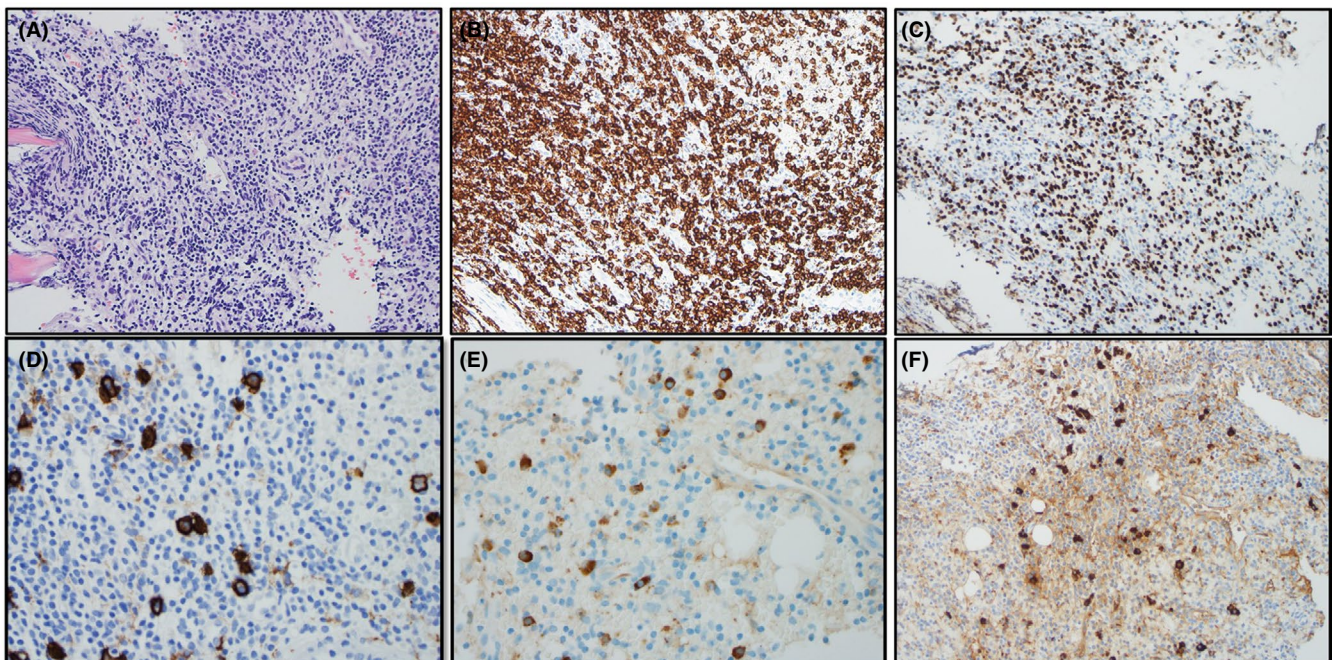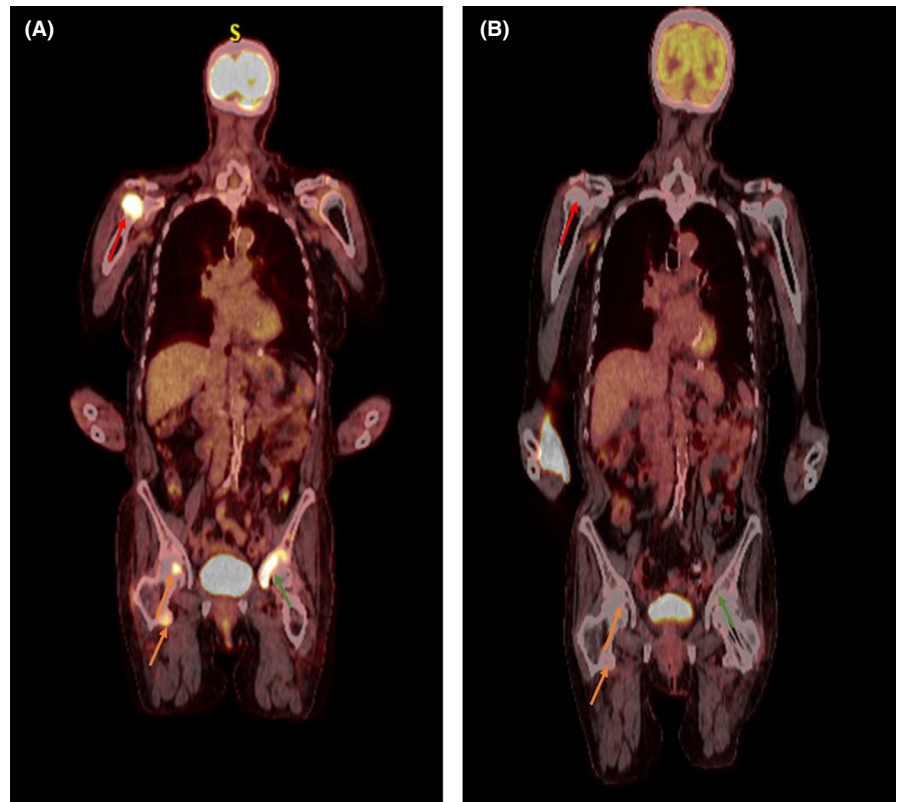

FIGURE 2 The biopsy of the lytic bone lesion at left anterior acetabulum showed diffusely proliferation of small lymphocytes (A, H&E ×20), which are positive for CD20 (B, IHC ×20) and PAX5 (C, IHC ×20). Scattered plasma cells were highlighted CD138 (D, IHC ×40), and IgA (E, IHC ×40) with lambda light chain restriction (F, IHC ×40)

with 5%–9% lambda-light chain-restricted plasma cells with a normocellular marrow (30%–40%) with otherwise morphologically unremarkable trilineage hematopoiesis. There were no morphologic or immunophenotypic features of a lymphoid neoplasm. Immunophenotyping by flow cytometry identified a lambda light chain-restricted plasma cell population that expressed CD38 and CD138 and did not express CD19 or CD45. These findings were most consistent with a lymphoplasmacytic lymphoma.

Given the diagnosis of lymphoplasmacytic lymphoma in a frail patient with advanced Parkinson's disease and an ECOG (Eastern Cooperative Oncology Group) performance status of 2, it was decided to treat the patient with chemoimmunotherapy consisting of IV rituximab 375 mg/m^2, IV cyclophosphamide 300 mg/m^2, and IV dexamethasone 20 mg given every 21 days. The patient completed six cycles of treatment. Treatment was complicated by the development of grade 2 neutropenia and grade 1 anemia. The patient also developed a grade 2 urinary tract infection that needed treatment with oral antibiotics and grade 2 herpes labialis which required acyclovir treatment for 10 days after cycle 4 causing cycle 5 to be delayed by 1 week. Following completion of the six cycles of treatment, the patient had complete resolution of lytic lesions on PET-CT (Figure 1B) and no detectable IgA-kappa monoclonal protein on serum protein electrophoresis or immunofixation. The patient went on to start maintenance therapy with single-agent rituximab every 3 months for up to 2 years. The patient still had some back pain which is likely related to her underlying degenerative joint disease and severe facet arthrosis in the lumbar spine so she will follow up with neuroradiology for possible facet joint injections and/or potential kyphoplasty.

3 | DISCUSSION

We described a case of an IgA lambda, MYD88L265 mutation + lymphoplasmacytic lymphoma with lytic bone lesions that was successfully treated with rituximab, cyclophosphamide, and dexamethasone resulting in a complete response. This regimen was chosen over bendamustine and rituximab because at the age of 81, we did not think the patient would tolerate bendamustine well due to the possibility of bone marrow suppression and cytopenias which are common with bendamustine. Furthermore, rituximab cyclophosphamide, and dexamethasone have been shown to have comparable efficacy and toxicity compared to bendamustine and rituximab.[17] Ibrutinib was not chosen because the patient was having considerable bone pain and discomfort and we wanted to achieve a rapid response. Single-agent ibrutinib is slow to act with no complete responses and a median time to best

response of 7.5 months with very good partial responses occurring after a median of 15.5 months.[18] We decided to give the patient maintenance rituximab because an observation study of 248 rituximab-naïve patients who responded to a rituximab-containing regimen revealed that maintenance rituximab for 2 years resulted in superior progression-free survival and overall survival.[19] It is important to note that no patients in this study received bendamustine. However, rituximab maintenance is controversial as the results of the MAINTAIN trial failed to show progression-free or overall survival benefit for patients with Waldenstrom's macroglobulinemia who were treated with front line bendamustine and rituximab and then went on to receive either 2 years of rituximab maintenance or observation.[20] Thus, perhaps there is no benefit to rituximab maintenance when bendamustine and rituximab are given front line but there may be a benefit to rituximab maintenance if non-bendamustine-containing regimens are used. A multitude of novel agents are approved for the treatment of WM/LPL such as BTK inhibitors, proteasome inhibitors, and monoclonal antibodies and many more next-generation therapies in these drug classes are under development in addition to BCL2 inhibitors such as venetoclax and phosphatidylinositol 3 kinase inhibitors such as idelalisib and umbralisib.[21] However, the efficacy of these agents in WM/LPL patients with lytic bone disease is unknown. The efficacy of agents such as proteasome inhibitors, immunomodulatory drugs, and alkylating agents on bone remodeling in MM is well established.[22] In lymphoid malignancies such as chronic lymphocytic leukemia (CLL), only BTK inhibitors such as ibrutinib have shown promising therapeutic response in patients with osteolytic lesions.[23-25] There is evidence that the BTK inhibitor ibrutinib can suppress bone resorption by inhibition of both osteoclast differentiation and function, predominantly by downregulation of expression of nuclear factor of activated T cells 1 (NFATc1), the key transcription factor for osteoclastogenesis, and disruption of the formation of the actin ring in mature osteoclasts.[26] In one case of an elderly woman with relapsed CLL/SLL (chronic lymphocytic leukemia/small lymphocytic lymphoma) with widespread lytic disease and pathological fractures, treatment with ibrutinib monotherapy (420 mg q.d.) with monthly denosumab (120 mg s.c.) for only 9 months resulted in remineralization of her skeletal lesions and partial disease response. The combination of a BTK Inhibitor with a bone-resorptive agent provided significant clinical benefit with remarkable improvement in patient mobilization after about 12 months of treatment with sclerosis of skeletal lesions as noted on serial CT and MRI scans.[27]

Although rare, multiple studies have reported lytic bone lesions in cases of WM/LPL with little guidance

on management. In the large study series of 37 patients by Schuster et al, the inclusion criteria considered were the presence of IgM monoclonal protein and ≥10% plasma cells in the bone marrow biopsy in addition to the characteristic lytic bone lesions with or without the most common cytogenetic abnormality of IgM myeloma ie, translocation t(11;14). This study did not include patients based on non-specific clinical features of myeloma such as the presence of anemia, hypercalcemia, and renal failure or their immunophenotype.[4-7] The case study by Rothschild et al was used to differentiate similarly presenting cases based on the specific differences in the gross appearance of bony lesions. The lytic lesions of WM were either sharp spheroid lesions or abundant coalescing pits that were identifiable from the numerous frontally resorptive non-spheroid leukemic lesions and the pit less although spheroid lesions of MM.[8] This is in contrast with MM, which tends to show four different forms of destructive bone changes on imaging studies—single expansile plasmacytoma, disseminated punched-out lytic lesions, diffuse skeletal osteopenia, or osteosclerosis.[30,31] Based on another retrospective investigation conducted by Papanikolaou et al, focal lytic bone disease was evident in 17%–24% of WM cases on MRI or PET-CT imaging, respectively.[29] Regardless, there is scarce literature on optimal treatment for patients with WM/LPL and lytic bone disease. The modulation of bone remodeling by anti-myeloma agents such as immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies provide insight into their potential efficacy and mechanism of action in patients with WM/LPL.[28] Via interactions with the bone marrow microenvironment, malignant plasma cells are able to orchestrate the production of osteoclast-activating factors (ie, RANKL) and osteoblast-inhibitory factors which leads to asynchronous bone turnover, net bone loss, and osteolytic lesions. Proteasome inhibitors such as bortezomib, carfilzomib, and ixazomib inhibit NF-κB (nuclear factor kappa-B) mediated osteoclast maturation and, ultimately, bone resorption via the RANKL and OPG (osteoprotegerin) pathway.[29] Terpos et al demonstrated that bortezomib also increased bone formation markers like bone-specific alkaline phosphatase (ALP) and osteocalcin levels with only four cycles of treatment in 34 relapsed MM patients.[32] Furthermore, bortezomib has shown inhibition of osteoclastogenesis in combination with the immunomodulatory drug lenalidomide in vitro.[33] Both of these agents have also shown the ability to reduce tumor burden in MM patients through their inhibitory effect on osteoclast-derived growth and survival factors and blocking of RANKL secretion from bone marrow stromal cells.[33,34] Lenalidomide inhibits osteoclastogenesis as evidenced by decreased serum biochemical markers of bone turnover.[34] Pomalidomide, another immunomodulatory drug, has shown potent osteoclast inhibitory activity in vitro with its downregulating effect on transcription factor PU.1 and significant blunting of RANKL upregulation, thus normalizing the RANKL-OPG ratio.[35] Daratumumab, an anti-CD38 monoclonal antibody, inhibits bone remodeling by blocking the interaction of CD38-expressing monocytes and osteoclast-progenitor cells thus inhibiting bone resorption activity in bone marrow cells of MM patients.[36,37] In a study of 51 MM patients, high dose chemotherapy with melphalan followed by autologous stem cell transplant (ASCT) resulted in a significant reduction of sRANKL/OPG ratio, with a concomitant decrease in markers of bone resorption starting the second month post-ASCT.[38] Further investigation is needed on whether these active anti-MM agents have similar effects on bone turnover in patients with non-Hodgkin lymphomas such as WM/LPL with lytic bone lesions.

Although chemoimmunotherapy combinations are current standard treatment regimens and are highly active with high response rates, they can cause immunosuppression and cytopenias which may not be well tolerated by elderly, frail patients. With a median age of diagnosis of WM/LPL being 70 years, consideration must be given to patient frailty and ability to tolerate such a treatment. However, cyclophosphamide is well tolerated in elderly patients when used as a combination regimen with rituximab and dexamethasone (DRC). This was demonstrated in a study conducted by Dimopolous et al in a large multicenter trial of 72 patients with WM, whose median age was 69 years and among which 63% patients were older than 65 years old. Based on analysis of this study, therapy with DRC was well tolerated and only about 10% of patients experienced grade 3 or 4 neutropenia, and 10% of patients developed neutropenic fever requiring hospitalization and intravenous antibiotics. No patients developed grade 3 or 4 thrombocytopenia. Therefore, DRC is a safe and well-tolerated regimen, even in elderly frail patients.[39] The DRC regimen was also used successfully in a 64-year-old patient who was diagnosed with WM and had mixed lytic and sclerotic lesions on skeletal radiographs and CT scans. The patient tolerated six cycles of DRC treatment with no significant toxicity or signs of lymphoma progression after a follow-up of 32 months. The majority of the patient's bone lesions also disappeared with treatment except for one persistent bone lesion which was treated with 8 Gy of radiation therapy.[40] Based on the available data, including our case report, DRC is an efficacious regimen for patients with WM and lytic bone lesions.

Interestingly, our patient was on denosumab every 6 months for osteoporosis, but there are no consensus

guidelines on the use of anti-resorptive agents for patients with WM/LPL and lytic bone lesions. Many preclinical and randomized control studies of bisphosphonates and RANKL (receptor activator of nuclear factor-kappa B ligand) inhibitors in MM have demonstrated not only reduction of bone complications but also potential anti-MM effects as well.[32] The risk of high bone turnover and premature osteoporosis in lymphoma patients due to treatment with high dose corticosteroids can be counteracted by the prophylactic use of anti-resorptive agents. In patients with lymphoma receiving chemotherapy, treatment with the second-generation bisphosphonate pamidronate every 3 months for 1 year reduced both bone loss and the risk of new vertebral fractures.[41] A prospective randomized phase III trial investigated the benefit of using zoledronic acid (ZA) in 74 newly diagnosed lymphoma patients undergoing chemotherapy and with a baseline bone mineral density (BMD) of ≥-2.0. A dose of 4 mg IV ZA was given at trial enrollment and at 6 months along with oral calcium (1200 mg) and vitamin D (400 or 800 IU). Fifty-three patients were evaluable for response: 24 received ZA and had stable BMD during the observation period, whereas 29 patients in the control group had decreased BMD ($p < 0.05$ at lumbar spine and bilateral femoral neck).[42] Further investigation into the use of anti-resorptive agents for patients with WM/LPL and lytic bone lesions is warranted.

4 | CONCLUSION

Lytic bone lesions associated with non-Hodgkin's lymphomas such as CLL and WM/LPL are well reported in the literature. However, the biology of these bone lesions is poorly understood as is the optimal therapeutic management of patients with lytic bone disease. Drugs and anti-resorptive agents that are active in MM have efficacy in WM/LPL yet their role in WM/LPL patients with lytic bone lesions is unknown. Our case demonstrates the efficacy of the chemoimmunotherapy regimen DRC in causing a complete response with resolution of lytic bone lesions in a patient with LPL. Further research is warranted on the ability of novel agents to reverse bone turnover in WM/LPL patients as well as on the utility of anti-resorptive agents in non-Hodgkin's lymphomas with lytic bone disease.

AUTHOR CONTRIBUTIONS
M.B. and R.D.P wrote the manuscript; L.J obtained the pathology images for the case; M.B, R.D.P, U.B, L.J, V.A, V.R, T.S, A.C-K, and S.A edited and finalized the manuscript.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID
Mizba Baksh https://orcid.org/0000-0002-3604-5353
Unnati Bhatia https://orcid.org/0000-0002-5035-1138
Sikander Ailawadhi https://orcid.org/0000-0002-8377-8111
Ricardo D. Parrondo https://orcid.org/0000-0002-9314-9933

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