Non-secretory Multiple Myeloma Associated with Diffuse Osteosclerotic Bone Lesions: A Case Report and Review of Cases since 1997

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Case Report

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Abstract

Background: Multiple myeloma is the second most common hematologic malignancy typically involving monoclonal immunoglobulin secretion by malignant plasma cells and lytic bone lesions. Sclerotic lesions appear in 3% of cases, and only 1-3% of multiple myeloma patients produce no detectable paraprotein. This case involves a challenging diagnosis of a rare presentation of both non-secretory and osteosclerotic multiple myeloma.

Case Presentation: A 59-year-old woman with prior history of breast cancer presented with 2 months of back pain and was found to have T1 and T11 sclerotic lesions on imaging. Positron emission tomography (PET) revealed additional L4 sclerotic lesions and right manubrium as well as a single lytic lesion of the right ilium. Biopsy revealed 40% plasma cell infiltrate producing monoclonal lambda light chains. Protein electrophoresis was normal. The patient was absent of POEMS Syndrome features. The patient was diagnosed with osteosclerotic multiple myeloma (OMM) and initiated on chemotherapy and received an autologous stem cell transplant. Repeat PET demonstrated stabilization of sclerotic lesions and decreased metabolic activity of the lytic lesion. She is currently on maintenance Revlimid.

Conclusions: OMM is an extremely rare subtype of classical multiple myeloma (CMM), with less than 50 cases reported prior to 1997. This paper presents the most comprehensive current review of OMM since. OMM presents in younger patients with no sex preference most commonly with back pain, dyspnea, and weakness/fatigue. 29% of patients reviewed were South Asian, warranting further research into risk factors for this population. Hypercalcemia is rare in OMM, while renal insufficiency and anemia are more common than in CMM. OMM has median infiltrate of 45% with even distribution of kappa and lambda chain monoclonal gammopathy. It most commonly involves the vertebrae but has greater involvement in the pelvis and long bones than CMM. OMM is more indolent with better survival. Our case represented a challenging diagnosis with normal typical laboratory markers of MM and unremarkable findings on SPEP given that the OMM also was non-secretory. Although rare, OMM should be considered in diagnosis of patients with persistent back pain despite 1-2 months of conventional conservative treatment using computed tomography or magnetic resonance imaging.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, with approximately 32,000 new cases annually (1). MM involves the malignant proliferation of clonal plasma cells within the bone marrow that often secrete monoclonal immunoglobulins. Diagnosis is based on evidence of > 10% clonal plasma cells in the bone marrow and at least one manifestation of end-organ damage or myeloma defining event such as osteolytic bone lesions, hypercalcemia, renal insufficiency, or anemia (SLiMCRAB) (2). The majority of MM cases involve intact immunoglobulin, and less commonly, 15% of cases produce only free light chain (FLC) (3). The non-secretory subtype, in which myeloma cells secrete no detectable monoclonal proteins, accounts for approximately 1–2% of MM cases (4).

One hallmark feature of multiple myeloma is lytic bone lesions. Sclerotic lesions presenting with monoclonal gammopathy are most often attributed to POEMS Syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Sclerotic lesions are seen in only 3% of MM cases, but they present with slower growth and are prognostically favorable to classic lytic lesions (5). Given the rarity of the non-secretory subtype of MM and concurrent sclerotic lesions, diagnosis can be difficult. Here, we review the case of a 59-year-old woman with non-secretory osteosclerotic multiple myeloma and present a review of the literature on osteosclerotic MM since 1997.

Case Presentation

A 59-year-old female with a past medical history significant for Stage I (pT1b, NO, M0) breast cancer, hypertension, diabetes mellitus type II, and hypercholesterolemia, presented with a two-month history of worsening back pain. The patient was treated for pT1b N0 M0 grade 2 invasive ductal carcinoma of the right breast with partial mastectomy and radiation therapy 5 months prior to the current presentation. She was subsequently placed on anastrozole. She then began experiencing back pain 3 months after the completion of radiation therapy, which did not improve. Her presentation also included weight loss, diaphoresis, hot flashes, and generalized weakness. However, these symptoms were normal to her baseline following breast cancer treatment. Given that the patient had no challenges such as access, financial, or cultural barriers to testing, a thorough diagnostic exam was conducted. Given her recent history of breast cancer, she underwent a CT scan of the thoracic spine, which demonstrated T1 (Fig. 1) and T11 vertebral body sclerotic lesions presumed to be related to breast cancer.

Physical examination revealed no palpable lymphadenopathy, with the liver edge palpated within normal limits and no splenomegaly or skin abnormality. There were no focal nerve deficits or peripheral neuropathy.

PET/CT confirmed these T1 (SUV of 11.6) and T11 (SUV of 3.0) sclerotic bone lesions (Fig. 2) and revealed sclerotic hypermetabolic osseous lesions of the L4 vertebral body (SUV of 2.9), right ilium (SUV of 32.6) (Fig. 3), and right aspect of the manubrium (SUV of 12.1) (Fig. 4). The right iliac lesion alone was lytic, whereas the remaining lesions were sclerotic.

Technetium-99 whole body nuclear scan revealed increased activity in the right aspect of the manubrium but provided no evidence for osteoblastic activity in T1 or T11 sites (Fig. 5).

A CT-guided biopsy of the manubrial lesion revealed CD138+ lambda restricted plasma cell infiltrate (Fig. 6 and Fig. 7). Bone marrow aspiration and biopsy of the iliac crest revealed a 40% lambda-restricted plasma cell infiltrate. Fluorescence in situ hybridization did not show any evidence of 1p32.3 gene deletion, 1q21 gene amplification, IgH translocations, chromosomal changes in chromosomes 9 or 15, RB1 deletion, or TP53 deletion.

Laboratory results were as follows: Serum markers revealed a normal SPEP with no monoclonal spike identified on immunofixation (IFE), normal kappa free light chain (FLC) at 16 mg/L, normal lambda FLC

at 17 mg/L, and normal kappa/lambda ratio of 0.94. No M spike was detected on urine electrophoresis and IFE. Serum immunoglobulins were normal. Complete blood counts, serum creatinine, calcium (albumin adjusted), and albumin levels were normal, with a mildly elevated lactate dehydrogenase (LDH) level of 227 U/L and a normal beta-2 microglobulin of 1.50 mg/L. Most relevant findings for the case report are summarized in Table 1.

Table 1. Laboratory Values	
Hgb	12.2 g/dL
Calcium albumin adjusted	9.1 mg/dL
Creatinine	0.65 mg/dL
IgA	285 mg/dL
IgG	873 mg/dL
IgM	48 mg/dL
VEGF	86 pg/mL
Serum Free Light Chains	
Kappa FLC, Serum	16.06 mg/L
Lambda FLC, Serum	17.05 mg/L
Kappa/Lambda FLC Ratio	0.94
ESR	16 mM/Hr

Given the presence of sclerotic lesions, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) was on the differential, but absence of these overlapping disease features made POEMS syndrome unlikely. Further, vascular endothelial growth factor (VEGF) level was normal at 86 (normal < 96.2 pg/mL). A diagnosis of osteosclerotic multiple myeloma was made.

The patient was initiated on induction treatment with lenalidomide, bortezomib, and dexamethasone (RVD) for 5 cycles. Follow up PET/CT after 3 cycles of induction showed improvement/stabilization of T1, T11, and right manubrium sclerotic bony lesions with attenuation of the L4 sclerotic lesion. PET/CT also revealed improvement of the lytic right iliac bone lesion with decreased FDG avidity. The patient underwent an autologous stem cell transplant and a repeat PET/CT scan at 100-day staging showed resolution of the lesions.

Eight months after starting treatment, repeat PET/CT demonstrated no change in sclerotic lesions and decreased FDG avidity in the right iliac lytic lesion to an SUV of 1.7 from the initial presentation of 32.6, suggesting a good response to treatment (Fig 8). The patient is now on maintenance lenalidomide at 19

months after diagnosis. Tolerance to treatment was assessed at every clinic visit, where patient reported she was tolerating therapy well with only mild complaints of bone pain after Zometa injections, taking Duloxetine and Acetaminophen as needed.

The patient kindly provided her reflection on her diagnosis and treatment. She stated that the day before she began chemotherapy, she had to quit her job, which was difficult because she loved her job but was too fatigued to continue. With the onset of chemotherapy, she began experiencing brief memory issues during conversations with others, which she states she asked her friends about. She was told that this was a side effect of chemotherapy for some individuals. She states that it was tough learning that she had another cancer after “beating” her prior breast cancer, but her goal now is to be cancer-free. She lives with her husband at home and is able to cook for herself still. She does note that after taking her Revlimid, she becomes fatigued for one or two hours and must rest, but then she picks herself up and stays busy around the house. She’s been drinking lots of water which has led to multiple nighttime awakenings to urinate and has led to only 4-5 hours of sleep at night but compensates with early morning naps. She remembers the transplant being very tiring, but through this all, she has taken great comfort in her spirituality and states she could not have asked for a better care team. She states she is optimistic and determined to get better.

Discussion

Multiple myeloma is a bone marrow cancer involving neoplastic uncontrolled proliferation of monoclonal plasma cells. The International Myeloma Working Group (IMWG) criteria for the diagnosis of Multiple Myeloma include clonal plasma cells making up greater than 10% of bone marrow cells and at least one CRAB (hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesion) criteria or one myeloma-defining event. Myeloma-defining events include: greater than 60% clonal plasma cell makeup of the bone marrow, serum involved/uninvolved free light chain ratio of at least 100, or more than one focal lesion of size 5 mm or greater on advanced imaging such as MRI (2).

Our case features a combination of two uncommon characteristics: diffuse osteosclerotic lesions and a lack of monoclonal immunoglobulin secretion. One of the classic features of MM is lytic lesions. Multiple myeloma with diffuse osteosclerotic lesions is very rare, accounting for approximately 3% of cases (5). When evaluating sclerotic lesions, an important distinction must be made from POEMS syndrome. In order for a diagnosis of POEMS syndrome to be made, at least 3 major criteria, including polyradiculoneuropathy and monoclonal plasma cell disorder, and 1 minor criteria must be met (6). Our patient lacked any of these cardinal aspects and did not have elevated VEGF levels. A bone biopsy was also performed to ensure that the sclerotic lesions were unrelated to her recent breast cancer diagnosis.

Our literature review reveals that this case is one of a select few reports of non-secretory multiple myeloma with diffuse osteosclerosis (7, 8, 9).

Literature Review

The first published case of multiple myeloma involving osteosclerosis appeared in 1933 (10). A case series of 5 cases by Langley et al. was published in 1966 (11). Kelly et al reviewed osteosclerotic myeloma cases at the Mayo Clinic over a decade and reported their results in 1983 (12). Since then, there has only been one review publication by Lacy et al. that summarizes all 15 published cases of diffuse osteosclerosis with multiple myeloma until 1997 (13). These three publications together represent the sum of all comprehensive publications on osteosclerotic myeloma; the remaining literature comprises mostly of case reports. Approximately 50 cases have been published prior to 1997 (10). This paper's greatest strength is that it provides the most comprehensive current review of osteosclerotic multiple myeloma, diffuse or otherwise, distinct from POEMS syndrome since 1997. We identified 17 patients in the literature as well as our own case, the features of whom are summarized in Table 2. Given the extreme rarity of OMM, we chose to present the unique data of each case rather than in a summary table so that providers might more easily identify similarities that may inform treatment and prognosis between past cases and future.

[Insert Table 2. here during production for final manuscript.]

History and Demographics

Previous literature prior to 1997 reported that patients with osteosclerotic myeloma are younger, present commonly with neuropathy, and less commonly with bone pain than those with classical multiple myeloma (CMM) (13). Of the 17 cases since 1997, age at time of diagnosis ranged from 32 to 82 years, with a mean and median of 60 years compared to the median of 66 to 70 years in CMM (14). OMM does appear to present at a younger age, however, neuropathy is in fact a rare presentation. Of the 17 patients reviewed, only 1 presented with neuropathy, 1 with skin changes, 1 with organomegaly, and 2 with lymphadenopathy. These cases were diagnosed as osteosclerotic MM despite the presence of 1 or 2 POEMS syndrome features because they lacked sufficient criteria to be categorized as POEMS in addition to fulfilling criteria for diagnosis of MM. The most common presenting symptoms in OMM include back pain (35%), dyspnea (35%), weakness/fatigue (35%), weight loss (29%), and chest pain (24%). In CMM, bone pain is the most common reported symptom at diagnosis in 58% of patients, followed by fatigue in 32% and weight loss in 24%. Only 2 patients reported bone pain, although patients may have chosen to describe bone pain by location as back pain, lowering subjective reports of bone pain. Distribution between the sexes was almost equal, with 9 (56.25%) men and 7 (43.75%) women, reflective of the established equal sex distribution in multiple myeloma. This contrasts with previous literature, which reported that osteosclerotic myeloma more commonly presents in men than women at a 4:1 ratio (10). CMM is reported to be twice as common in African-Americans compared to Caucasians and less common in Asians (1). In OMM, 29% of patients were South Asian. The reasons for this are unclear. Prior literature reviews of OMM by Lacy et al. also surveyed English-language literature, and while they did not report race, none of the cases they reviewed were authored in India. Incidence of CMM in India remains low at 1.0 per 100,00 compared to 4.1 per 100,000 individuals in the West (15). Further research is needed to determine if this population has genetic factors that would classify them as a higher risk group or change treatment or prognosis.

Laboratory Tests

Of the 47% of cases reporting serum calcium values, none were hypercalcemic (>12 mg/dL). Of the 64.7% reporting serum creatinine, 45.5% were elevated (>2 mg/dL). Of the 82.4% of cases reporting hemoglobin, 57.1% were anemic (<10 g/dL). Reference values were taken from the IMWG criteria (2). Table 3 compares presentation of laboratory evidence of end-organ damage at initial presentation between OMM and CMM. The lack of hypercalcemia among OMM can be attributed to the comparative lack of lytic bone processes releasing calcium into the bloodstream. Our study supports the previously reported findings that hypercalcemia is rare in OMM, but renal insufficiency, rather than being rare per prior literature, actually appears more common than in CMM (13). These observations are limited due to sample size which preclude tests of statistical significance.

Table 3. Laboratory Evidence of End-Organ Damage at Initial Presentation in Osteosclerotic versus Classical Multiple Myeloma

	Osteosclerotic Multiple Myeloma		Classical Multiple Myeloma	
	No. of patients	% of patients	No. of patients	% of patients
Hypercalcemia (Serum Calcium >12 mg/dL)	8	0	1018	13*
Renal Insufficiency (Serum Creatinine > 2 mg/dL)	11	45	1020	19
Anemia (Hemoglobin < 10g/dL)	14	57	1025	35

Data for classical multiple myeloma taken from Kyle et al. and are not original to this paper (16).
*Kyle et al. reported serum calcium only above 11 mg/dL not the 12 mg/dL criteria described by the International Myeloma Working Group, so the real percentage of CMM with serum calcium >12 mg/dL is likely lower than 13%

Our review revealed a wide range of abnormal plasma cells on bone marrow biopsies, ranging from 0.8% to 86%, with a mean of 49% and median of 45% for the 12 cases reporting percent infiltration. OMM has comparable plasma cell infiltration to CMM, which has a median infiltrate of 50% (16). Prior review reported plasma infiltrates mostly <5% plasma cells (13). Of the 17 patients reviewed, including our own, 10 (59%) had specified monoclonal gammopathy type, evenly split with 5 cases of kappa and 5 cases of lambda chain monoclonal gammopathy. Kappa chain monoclonal gammopathy cases were mostly associated with immunoglobulin G heavy chain, while lambda chain monoclonal gammopathy cases were mostly associated with immunoglobulin A heavy chain. The frequency with which IgG and IgA were represented were reflective of how commonly these immunoglobulins are produced in CMM. Four cases, including our own, reported non-secretory MM (7, 9, 17).

Radiologic Studies

Rousseau was the first to further classify osteosclerosis with multiple myeloma in 1978 into four groups: diffuse (37%), focal areas of osteocondensation (30%), bony spiculation on the surface of the bone (20%), and sclerotic reaction at the rim of the lytic lesion (13%) (18, 19). Given that these radiologic classifications were created several decades ago, we reviewed these groups. In doing so, we identified a case that did not fit the previously hypothesized categories for radiological features. Sufficient information to determine the osteosclerosis subgroups was provided for 16/17 cases. One case described two focal mixed lesions that were primarily osteosclerotic at the center, with peripheral lytic activity (7). Two cases had findings in two categories. The first patient had diffuse sclerotic lesions and one primarily lytic lesion with peripheral sclerosis at the rim (20). The second had focal areas of condensation as well as bony spiculation on the surface of the bone (21). Otherwise, diffuse sclerosis was most common at 73% (12/16), followed by focal areas of osteocondensation at 19% (3/16), bony spiculation on bone surface at 6% (1/16), and sclerotic reaction at the rim of lytic lesion at 6% (1/16). The distribution of CMM parallels red marrow distribution and thus mostly occurs in the axial skeleton and proximal appendicular skeleton. Most common sites of lytic lesions in CMM include the vertebrae (66%), ribs (45%), skull (40%), pelvis (30%), and long bones (25%) (22). Other less common sites include the jaw in 20-30% of cases (23, 24), sternum, and phalanges. No literature was found reporting rate of sternal or distal extremity, or phalangeal, involvement. Table 4 compares the common sites for OMM against CMM. OMM most commonly involves the vertebrae like CMM but has greater involvement in the pelvis and long bones than CMM. 59% of OMM cases were purely sclerotic without any lytic lesions.

Table 4. Frequency of involvement of different anatomical regions in 16 osteosclerotic multiple myeloma and multiple myeloma

	Osteosclerotic Multiple Myeloma n = 16*			Multiple Myeloma
	Number of patients with sclerotic lesions	Number of patients with lytic lesions	Number of patients with sclerotic or lytic lesions	Lytic Lesions Only
Vertebrae	12/16 (75%)	1/16 (6%)	13/16 (81%)	66%
Ribs	4/16 (25%)	2/16 (13%)	6/16 (38%)	45%
Skull	5/16 (31%)	3/16 (19%)	8/16 (50%)	40%
Pelvis	7/16 (44%)	3/16 (19%)	10/16 (63%)	30%
Long Bones	7/16 (44%)	2/16 (13%)	9/16 (56%)	25%
Jaw	1/16 (6%)	(-)	1/16 (6%)	30%
Sternum	2/16 (13%)	(-)	2/16 (13%)	N/A
Phalanges	1/16 (6%)	1/16 (6%)	2/16 (13%)	N/A

Percentages for lytic lesions in MM were retrieved from prior research and are not generated by this review (22). No counts (n) were reported for classic MM and small sample size of OMM precluded any comparison using statistical tests for significance.

*One patient was excluded because no lesions were reported on imaging and site of bone marrow biopsy demonstrating osteosclerosis was not specified.

(-) Indicates no patients had lesions of the indicated type.

N/A Indicates that the literature does not report frequency of the specified site for lesions in multiple myeloma

Prognosis and Treatment

Although MM remains incurable, recent advancements in therapeutic options and increased use of stem cell transplants have increased median survival for CMM from 33 months at the turn of the century to 6 years (1, 16). OMM is more indolent than MM, but given its rarity, it is difficult to determine survival. Most case reports report treatment response at 1 year. Only 1 patient demise was reported, which occurred prior to biopsy due to rapid deterioration from GI bleed and DIC. 24% received either bone, hematopoietic, or stem cell transplant. OMM had no significant differences in treatment to MM, but patients were more likely to receive a transplant (16).

Pathophysiology of Osteosclerosis

The pathophysiology behind osteosclerosis in multiple myeloma remains unclear. Although previous reports have theorized alkaline phosphatase might contribute to this process, only 3 cases reported

elevated alkaline phosphatase levels (25, 26, 27). More likely, sclerosis results from an imbalance between osteoblasts and osteoclasts in favor of greater bone building and/or lesser resorptive activity. The same mediators thought to be involved in the production of lytic lesions via the uncoupling between blastic and lytic activity should be studied. These include Rank-L, MIP-1α, IL-1β, IL-3 , IL-6, IL-7, and TNF-α (28). There may also be parallels between the pathophysiology of sclerotic lesions in MM and prostate cancer given that prostate cancer is typically blastic. This would benefit from the study of PDGF and other mediators of prostatic sclerotic lesions, as suggested by Lacy (13).

Conclusion

Osteosclerotic Multiple Myeloma (OMM) is an extremely rare subtype of Classical Multiple Myeloma (CMM), with less than 50 cases reported in the literature prior to 1997. An updated review of English-language published case reports since 1997 calls into question many of the characteristics assigned to osteosclerotic multiple myeloma. Our review found a sex distribution comparable to CMM and lower rates of neuropathy compared to previous reports of 50%. This report confirmed prior findings that OMM presents in younger patients. While prior research identified that bone pain was a rare presenting symptom in OMM, our review went further to identify the most common initial symptoms of back pain, dyspnea, and weakness/fatigue. A novel finding included that 29% of patients reviewed were South Asian, warranting further research into risk factors for this population. Hypercalcemia is rare in OMM because the majority of OMM has no lytic involvement. This review also found that renal insufficiency and anemia are more common than in CMM, although a larger sample size is required to determine statistical significance. Although previous reports described minimal plasma cell infiltrate, this review found that OMM has a median infiltrate of 45%, which is comparable to 50% in CMM, with even distribution of kappa and lambda chain monoclonal gammopathy (10, 13). The distribution of skeletal involvement in OMM differs than that in CMM, both most commonly involving the vertebrae but with OMM having greater involvement in the pelvis and long bones. This review also suggests that cases of osteosclerotic multiple myeloma do not all fall under the umbrella of existing radiologic categories for the classification of osteosclerotic lesions, and further research might be directed at an updated radiological classification of OMM. Our finding that OMM is more indolent with better survival supports prior research, although length of survival requires further research as many of the cases described here were case reports which followed patients for a limited time. Bone sclerosis is a relatively less aggressive process than osteolysis, allowing for osteoblastic repair and thus a more indolent course.

Our case represented a challenging diagnosis due to a lack of hypercalcemia, renal insufficiency, or anemia typically associated with CMM and unremarkable findings on SPEP, UPEP, or free light chain analysis due to an underlying rare non-secretory and osteosclerotic pathophysiology. Although rare, OMM should be considered in diagnosis of patients with persistent back pain despite 1-2 months of conventional conservative treatment using computed tomography or magnetic resonance imaging.

Abbreviations

CMM: Classical multiple myeloma

MM: multiple myeloma

POEMS Syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome

'p' in pT1b: pathological stage

TNM: as used in cancer staging with 'T' describing size of tumor, 'N' describe spread to nearby lymph nodes, and 'M' describing metastasis

SPEP: serum protein electrophoresis

UPEP: urine protein electrophoresis

IFE: immunofixation

FLC: free light chain

LDH: lactate dehydrogenase

VEGF: vascular endothelial growth factor

RVD: Revlamid (Lenalidomide), Bortezomib (Velcade), Dexamethasone

PET: Positron emission tomography scan

CT: computed tomography

MRI: magnetic resonance imaging

SUV: standard uptake value

FDG: F-fluorodeoxyglucose

Tc99m-HDP: technetium Tc 99m hydroxydiphosphonate

RB1: retinoblastoma gene 1

TP53: tumor protein 53

IMWG: International Myeloma Working Group

CRAB: hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesion

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: All individual patient data for this case report including images were obtained with consent by the individual for publication.

Availability of data and materials: Data collected from individual case reports can be found within references as well as hyperlinked in the relevant table. All data gathered and analyzed during this study are included in the published article.

Competing interests: G.K. declares financial competing interests due to her work consulting/honoraria with the following corporations: BMS, Janssen, Sanofi, Arcellx, Kedrion, Pfizer. The remaining authors declare that they have no competing interests.

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Author's Contributions: TV was a major contributor in writing the manuscript, conducted review of available literature surrounding osteosclerotic multiple myeloma, and analyzed data collected from case reports. GK, LA, JD, and JJ contributed significantly to writing the manuscript. GK served as oncologist to the patient and contributed to table creation. JD read and interpreted all radiologic imaging. JJ performed the examination of the bone marrow biopsies and immunohistochemical analysis as well as interpretation of results. All authors read and approved the final manuscript.

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References

1. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97(8):1086-107.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.
3. Ghosh S, Wadhwa P, Kumar A, Pai K, Seshadri S, Manohar C. Abnormal radiological features in a multiple myeloma patient: a case report and radiological review of myelomas. Dentomaxillofac Radiol. 2011;40(8):513-8.
4. Dupuis MM, Tuchman SA. Non-secretory multiple myeloma: from biology to clinical management. Onco Targets Ther. 2016;9:7583-90.
5. Mugera C, Suh KJ, Huisman TA, Weber K, Belzberg AJ, Carrino JA, et al. Sclerotic lesions of the spine: MRI assessment. J Magn Reson Imaging. 2013;38(6):1310-24.
6. Dispenzieri A. POEMS syndrome. Blood Rev. 2007;21(6):285-99.

7. Mazzeo A, Granata F, Vinci S, Musolino C, Nastasi V, Autunno M, et al. Osteosclerotic myeloma with spinal leptomeningitis and severe polyneuropathy: A case report. J Comput Assist Tomogr. 2006;30(4):649-52.
8. Raman S, Frame B, Saeed SM, Tolia K, Raju U, Kottamasu S. Diffuse nonsecretory osteosclerotic myeloma with extensive erythrophagocytosis. Am J Clin Pathol. 1983;80(1):84-8.
9. Prasad R, Yadav RR, Singh A, Mathur SP, Mangal Y, Singh M. Case report. Non-secretory multiple myeloma presenting with diffuse sclerosis of affected bones interspersed with osteolytic lesions. Br J Radiol. 2009;82(974):e29-31.
10. Hall FM, Gore SM. Osteosclerotic myeloma variants. Skeletal Radiol. 1988;17(2):101-5.
11. Langley GR, Sabean HB, Sorger K. Sclerotic lesions of bone in myeloma. Can Med Assoc J. 1966;94(18):940-6.
12. Kelly JJ, Jr., Kyle RA, Miles JM, Dyck PJ. Osteosclerotic myeloma and peripheral neuropathy. Neurology. 1983;33(2):202-10.
13. Lacy MQ, Gertz MA, Hanson CA, Inwards DJ, Kyle RA. Multiple myeloma associated with diffuse osteosclerotic bone lesions: a clinical entity distinct from osteosclerotic myeloma (POEMS syndrome). Am J Hematol. 1997;56(4):288-93.
14. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016;43(6):676-81.
15. Kumar L, Nair S, Vadlamani SP, Chaudhary P. Multiple myeloma: an update. Journal of Current Oncology. 2020;3(2):72-80.
16. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33.
17. Divakar M, Shyam A, Hadgaonkar S, Sancheti P, Aiyer SN. Osteosclerotic Multiple Myeloma without POEMS Syndrome - A Rare Case Report. J Orthop Case Rep. 2022;12(1):18-21.
18. Rousseau JJ, Franck G, Grisar T, Reznik M, Heynen G, Salmon J. Osteosclerotic myeloma with polyneuropathy and ectopic secretion of calcitonin. Eur J Cancer (1965). 1978;14(2):133-40.
19. Blaquière RM, Guyer PB, Buchanan RB, Gallagher PJ. Sclerotic bone deposits in multiple myeloma. Br J Radiol. 1982;55(656):591-3.
20. Wang Y, Liu Y, Ma L, An C, Zhang W. Rare Distribution of Sclerotic Bony Lesions in Multiple Myeloma: A Case Report. Clin Nucl Med. 2022;47(4):e344-e5.
21. Crispin PJ, Cheah PL. Autoimmune haemolytic anaemia and neuropathy with IgA osteosclerotic myeloma: a case report. Pathology. 2017;49(6):646-7.
22. Collins CD. Multiple myeloma. Cancer Imaging. 2004;4 Spec No A(Spec No A):S47-53.
23. Epstein JB, Voss NJ, Stevenson-Moore P. Maxillofacial manifestations of multiple myeloma. An unusual case and review of the literature. Oral Surg Oral Med Oral Pathol. 1984;57(3):267-71.
24. Pisano JJ, Coupland R, Chen SY, Miller AS. Plasmacytoma of the oral cavity and jaws: a clinicopathologic study of 13 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod.

1997;83(2):265-71.
25. Mulleman D, Gaxatte C, Guillerm G, Leroy X, Cotten A, Duquesnoy B, et al. Multiple myeloma presenting with widespread osteosclerotic lesions. Joint Bone Spine. 2004;71(1):79-83.
26. Najib D, Talmud D, Srour S, Khamisy-Farah R, Farah R. Rare Aggressive Form of Multiple Myeloma with Diffuse Osteosclerosis and Elevated CA 15-3 Levels. Open Journal of Internal Medicine. 2016;Vol.06No.01:4.
27. Patolia S, Schmidt F, Patolia S, Gulati N, Muhammad P, Narendra D, et al. Multiple Myeloma With Mixed Lytic and Blastic Bone Lesions With Lymphadenopathy: Rare Manifestation of a Common Disease-Case Presentation and Literature Review. World J Oncol. 2012;3(2):78-82.
28. Hameed A, Brady JJ, Dowling P, Clynes M, O'Gorman P. Bone disease in multiple myeloma: pathophysiology and management. Cancer Growth Metastasis. 2014;7:33-42.
29. Chen M, Green R. Circulating plasma cells with Russell bodies in osteosclerotic myeloma. Blood. 2013;122(2):160.
30. Mohamed M, Brain T, Khalafallah A. Dramatic response of diffuse osteosclerosis secondary to multiple myeloma using thalidomide with melphalan and prednisolone. J Clin Oncol. 2014;32(23):e85-7.
31. Ram R, Kumar VS. Osteosclerotic & osteolytic lesions in multiple myeloma. Indian J Med Res. 2014;140(3):441-2.
32. Vignon M, Senot N, Bousson V, Meignin V, Frazier A, Arnulf B. A case of multiple myeloma presenting with diffuse osteosclerosis and multiple bone infarcts. Joint Bone Spine. 2018;85(5):631-3.
33. Patir DC, Peker A, Ceylan C, Akar H. Multiple myeloma associated with osteosclerotic and osteolytic lesions. Demiroglu Science University Florence Nightingale Journal of Medicine. 2019;5(3):176-8.
34. Terao T, Matsue K. Osteosclerotic myeloma without features of POEMS syndrome. Int J Hematol. 2019;110(5):517-8.
35. Zheng W, Low MSY. Rare presentation of myeloma with diffuse osteosclerotic lesions without features of POEMS. Ann Hematol. 2022;101(2):429-30.

Table

Table 2 is available in the Supplementary Files section

Figures

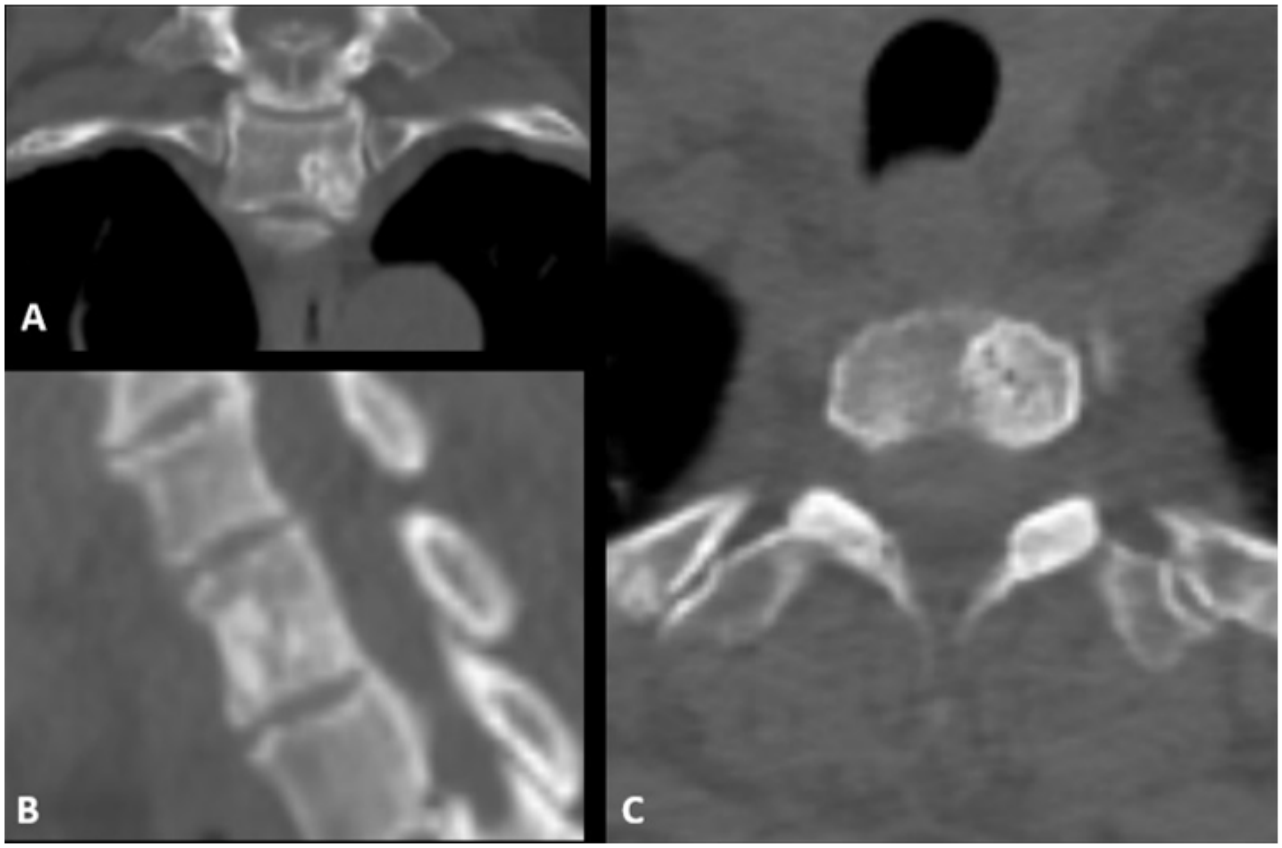

Figure 1

(A) Coronal, (B) sagittal, and (C) axial CT images demonstrate a heterogeneously sclerotic lesion in the left aspect of the T1 vertebral body.

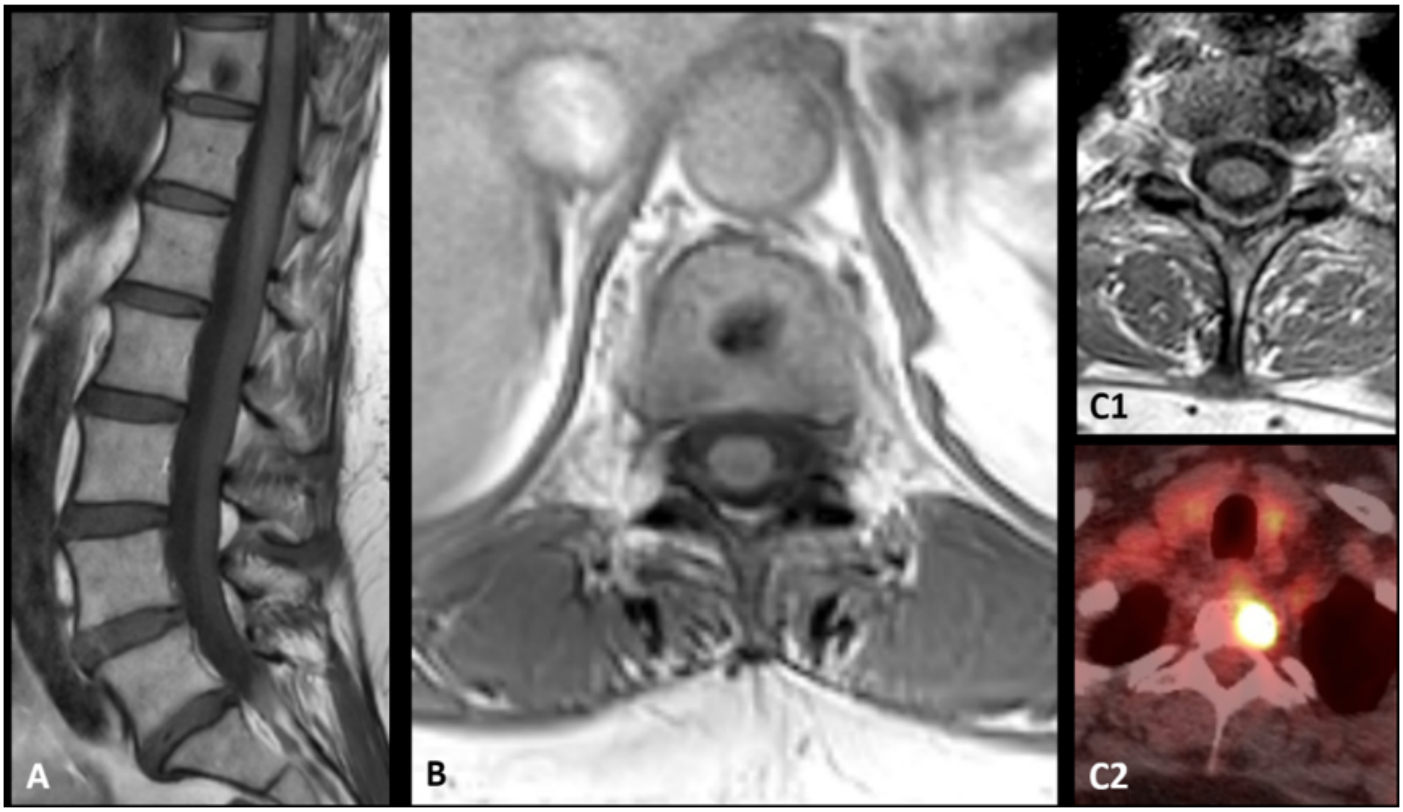

Figure 2

Sagittal (A) and Axial (B) T1-weighted images of T11 demonstrate hypointense sclerotic lesion. (C1) Axial T1-weighted image of T1 hypointense sclerotic lesion. (C2) Axial image using 18FDG-PET demonstrates strong FDG avidity in the T1 sclerotic lesion. No significant activity was appreciated in the T11 lesion.

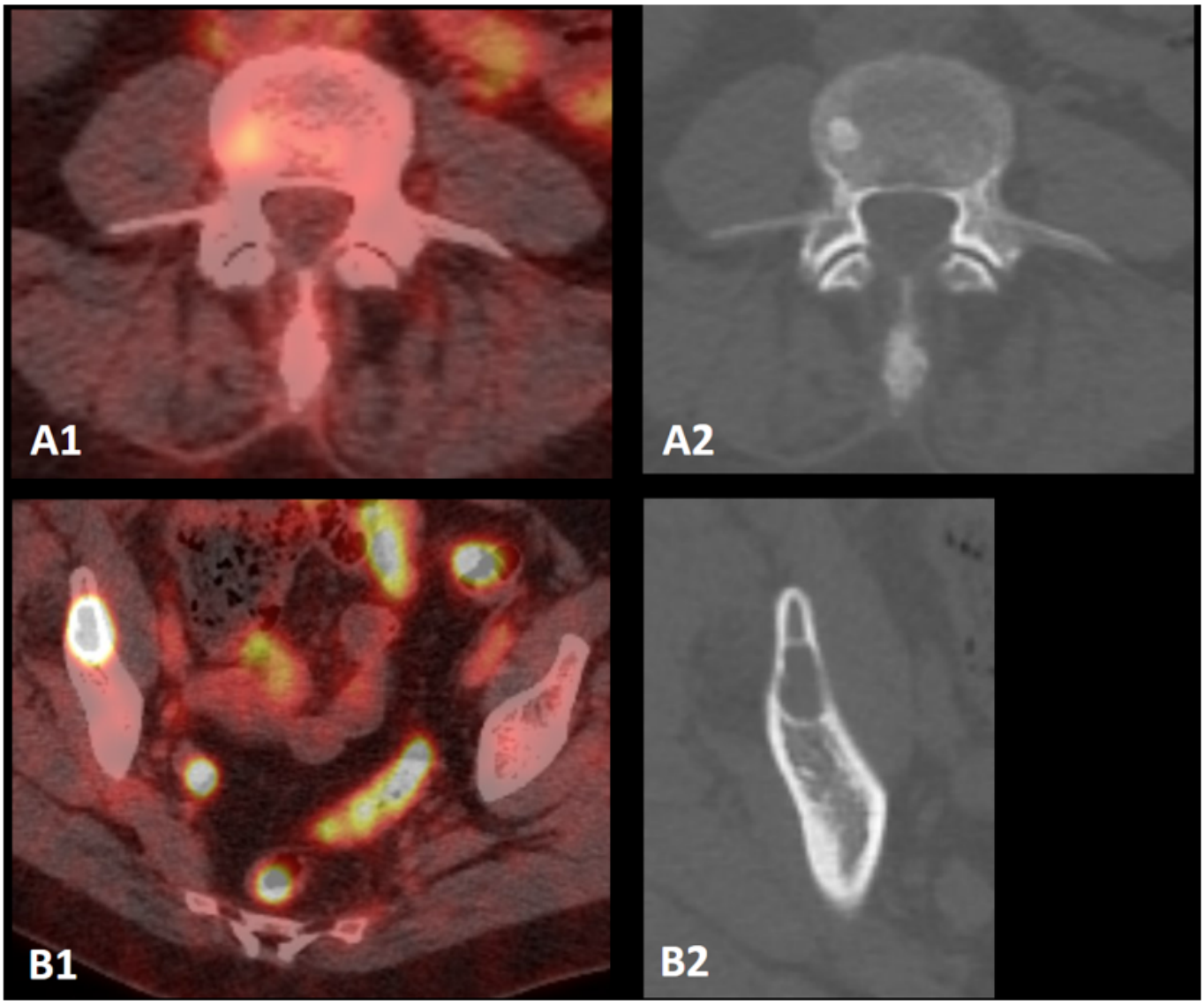

Figure 3

(A1, A2) Axial CT and 18FDG-PET images demonstrate an FDG avid sclerotic lesion in the right aspect of L4. (B1, B2) Axial CT and 18FDG-PET images demonstrate an FDG avid lytic lesion in the right iliac bone.

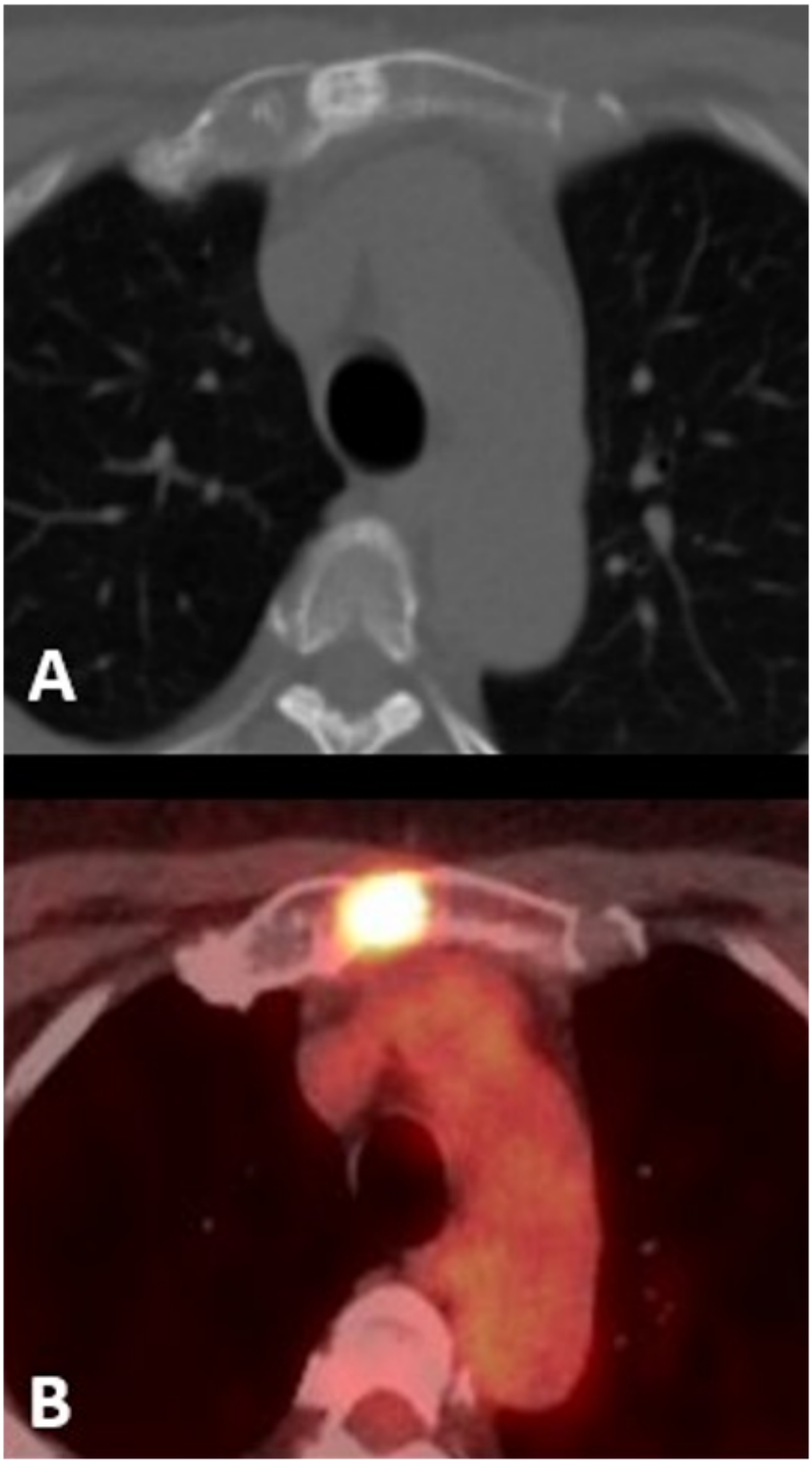

Figure 4

(A) CT and (B) PET demonstrating FDG avid sclerotic lesion of right manubrium.

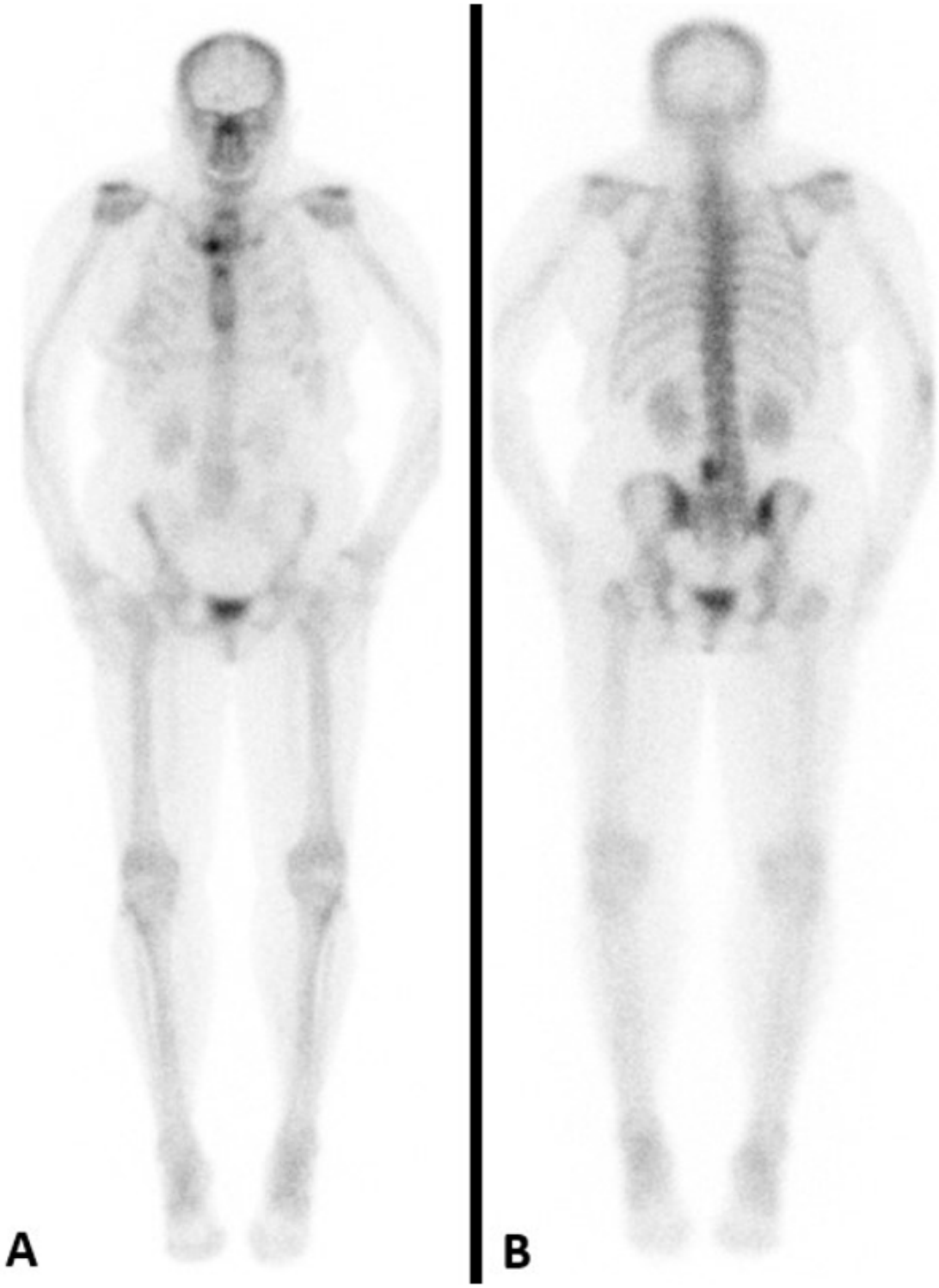

Figure 5

(A) Anterior view bone scan using Tc99m-HDP demonstrates strong uptake in the right manubrium correlating with the FDG avid sclerotic lesion in Fig. 4 (B) Posterior “view” bone scan using Tc99m-HDP demonstrates no scintigraphic evidence of active disease in T1 or T11. Uptake in the region of L4 on the left was attributed to asymmetric advanced facet arthropathy.

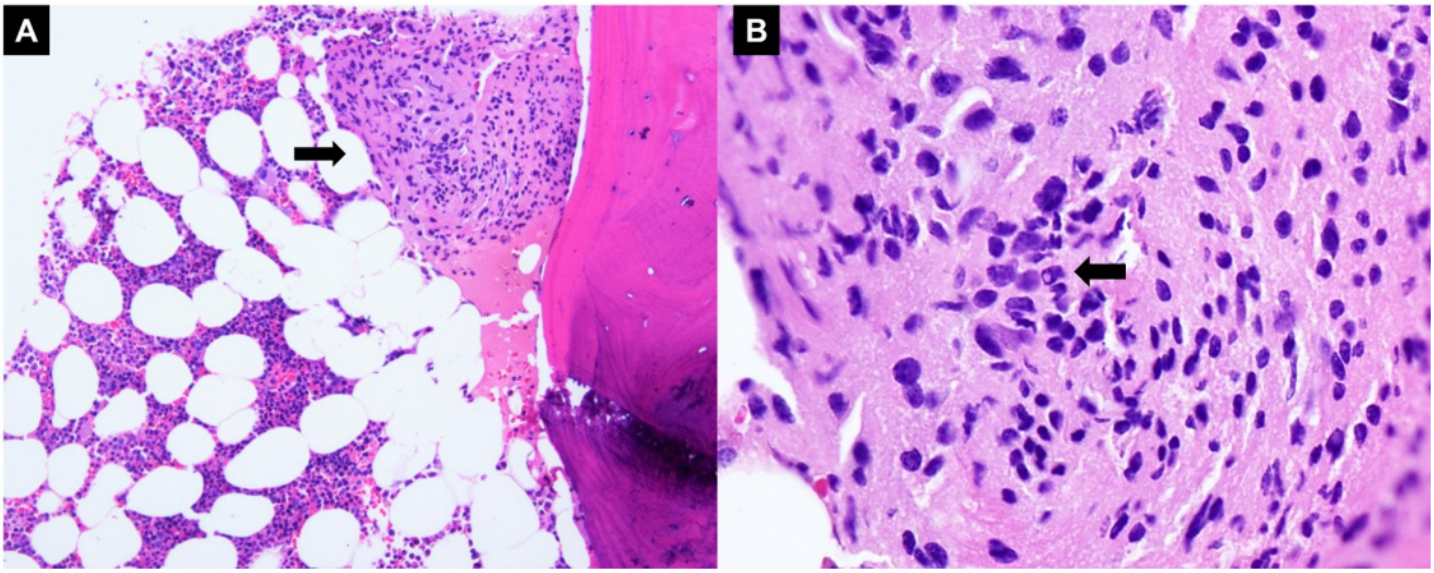

Figure 6

(A) Low-power view of the bone marrow core shows a sclerotic infiltrate (black arrow) adjacent to the trabecular bone *(hematoxylin and eosin, 10x)*. (B) High-power view shows variably sized atypical cells, and a rare cell containing intranuclear immunoglobulin (“Dutcher body”) (black arrow), suggestive of plasmacytic differentiation *(hematoxylin and eosin, 40x)*.

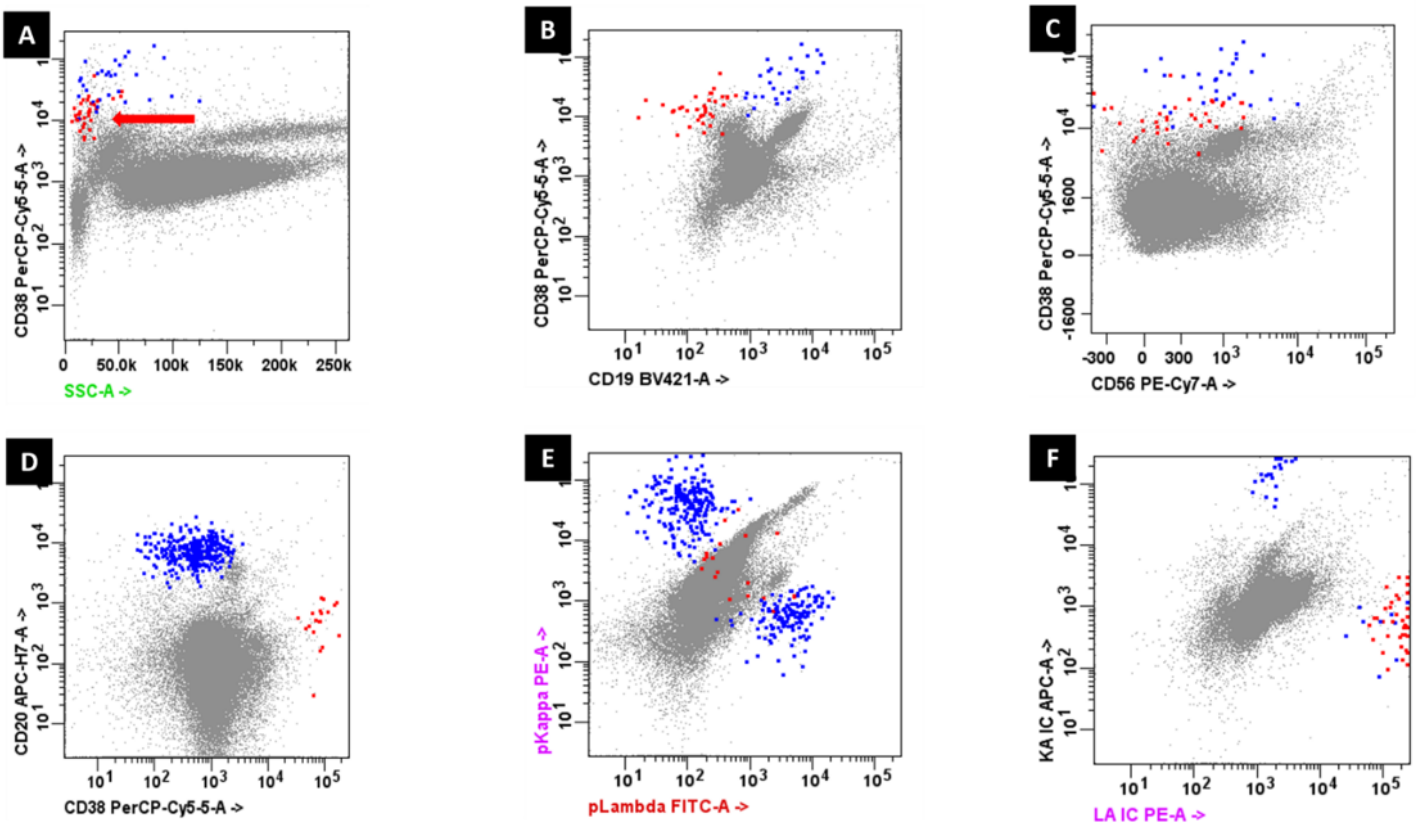

Figure 7

(A) Concurrent flow cytometry showed an aberrant plasma cell population (**red**) admixed with background polyclonal plasma cells (**blue**). Note the dim expression of CD38 in the atypical plasma cells, compared to background plasma cells (**red arrow**). **(B)** The atypical plasma cells showed aberrant, decreased expression of CD19**. (C)** Both populations showed variably dim expression of CD56. **(D)** The atypical plasma cells (**red**) showed bright CD38 expression compared to background B-lymphocytes (**blue**), with appropriate lack of CD20. **(E)** The B-lymphocytes show polyclonal, ***surface*** light chain expression. **(F)** The atypical plasma cells show monoclonal, ***cytoplasmic*** Lambda light chain expression (p=polyclonal; IC= intracytoplasmic).

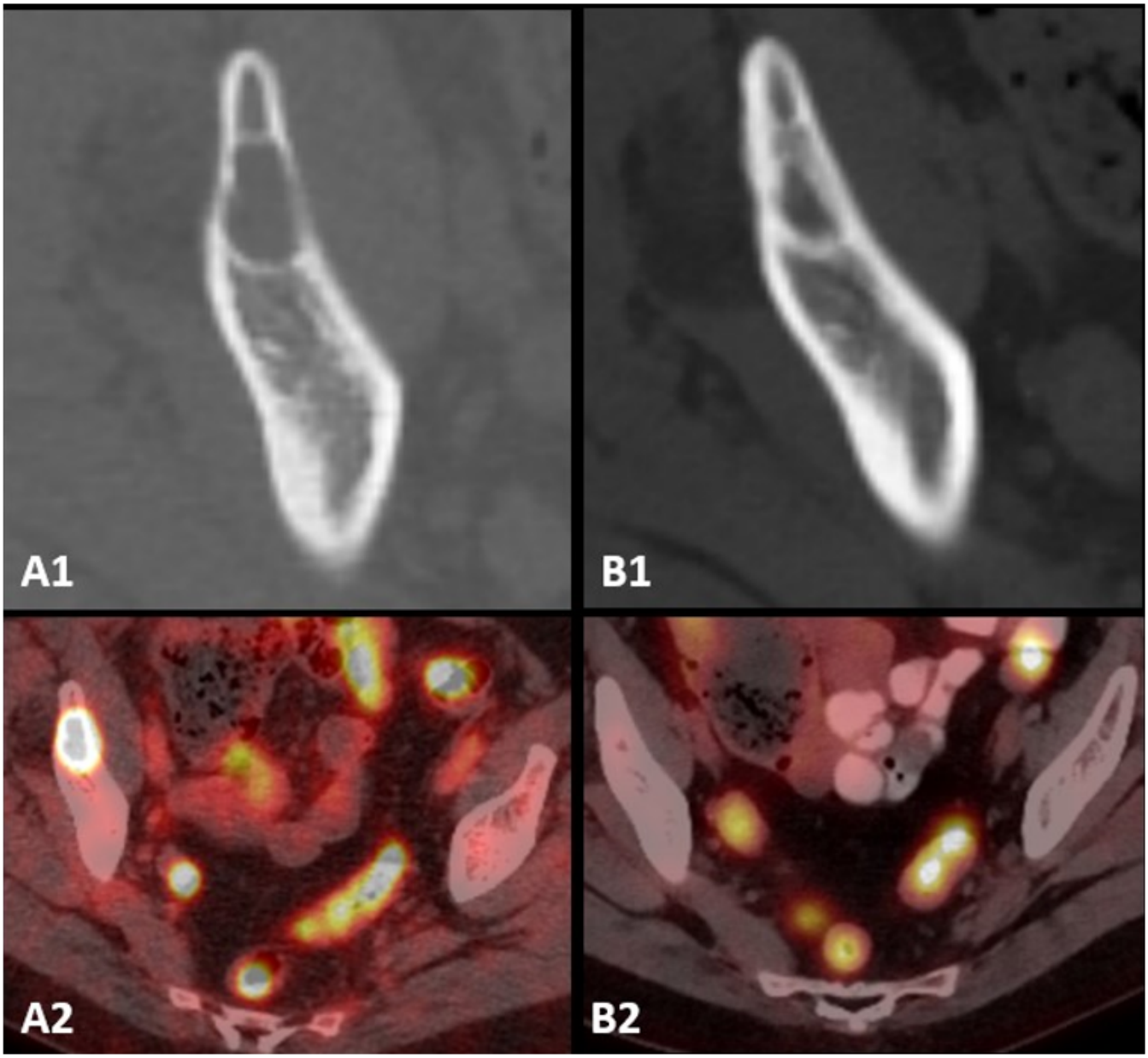

Figure 8

(A1) CT and (A2) PET of right iliac lytic lesion prior to treatment. (B1) CT and (B2) PET demonstrate decreased FDG avidity of right iliac lytic lesion 8 months post-treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.docx