Clinical Oncology: Case Reports

CASE REPORT

A SCITECHNOL JOURNAL

Complete Segmental Bone Resorption Followed by Complete Non-Operative Bone Restoration in the Setting of Multiple Myeloma

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Abstract

Advances in medical management of multiple myeloma have improved the potential for lesional bone healing, decreasing numbers of skeletal related events and need for radical surgical intervention. However, documented cases of complete lesion healing in a multiple myeloma patient are rare. In the current case, progressive post-operative lesional progression following ORIF of a subtrochanteric pathological fracture was followed by complete healing and bone restoration coincident with radiotherapy and a daratumumab based chemotherapy regimen in a patient with stage III high risk multiple myeloma. While research into the effects of daratumumab on bone healing is in its infancy, this agent demonstrates the potential to promote substantial lesional healing in multiple myeloma patients, beyond what has been demonstrated with other anti-myeloma regimens. This case is presented to raise awareness of the possibility of profound progressive bone osteolysis in myeloma and the potential for lesional healing through radiotherapy and medical management without radical surgery.

Keywords: Multiple myeloma; Bone lesion; Bone healing; Radiotherapy; Daratumumab

Introduction

Multiple myeloma is a malignancy of clonal plasma cells that accounts for approximately 1% of all cancers and 10% of hematologic cancers [1,2]. Bone involvement may be associated with hypercalcemia, bone pain, osteoporosis, spinal cord compression, and pathologic fracture [3]. In the past, myeloma bone lesions often persisted after treatment, and the need for surgical treatment was common, but recent advances in medical management have led to improved lesional healing potential. However, despite this promising potential for bone healing, some osseous plasmacytomas with extensive lytic destruction may still be considered for radical bone resection in order to prevent imminent fracture or hardware failure after less radical operative management such as internal fixation. Reported cases of complete healing of such extensive progressively destructive lesions in the setting of multiple myeloma remain rare.

We present a case of complete healing following dramatic progressive destruction of the proximal femur due to an osseous plasmacytoma in the setting of stage III high-risk multiple myeloma managed without radical bone resection. This case is presented to raise awareness of the potential for dramatic lesional healing through modern medical management and radiotherapy without radical surgery and to inform decision-making regarding similar cases.

Case Presentation

A 68-year-old male presented to the Emergency Department (ED) with a 1-week history of back pain and muscle spasms. Initial imaging consisted of Magnetic Resonance Imaging (MRI) of the thoracic and lumbar spine, chest x-ray, and Computed Tomography Angiography (CTA) of the thorax, abdomen, and pelvis that demonstrated osteopenia, a right iliac soft tissue mass involving the bone, a left 3rd rib fracture, and a chronic compression fracture of the T8 vertebral body. Skeletal survey showed innumerable classic punched out lytic bone lesions throughout the axial and appendicular skeleton, including the cervical, thoracic and lumbar spine, bilateral humeri, femurs, radii, tibiae, and fibulae. Serum protein electrophoresis showed elevation of total protein, albumin, gamma globulin, and an M spike. Immunoglobulin testing and serum free light chain assay showed elevation of IgG, beta-2 microglobulin, and lambda free light chain, decreased kappa/lambda ratio, and decreased IgA and IgM. Increased calcium and creatinine with decreased PTH were also found Table 1.

A bone marrow biopsy demonstrated hypercellular marrow almost completely replaced by sheets of immature plasma cells. FISH testing of the bone marrow sample revealed 17p deletion. The patient was subsequently diagnosed with stage III high-risk multiple myeloma (due to beta-2 microglobulin >5.5 mg/L and high-risk cytogenetics (17p deletion). Treatment began with Radiotherapy of the thoracic spine and right sided pelvis (3000 cGy in 10 fractions to each region) followed by induction chemotherapy with 6 cycles of bortezomib-lenalidomide-dexamethasone (VRd) followed by maintenance therapy with lenalidomide. While initiating medical oncology treatment, the patient was followed by both the orthopedic oncology and orthopedic spine services to monitor his bone lesions. Although not initially symptomatic, there was concern that both the left subtrochanteric and right distal diaphyseal femoral lesions represented impending pathologic fractures (Mirels [4] 10 on the left and 9 on the right with prophylactic stabilization suggested for 9 or greater).

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Received: November 23, 2023; Manuscript No: COCR-23-120997; **Editor Assigned:** November 27, 2024; PreQC Id: COCR-23-120997 (PQ); **Reviewed:** December 12, 2023; QC No: COCR-23-120997 (Q); **Revised:** December 18, 2023; Manuscript No: COCR-23-120997 (R); **Published:** December 26, 2023; DOI: 10.4172/cocr.6(11).322

Lab	Patient's Result	Reference Range	Units
Complete Blood Count			
WBC	4.4	4 - 10	$10x^3$/uL
*Hemoglobin	11.3	13.5 - 18	g/dL
*Hematocrit	32.5	41 - 53	%
*Platelets	147	150 - 400	$10x^3$/uL
*RBC	3.6	4.6 - 6.1	$10x^3$/uL
MCV	90.2	80 - 96	fL
Mean Cell Hemoglobin	31.4	27 - 33	pg
MCHC	34.8	32.0 - 36.0	g/dL
Red Cell Distribution Width	12.7	11.5 - 14.5	%
Chemistry Profile			
Bicarbonate	23	22 - 29	mmol/L
*Sodium	124	136 - 145	mmol/L
Potassium	3.8	3.4 - 5.1	mmol/L
*Chloride	93	98 - 107	mmol/L
Blood Urea Nitrogen	23	8 - 23	mg/dL
*Creatinine	1.65	0.70 - 1.20	mg/dL
Glucose	127	70 - 140	mg/dL
*Calcium	11	8.8 - 10.2	mg/dL
Phosphorus	4.4	2.5 - 4.5	mg/dL
Magnesium	1.8	1.6 - 2.4	mg/dL
*Albumin	3.2	3.5 - 5.2	g/dL
ALT/SGP	17	< 41	U/L
AST/SGO	13	< 40	U/L
Alkaline Phosphatase	89	40 - 129	U/L
Anion Gap	9	8 - 15	mmol/L
Bilirubin, Total	0.4	< 1.2	mg/dL
BUN/Cr Ratio	14	0	mg/dL
*GFR	41	> 60	mL/min/1.73m^2
*Osmolality	264	275 - 300	mosm/kg
*Beta 2 Microglobulin	10.6	0.8 - 2.2	mg/L
Serum Protein Electrophoresis			
*Total Protein	9.1	6.4 - 8.3	g/dL
*Albumin	3.49	3.80 - 5.78	g/dL
Alpha 1 Globulin	0.15	0.08 - 0.23	g/dL
Alpha 2 Globulin	0.52	0.45 - 0.92	g/dL
Beta Globulin	0.53	0.50 - 1.03	g/dL

*Gamma Globulin	4.4	0.54 - 1.30	g/dL
*M-Spike	4.1	0	g/dL
Immunoglobulins			
*IgA	36	70 - 400	mg/dL
*IgG	5,134	700 - 1,600	mg/dL
*IgM	22	30 - 230	mg/dL
Kappa Free Light Chains	15.18	3.30 - 19.40	mg/L
*Lambda Free Light Chains	1,790.04	5.71 - 26.30	mg/L
*Kappa/Lambda Ratio	<0.01	0.26 - 1.65	mg/L
Parathyroid			
*PTH	2	15 - 65	pg/mL
* represents abnormal results			

Table 1: Initial labs completed during patient's initial admission and subsequent diagnosis with multiple myeloma.

The novel myeloma specific fracture risk classification of Levin et al. echoed concern more for the left than the right femoral lesions (myeloma-specific 7 on left, 4 on right with prophylactic stabilization suggested for 6 or greater) [5] Figure 1.

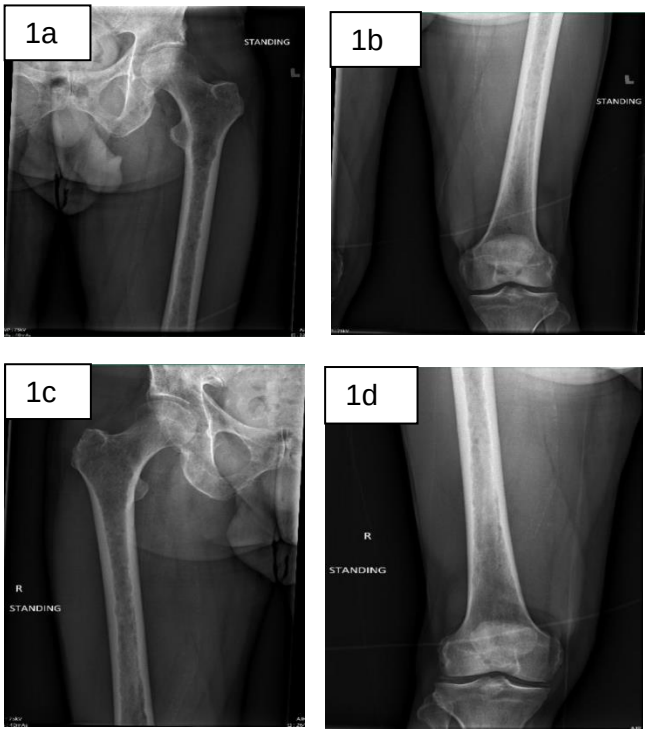

Figure 1. X Figure 1. X-rays from the skeletal survey specific to the bilateral femurs, taken at the time of diagnosis(1a) AP view of the proximal left femur, demonstrating multiple lytic lesions throughout the bone, with the subtrochanteric lesion most prominent. (1b) AP view of the distal left femur, demonstrating multiple lytic lesions throughout the bone.(1c) AP view of the proximal right femur, demonstrating multiple lytic lesions throughout the bone. (1d) AP view of the distal right femur, demonstrating multiple lytic lesions throughout the bone with the distal femoral shaft lesion most prominent.

Computed Tomography (CT) scan was obtained to further assess possible need for prophylactic stabilization. This showed that both lesions were centrally located without substantial cortical involvement Figure 2. Given the lower likelihood of pathologic fracture from a biomechanical standpoint due to the lack of cortical involvement and the minimal pain, it was decided to continue to observe these lesions with serial x-rays. The spinal lesions were also deemed non-operative due to the multilevel extent of the lesions and poor bone quality, precluding fixation, and were managed with a TLSO (Thoracic-Lumbar-Sacral Orthosis) brace and monitoring.

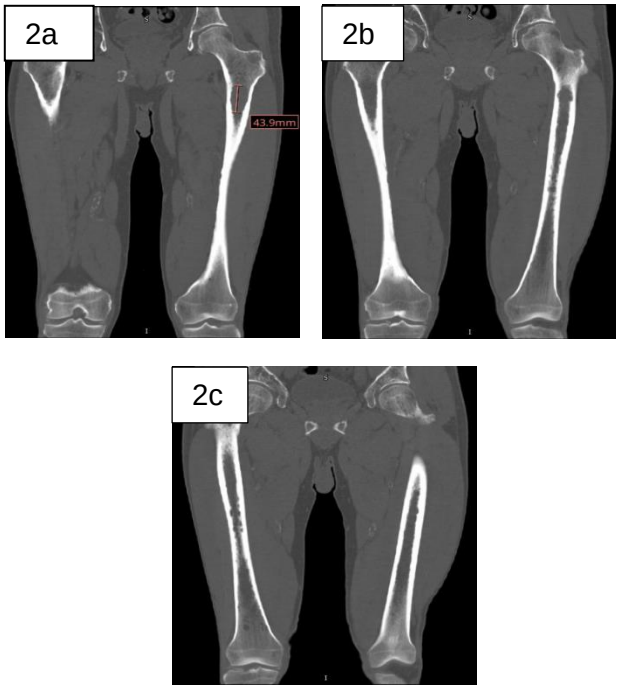

Figure 2. CT scans of the bilateral femurs taken one month after initial diagnosis. The demonstrated lesions are centrally located and lack substantial cortical involvement even though they occupy

greater than two thirds the width of the bone.(2a) CT scan with marker demonstrating left proximal femoral subtrochanteric lesion size. (2b) CT scan demonstrating punched out lytic lesions throughout the left femur.(2c) CT scan demonstrating punched out lytic lesions throughout the right femur.

Five months later (6 months after diagnosis), having had medical management and RT to the thoracic spine and right pelvis only, the patient described worsening left hip pain, and repeat x-rays and CT showed enlargement of the left proximal femur lytic lesion Figure 3.

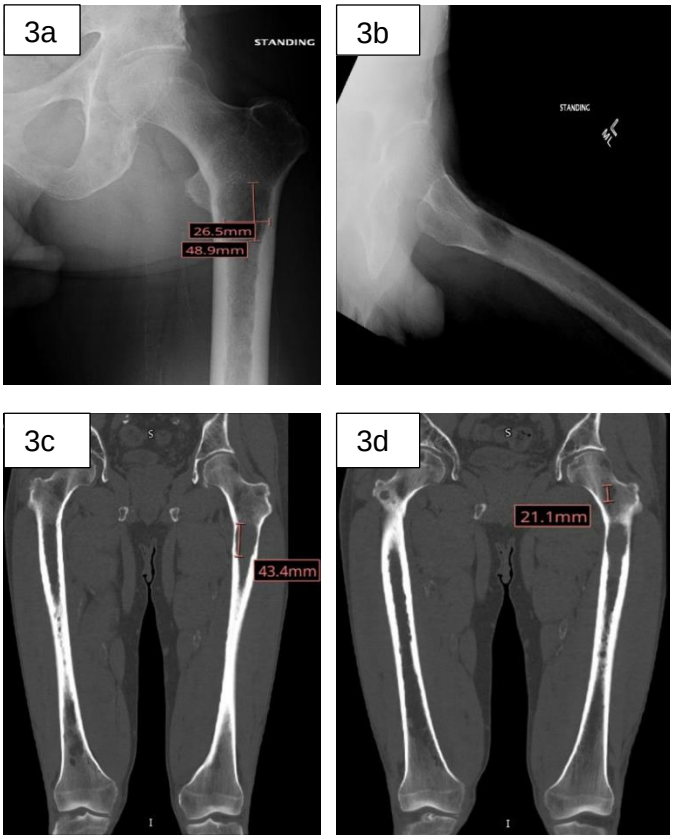

Figure 3. X-ray and CT images of the left femur taken 6 months after initial diagnosis demonstrating enlargement of the left proximal femoral subtrochanteric lesion. (3a) AP view X-ray with marker demonstrating left proximal femoral subtrochanteric lesion size. (3B) Lateral view X-ray (3C) CT scan with marker demonstrating proximal femoral subtrochanteric lesion size.(3d) CT scan with marker demonstrating left femoral intertrochanteric lesion size.

The Mirels score at that point was revised to 12 and the novel myeloma specific score to 9 for the left subtrochanteric lesion. The patient agreed to open biopsy and prophylactic stabilization of the left femur. Discussion also began regarding changing the patient's chemotherapy regimen to second line treatment with Daratumumab-lenalidomide-dexamethasone (Dara Rd) due to the failure of response to 1st line treatment. However, prior to scheduled prophylactic surgery and change in chemotherapy, the patient presented to the ED with immediate pain and swelling in his left hip following a sneeze. Left femur x-ray demonstrated a displaced pathologic fracture through the previously identified lytic lesion Figure 4.

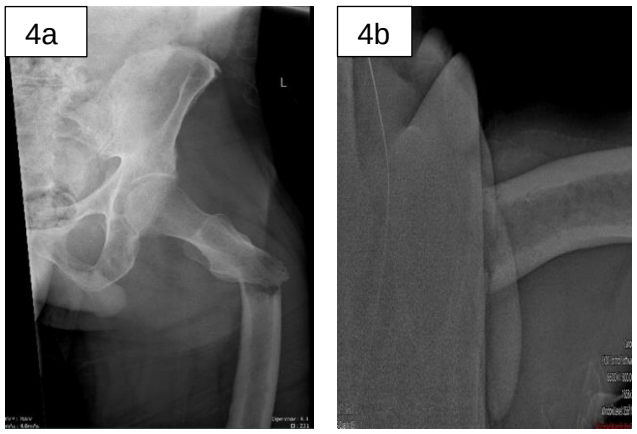

Figure 4. Anterior-posterior (AP) and lateral views of the left femur taken six months after initial diagnosis demonstrating a moderately angled oblique fracture of the proximal subtrochanteric aspect of the left femur at the level of the previously identified lytic lesion, representing a pathological fracture. (4a)AP view (4b) Lateral view.

The patient underwent ORIF of the left femur with an antegrade cephalomedullary femoral nail using a single distal locking screw Figure 5.

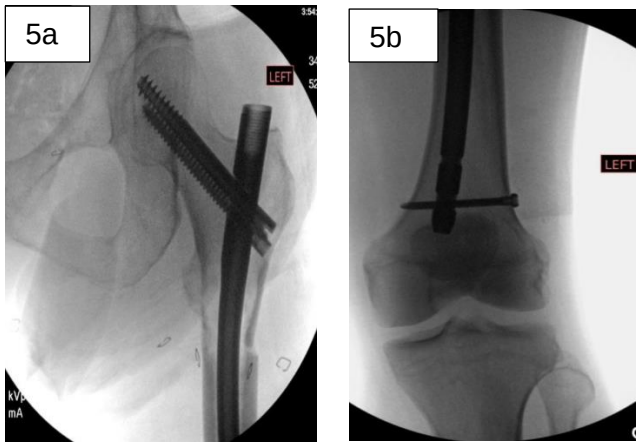

Figure 5. Intra-operative images of the left proximal femoral subtrochanteric fracture following ORIF with intramedullary rod demonstrating adequate stabilization and fixation. (5a) Proximal femur AP view (5b) Distal femur AP view.

At 6-week follow-up after ORIF (~8 months post diagnosis), further progressive enlargement of the lesion in the left subtrochanteric femur prompted recommendation for placement of an additional distal locking screw Figure 6, but the patient elected not to proceed with surgery.

Three days later, the patient again presented to the ED with left leg pain following a sneeze. X-rays showed a new displaced pathologic fracture of the lesser trochanter adjacent to the large lytic region.

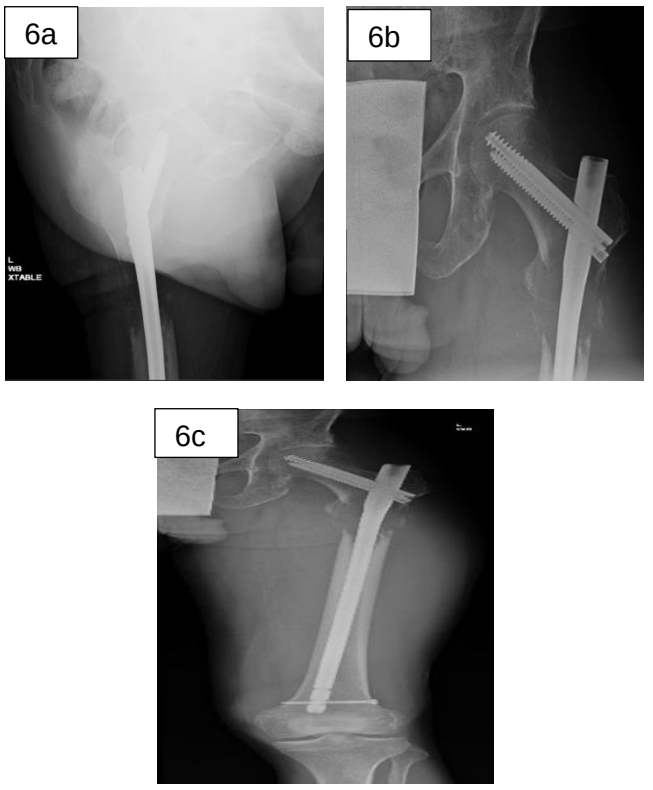

Figure 6. AP and lateral X-rays of the left femur taken six weeks following ORIF (eight months after initial diagnosis) showing significant loss of bone in the subtrochanteric region.(6a) Proximal femur lateral view (6b) Proximal femur lateral view (6c) Whole femur AP view

Figure 7 Non-operative treatment including RT was recommended.

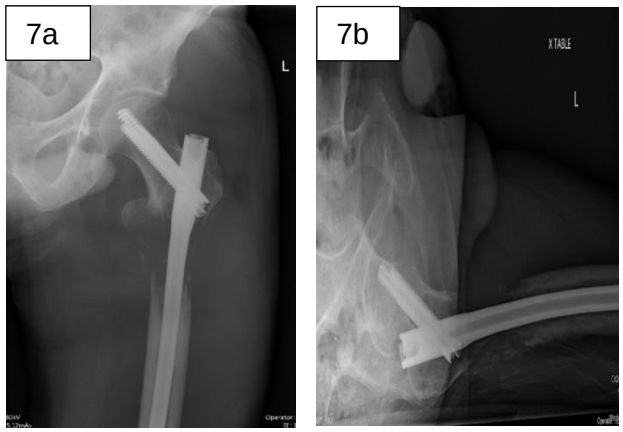

Figure 7. AP and lateral x-rays of the left femur taken six weeks and three days after ORIF (eight months after initial diagnosis) demonstrating progression of the left proximal femur lesion with a lesser trochanter fracture. The previously placed IMN is shown to be in place with no evidence of hardware failure.(7a) Whole femur AP view (7b) Lateral view

Over the next 10 days, prior to initiation of RT, the patient again developed worsening pain and swelling in his left lower extremity, causing functional impairment that limited him to use of a wheelchair for long distances. Second line chemotherapy with Dara Rd was initiated. Follow up X-rays of the left femur taken 3 days after the start of Dara Rd therapy and prior to initiation of femur RT demonstrated continued progression of bone loss in the subtrochanteric region. Figure 8 Six days later, RT to the left femur commenced and was completed over the course of the subsequent 8 days (2400 cGy in 6 fractions).

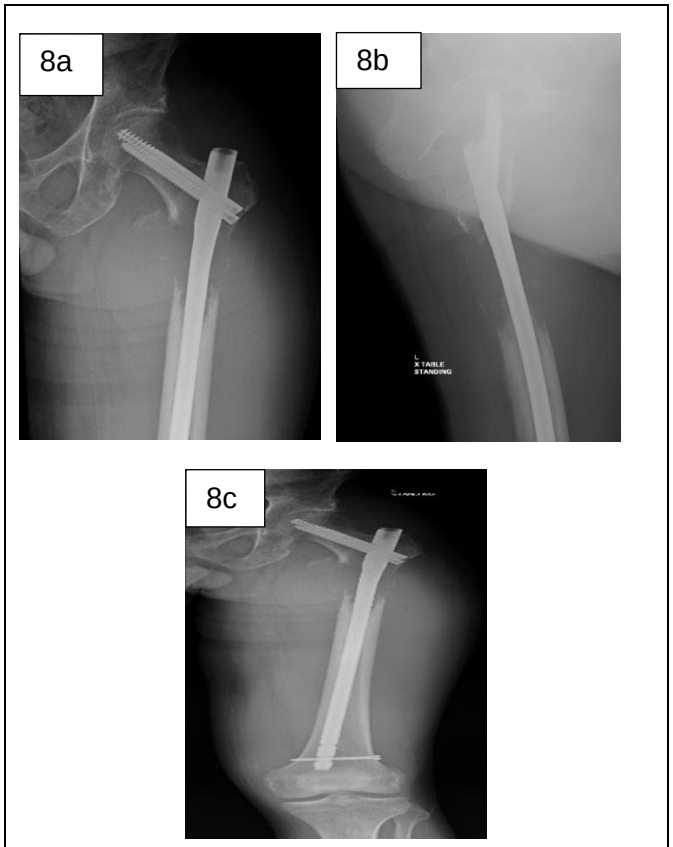

Figure 8. AP and lateral X-rays of the left femur taken two months post ORIF (8.5 months following initial diagnosis) demonstrating progression of bony destruction in the left subtrochanteric region.(8a) Proximal femur AP view (8b) Proximal femur lateral view (8c) Whole femur AP view

At follow up 3 weeks post RT and 4 weeks after starting second line Dara Rd chemotherapy, the patient reported decreased pain, decreased swelling, and improved function with ability to ambulate with crutches. Despite the clinical improvement, x-rays of the left femur showed continued progression of bone loss, prompting consideration for possible eventual radical proximal femoral resection and reconstruction with a proximal femoral replacement megaprosthesis Figure 9.
The patient instead went on to complete treatment with Dara Rd and was transitioned to daratumumab maintenance chemotherapy.

The patient's disease improved and stabilized on daratumumab, and he returned to unassisted walking without aids over the ensuing 11 months after initiating Dara Rd chemotherapy and 10 months after completing RT.

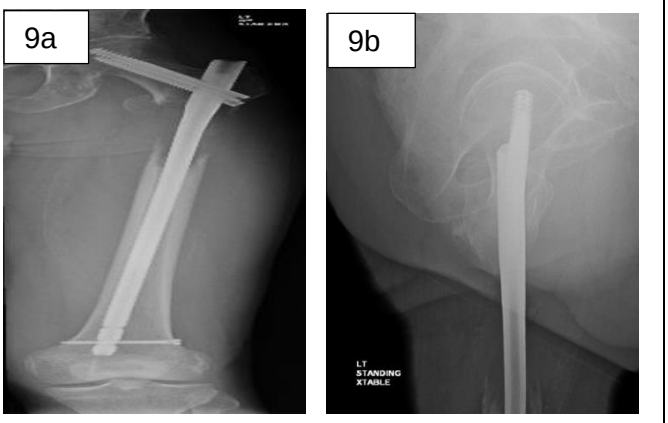

Figure 9. AP and lateral x-rays of the left femur 3 weeks following RT (3 months following ORIF; 9.5 months following initial diagnosis) demonstrating continued progression of bone loss in the subtrochanteric region.(9a) AP view (9b) Lateral view

Although he remained under the care of his medical oncologists, the patient did not return for orthopedic follow up until 15 months later (22 months post initial diagnosis, 16 months post ORIF, 14 months after initiating Dara Rd and 13 months after completing RT). He presented at that time with left lower back pain of 2 weeks duration and was found to have a soft tissue plasmacytoma in the L2-3 paraspinous region. Radiotherapy to the lumbar spine was initiated (total of 3000 cGy in 10 fractions) and plans were made to change the chemotherapy regimen to third line treatment with carfilzomib-pomalidomide-dexamethasone (KPd). X-ray of the patient's left femur at that time showed remarkable complete healing of the previously identified destructive segmental lytic lesion 2 years after initial diagnosis, 1.5 years post ORIF, 16 months post initiation of Dara Rd, and 15 months after completing RT Figure 10.

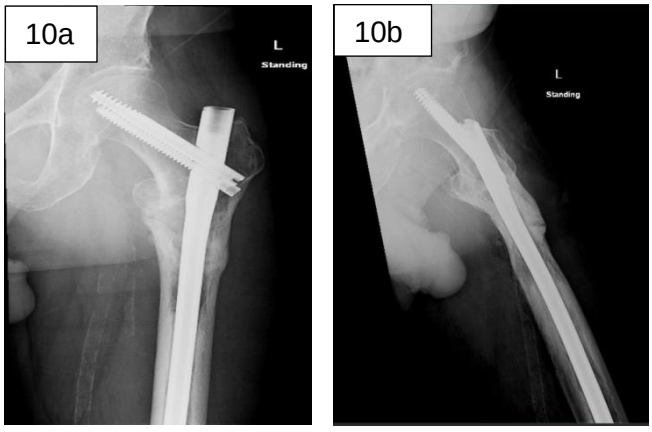

Figure 10. AP and lateral x-rays of the left femur 1.5 years following ORIF and 2 years following diagnosis of multiple myeloma demonstrating complete healing of the proximal metaphyseal (subtrochanteric) lesion.(10a) AP view.(10b) Lateral view

Healing of the lesion has continued to progress and no additional surgical intervention has been required through latest follow-up 2.5 years after initial diagnosis Figure 11.

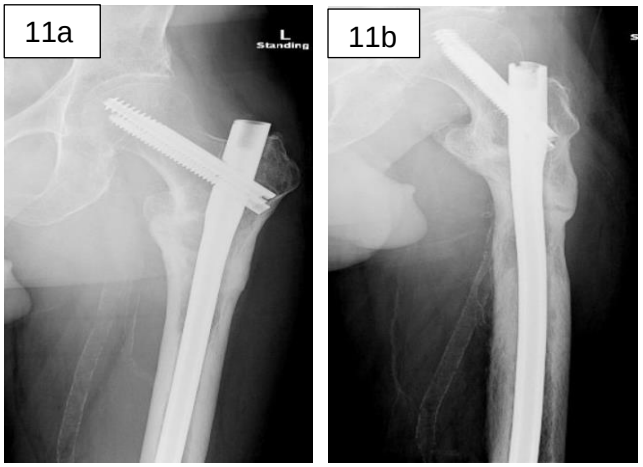

Figure 11. AP and lateral x-rays of the left femur 2.5 years after initial diagnosis demonstrating continued progressive healing of the proximal metaphyseal (subtrochanteric) lesion (11a)AP view(11b) Lateral view

Discussion

The lytic bone lesions that characterize multiple myeloma were classically thought to resist healing even when the patient achieved remission due to continued suppression of osteoblast activity [6,7]. However, modern chemotherapy regimens have been shown to increase bone formation, decrease bone resorption, and decrease SREs [8-20]. The improved response of bone lesions to these non-operative treatments has almost certainly decreased the need for radical surgical intervention. The presented case of dramatic osseous restoration of a segmental area of subtrochanteric bone destruction in a plasmacytoma is important as it demonstrates the remarkable potential for bone healing possible with current myeloma treatments. In this case, the combination of radiotherapy and long-term treatment with daratumumab appears to have led to complete lesional healing and prevented further need for surgical intervention.

Modern myeloma treatments have been shown to promote lesional bone healing. Multiple studies have demonstrated the beneficial effects of bortezomib based chemotherapy regimens on bone healing, manifested as radiographic evidence of sclerosis around existing lytic lesions, increased osteoblastic cells/mm2 of bone, increased bone formation markers (such as bone alkaline phosphatase and osteocalcin), and decreased bone resorption markers (such as dickkopf-1) [8-14]. Most importantly, bortezomib chemotherapy reduces Skeletal Related Events (SREs) compared to older conventional chemotherapy regimens [15]. Carfilzomib, a related drug, similarly leads to increased bone formation markers, decreased bone resorption markers, and a low rate of new SREs during treatment [16]. Other agents such as lenalidomide and thalidomide promote bone healing through osteoclastic inhibition [17,18]. Treatment with Chimeric Antigen Receptor (CAR) T cells targeting B Cell Maturation Antigen (BCMA) may lead to healing of both bone and soft tissue plasmacytomas [19], while autologous peripheral blood stem cell transplant decreases the number and size of bone marrow replacing lesions on MRI [20].

Recently there has been interest in bortezomib based treatment regimens to promote healing of previously untreated lytic lesions

in multiple myeloma. In a phase II study consisting of 35 patients, Hinge et all found that a five-drug combination of doxorubicin, cyclophosphamide, bortezomib, dexamethasone, and lenalidomide (ACVDL) promoted sclerosis in 68% of lytic lesions, but size reduction ≥30% diameter occurred in only 14% of the lesions Mohan et al. found that 43% (27/62) of large pelvic lesions demonstrated remineralization with woven-like bone of at least 1 mm thickness following treatment with melphalan, bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (melphalan-VTD-PACE). Interestingly, a case study published by Fukushima et al of a patient with relapsed multiple myeloma treated with bortezomib and dexamethasone demonstrated disappearance of two skull plasmacytomas on radiographic follow up after two 21 day cycles of treatment [21-23] .These studies show the ever improving response of multiple myeloma bone lesions to chemotherapy. However, continuous progression of our patient's lesion occurred while on the bortezomib based VRd regimen, and he was never exposed to the extensive five or eight drug regimens seen in these studies. This leads us to believe that while bortezomib based regimens show great promise, they were not the mechanism at work in the healing of our patient's lesion. Our patient also achieved much more substantial bone healing than was demonstrated in these studies, which may suggest an unusually robust response to medical therapy in this case.

Although our patient did not receive bisphosphonates, several case reports document bone healing with bortezomib based regimens when combined with bisphosphonate therapy. Szturz et al found >50% size reduction in a femoral lytic lesion following treatment of relapsed multiple myeloma with cyclophosphamide, bortezomib, and dexamethasone (CVD) coupled with bisphosphonates (zoledronate, ibandronate, and clodronate) [24]. Cyriac and Narayan report extensive healing of a 7 cm segment of a lytic lesion of the radius where the bone had previously been completely absent [25]. The patient had been treated with 6 months of bortezomib, lenalidomide, and dexamethasone (VRd) plus zoledronic acid. While initial chemotherapeutic treatment of our patient was the same as that of the patient reported by Cyriac and Narayan, as mentioned previously, our patient was not on this regimen at the time of his bone healing and in fact progressed despite that regimen. Our patient also did not receive bisphosphonates, having declined their use due to potential side effects.

Radiotherapy in our patient is a very plausible contributor to bone healing. In the setting of multiple myeloma RT yields 85% to 97.7% success in decreasing pain and improving function [26-28].Radiotherapy also reduces the rates of SREs in patients with untreated impending pathologic fracture and those treated with prophylactic stabilization, and it is superior to bisphosphonate therapy in preventing SREs [29]. RT has been classically thought to negatively affect bone marrow function and bone healing, and higher doses have been avoided particularly when stem cell transplant is a future consideration [30]. However, a retrospective study from Matuschek et al demonstrated recalcification of 48% of lesions following radiotherapy, with 23% showing complete recalcification and 25% showing partial calcification [27]. In addition, higher total doses of radiation (2 Gy equivalents, from 20 to 30 Gy total dose) were associated with increased likelihood of recalcification [27]. Similar results were previously reported by Stolting et al, with recalcification rates of 44.7% and greater likelihood of calcification seen with higher doses of radiation (40 - <50 Gy) [28].This is relevant in the case we present, as our patient underwent radiotherapy to his femur 10 weeks following initial ORIF and achieved almost immediate functional improvement, although the total dose was at the lower end of the range generally used (24 Gy), and the patient was also started on daratumumab at approximately the same time.

Based on this case, consideration has to be given to daratumumab for its potential positive effect on bone remodeling in multiple myeloma. Early reports do suggest some potential for positive effects on bone healing. Work by Terpos et al in patients with relapsed or refractory multiple myeloma has shown that treatment with daratumumab increases markers of bone formation, including osteocalcin (18.4%), bone specific alkaline phosphatase (92.6%), and procollagen type-I N-pro-peptide (10.2%) [31,32]. Furthermore, significant decreases were seen in levels of markers of osteoblast inhibition, including dickkopf-1(17.5%) and C-C motif ligand-3 (16.0%) [31,32]. Although documentation of bone healing with daratumumab is sparse, Divekar et al recently described a case of relapsed multiple myeloma treated with a regimen containing both daratumumab and bortezomib [33]. In that case, prophylactic stabilization initially planned for a femoral head lesion with a Mirels score of 10 was able to be avoided, with post-treatment Mirels score decreased to 8 due to complete pain resolution [33]. The potential benefits of daratumumab are especially relevant for the patient we present here, as he was transitioned to a daratumumab based chemotherapy regimen following pathologic fracture of his femoral lesion and then maintained on daratumumab maintenance therapy until the time at which healing of the lesion was discovered. Much like the case presented by Divekar et al, while on this regimen, he demonstrated remarkable healing of what was previously a very aggressive, progressively destructive lesion, and therefore was able to avoid further radical surgical intervention with proximal femoral resection and megaprosthesis.

Conclusion

Recent advancements in chemotherapy and radiotherapy have led to improved lesional healing. Several studies and case reports have demonstrated some degree of lesion healing with bortezomib based chemotherapy regimens, with or without bisphosphonates, as well as recalcification following radiotherapy. Early studies also show promise for bone healing with daratumumab based chemotherapy regimens, with the potential for a substantial degree of healing that allows for avoidance of surgical intervention. The information in this case is presented to raise awareness of dramatic healing through radiotherapy and medical management without radical surgery, and to encourage further research into the effects of daratumumab based chemotherapy regimens on lesion healing, as these regimens may allow for a greater degree of healing than previously studied regimens. Finally, this case highlights the importance of multidisciplinary collaboration in the management of multiple myeloma bone disease.

Acknowledgements

This research was supported by funding from the SUNY Upstate Medical University Department of Orthopedic Surgery and William Smyth Cancer Fund.

Author Contributions

Timothy A. Damron, Matthew Sullivan, and Michael Sun

participated in the study design.
Sarah Papa and Timothy A. Damron participated in data collection.
Sarah Papa and Timothy A. Damron participated in analysis and interpretation.
Sarah Papa and Timothy A. Damron participated in writing this article.
Timothy A. Damron participated in critical revision of this article.

Conflict of Interest

The authors declare that they do not have any personal or financial conflicts of interest.

Abbreviations

(ACVDL) Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone, and Lenalidomide, (AP) Anterior-Posterior, (BCMA) B Cell Maturation Antigen, (CAR) Chimeric Antigen Receptor, (cGy) Centigray, (CRAB) hypercalcemia, renal failure, anemia, lytic bone lesions, (CTA) Computed Tomography Angiography, (CT) Computed Tomography , (CVD) Cyclophosphamide, Bortezomib, and Dexamethasone, (Dara Rd) Daratumumab-Lenalidomide-Dexamethasone, (ED) Emergency Department, (Gy) Gray, (KPD) carfilzomib-pomalidomide-dexamethasone, (MDE) Myeloma Defining Event, (melphalan-VTD-PACE). Melphalan, Bortezomib, Thalidomide, Dexamethasone, Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide, (MRI) Magnetic Resonance Imaging (ORIF) Open Reduction Internal Fixation, (RT) Radiotherapy, (SRE) Skeletal Related Event, (TLSO) Thoracic-Lumbar-Sacral Orthosis, (VRd) Bortezomib-Lenalidomide-Dexamethasone.

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