Case Reports in Oncology

Case Rep Oncol 2024;17:423–429
DOI: 10.1159/000536675
Received: January 8, 2024
Accepted: January 31, 2024
Published online: March 5, 2024

Case Report

Isolated Non-Secretory Extramedullary Relapse of Multiple Myeloma Responded Completely to Localized Radiotherapy

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Keywords
Multiple myeloma · Relapse · Plasmacytoma · Extramedullary

Abstract
Introduction: Non-secretory multiple myeloma (NSMM) is a rare form of multiple myeloma (MM) that is often difficult to detect and has not yet been well characterized. This is due to the lack of production or the presence of monoclonal protein (MP) levels below levels detectable by testing such as serum/urine electrophoresis and immunofixation. ***Case Presentation:*** Two patients of ours were being treated for MM with typical courses of systemic therapy. By the third-line therapy, both developed an extramedullary mass, one in the pelvis and the other in the neck. In both cases, blood work showed no measurable MP, normal free light chain levels, and unremarkable skeletal surveys. Secondary malignancies were suspected due to the clinical presentation in each case, and biopsies confirmed the presence of non-secretory plasmacytomas. Both patients were only treated with localized radiotherapy with a total dose of 2,000 cGy in 5 fractions over 1 week. Ultimately, this resolved the original masses with no residual tumors. No changes had to be made to their systemic therapies, and both patients remained stable. ***Conclusion:*** NSMM relapse is not unusual and should be suspected in patients with relapsed refractory disease. Relapse should be confirmed by a tissue biopsy, and secondary malignancies should be ruled out. Radiotherapy is an excellent option to treat localized relapse and preserve the current line of systemic anti-myeloma therapy.

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Introduction

Multiple myeloma (MM) is a chronic hematological malignancy, due to abnormal proliferation of abnormal monoclonal plasma cells, and has a characterized relapsing-remitting course. Clinical manifestations include CRAB symptoms: hypercalcemia, renal insufficiency, anemia, and bone lesions. Plasmacytoma is a less common presentation occurring in 7% of cases [1]. Typically, MM cells produce large quantities of a single aberrant immunoglobulin protein, which is detected through serum/urine electrophoresis and immunofixation of immunoglobulins (usually IgG, IgA, IgM), or free light chains (FLCs) kappa or lambda [2]. These represent 54%, 21%, and 16% of MM cases, respectively. Another 3–5% of MM cases exhibit undetectable levels of monoclonal protein (MP) production, known as non-secretory multiple myeloma (NSMM). This is often due to erroneous Ig synthesis or secretion (85%) or the lack of Ig production altogether (15%) [3]. Patients with suspected NSMM should have bone marrow examination with intracellular immunoglobulin staining and work-up for end-organ damage by blood work and imaging, such as PET/CT or MRI [4]. Due to its low incidence, factors contributing to NSMM as well as its potential treatments are not well established. The following case provides insight on the potential value of radiotherapy to address localized relapse of plasmacytoma.

Case Presentation

An 88-year-old woman was diagnosed with IgG lambda MM in April 2019. Her past medical history included type 2 diabetes, hyperlipidemia, hypertension, and osteopenia, and she had a history of smoking (16 years). She presented with pathological tibial and humeral fractures. Imaging showed a permeative lytic lesion in the left tibia coupled with cortical disruption (Fig. 1a). It also showed a displaced left humeral fracture (Fig. 1b) along with multiple lytic lesions and compression fractures in the spine. Work-up showed mild macrocytic anemia (Hb 109 g/L, mean corpuscular volume 106 femtoliters), renal insufficiency (creatinine clearance 39 mL/min), and markedly elevated erythrocyte sedimentation rate, 105 mm/h. MP level was 63.5 g/L, IgG lambda was present, FLC lambda was 2,396 mg/L (normal range 3.30–19.40 mg/L), undetectable FLC kappa (normal range 3.30–19.40 mg/L), non-elevated calcium levels. Bone marrow examination showed 40% neoplastic plasma cells in the bone marrow (Fig. 2a), positive for CD138 (Fig. 2b), CD 45/38/81/56, with lambda light chain restriction (Fig. 2c) and negative for CD 20/19/79b/PAX-5. She had R-ISS stage II. FISH was negative for translocation *t*(4;14), and no mutations in p53 or 17p deletion were found. Her previous therapy is shown in Figure 3. In May 2023, she was getting third-line therapy with pomalidomide, cyclophosphamide, dexamethasone (PCd). She was overall in good health, tolerating anti-myeloma therapy well.

During her routine clinical visit prior to cycle 20 of PCd, she presented with an asymptomatic mass in her left neck that was round, flexible, 7 cm in diameter, with a rubbery consistence, and was more consistent with lymphadenopathy. At that time, myeloma work-up showed no measurable MP, and normal FLC and repeated skeletal surveys were unremarkable. Secondary malignancy (SM), lymphoma based on clinical presentation, was suspected, and the patient had a diagnostic core biopsy. It showed, however, features compatible with plasma cell neoplasm. Microscopic examination showed atypical plasmacytoid cells, involving soft tissue (Fig. 4a). Immunohistochemical stains showed positivity for CD138 (Fig. 4b), CD 45/38/81/56, and FLC lambda restriction (Fig. 4c). Cells were negative for CD 20/19/79 and EBV. KI-67 stained approximately 90% of the cells. Serum

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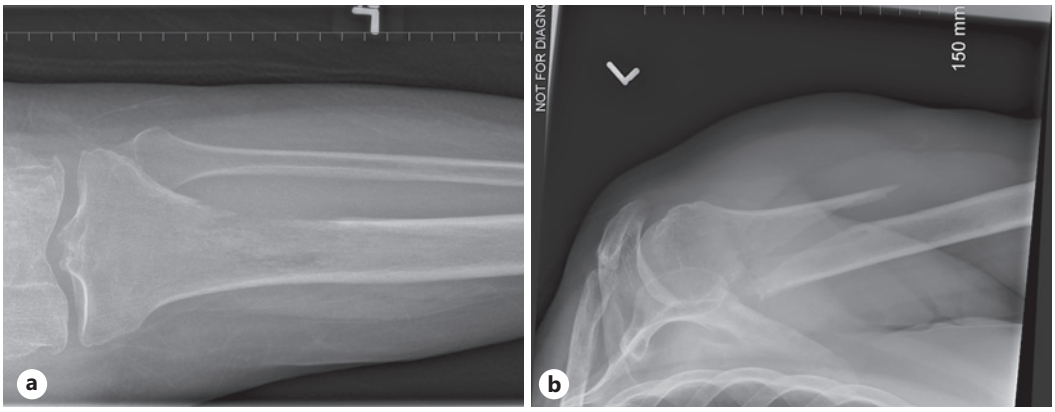

Fig. 1. a Pathological tibial fracture due to a permeative lytic lesion coupled with cortical disruption. **b** Displaced left humeral fracture.

electrophoresis was normal with no MP detectable, and FLC kappa and lambda were 18.8 and 26.0 mg/L, respectively. Repeated skeletal surveys were unremarkable. Thus, the localized relapse was non-secretory, consistent with extramedullary plasmacytoma. She declined PET. She was treated with localized palliative radiotherapy to the left neck for a total dose of 2,000 cGy in 5 fractions over 1 week and continued on PCd. Upon examination in August 2023, the mass had completely resolved with no evidence of residual tumor. Four months post-radiation, she remains in complete biochemical and clinical remission, continued on the same line of therapy. Unfortunately, the patient progressed 6 months after, with re-appearance of MP.

Recently, we had another patient with relapsed refractory myeloma who presented with localized non-secretory relapse as a pelvic plasmacytoma that was confirmed to be plasma cell neoplasm on biopsy. PET scans showed no other sites of disease. This patient was also on third-line therapy with isatuximab/carfilzomib/dexamethasone. Since the relapse was isolated plasmacytoma, it was treated with localized radiotherapy, similar to the patient described above. After a total dose of 2,000 cGy in 5 fractions over 1 week, the tumor resolved completely. There was no detectable MP or increase in FLCs during the time of relapse. The patient continued the same line of anti-myeloma therapy and remained in clinical and biochemical remission for 3 months.

Discussion

Most patients with MM respond to front-line therapy. However, relapse is ultimately inevitable. There is growing evidence that tumor progression, dissemination, and relapse in MM are driven by clonal evolution. It is a process of natural selection facilitating tumor plasticity and the ability to adapt to the environment, thus leading to formation of genetically complex and heterogeneous tumors [5]. One study found that the bone marrow specimens within 6 months preceding secondary extramedullary disease (EMD) diagnosis exhibited new structural variants in 40% of patients. These chromosomal abnormalities included a 1q duplication, 17p deletion, and MYC disruption at 23%, 16%, and 8% frequencies, respectively. They also found several predictive factors for the emergence of secondary EMD including a lower median age, a higher prevalence of 1q gain/amplification and *t*(4;14) mutations, and elevated lactate dehydrogenase levels on the date of diagnosis for MM [6].

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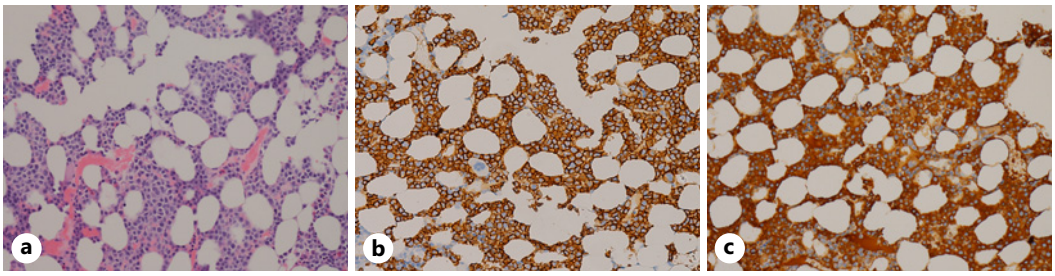

Fig. 2. **a** Bone marrow infiltration by neoplastic plasma cells. Hematoxylin and eosin staining. Objective ×60. **b** Plasma cells expressing bright cytoplasmic CD138 expression. **c** Lambda light chain restriction. Objective ×40.

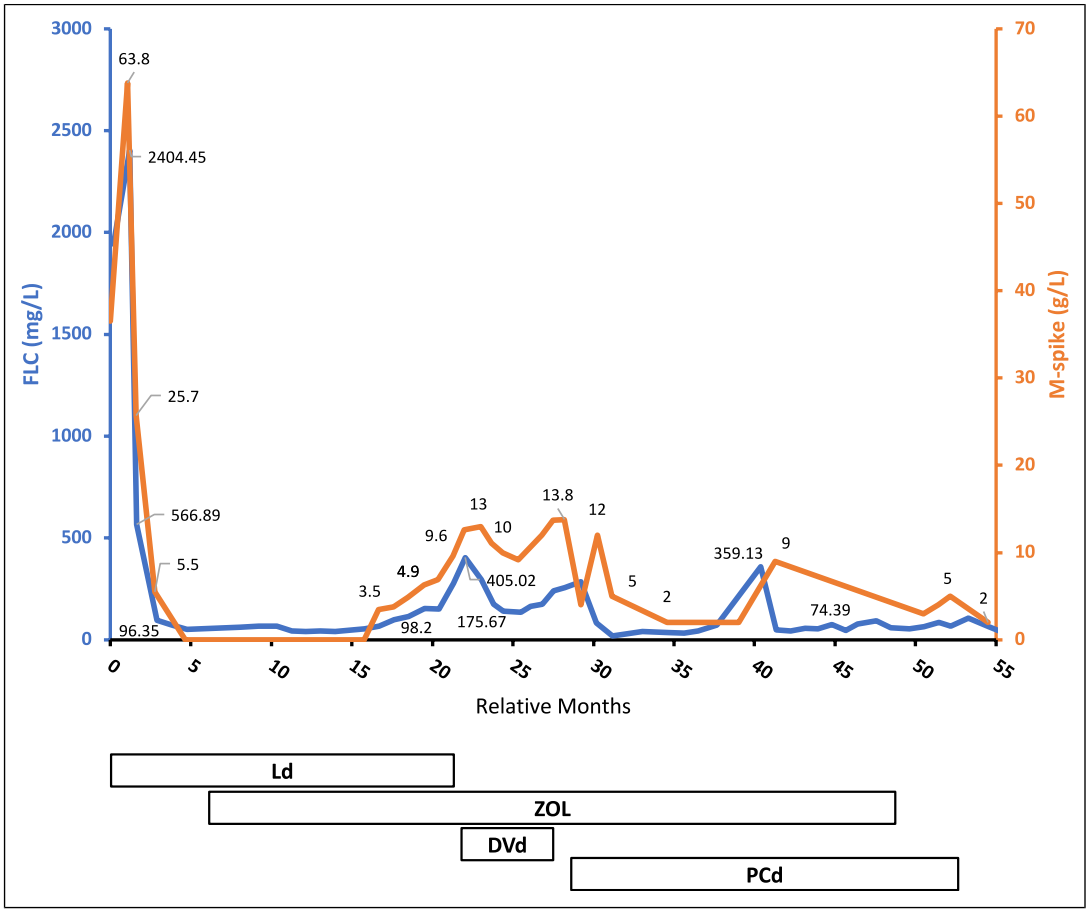

Fig. 3. Time course of anti-myeloma therapies. Ld, lenalidomide/dexamethasone; ZOL; zoledronic acid; DVd, daratumumab/bortezomib/dexamethasone; PCd, pomalidomide/cyclophosphamide/dexamethasone.

MM may relapse with the same tumor markers as initial presentation, FLC escape, or rarely as oligo-secretory or non-secretory relapse. Oligo-secretory disease is more frequent in relapsed MM, compared to newly diagnosed MM, reaching 10% of the patients with relapsed MM. In more advanced relapses, the frequency is increased up to 20% in the 3rd or 4th relapses. In this setting, oligo-secretory plasmacytoma is more frequent, reported at

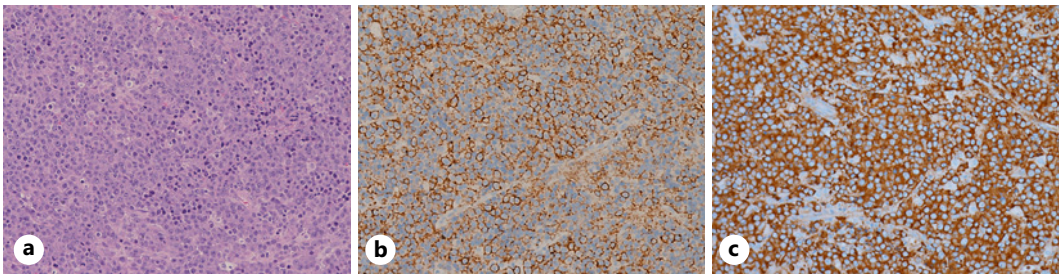

Fig. 4. **a** Atypical plasmacytoid cells, involving soft tissue. Hematoxylin and eosin staining. Objective ×60. **b** Plasma cells expressing bright cytoplasmic CD138 expression. Objective ×60. **c** Plasmacytoma cell showing lambda light chain restriction. Objective ×40.

53% [7]. In addition, the incidence of extramedullary relapse increases in relapsed myeloma. EMD represents between 3.4% and 14% of relapsed MM cases and has a poor prognosis. This often results from a growth of clonal PCs that spreads from a cortical bone disruption, one that has been hematogenously spread or due to an invasive procedure [8]. Further, EMD relapse risk has been shown to increase with an advanced stage of therapy (>2 lines) and increased duration of treatment (≥6 months) [9]. Similar to the published data, this was the case with our patient.

In concordance with previous studies, both of our patients experienced a relapse while on third-line therapy and late into the course of the disease. Both patients had non-secretory plasmacytoma, and investigation was driven by patient symptoms and physical exam findings. In our first patient, clinical presentation was more consistent with lymphoma, rather than myeloma. This emphasizes the importance of history and clinical examination, even in the era of advanced laboratory and molecular investigations. Clinicians treating patients with MM should be aware of the unusual manifestations of relapse and have a low threshold for initiating more detailed investigations, such as CT and PET scans and diagnostic biopsies if relapse is suspected. In the absence of any laboratory tests during therapy and follow-up, new cross-sectional imaging modalities such as PET-CT represent useful tools in clinical practice for disease monitoring, at least in that fraction of patients with detectable lesions at the onset. In the absence of radiologically detectable lesions, serial bone marrow examinations for quantification of neoplastic plasma cell infiltration remain the only way for disease monitoring [10]. Unfortunately, non-secretory relapse is not well characterized or understood, likely due to the rarity of this phenomenon. One study found that only 2.4% patients who experienced relapses following MM exhibited a non-secretory relapse [7]. At present, it appears there are no features unique to NSMM relapse.

A suspected relapse should be confirmed by a biopsy. Other lymphoproliferative disorders, such as marginal zone lymphoma, may occur. In elderly patients treated with multiple chemotherapy regimens with immunosuppressive potential, plasmablastic lymphoma and EBV-induced malignancies need to be ruled out. The plasmacytoma could have also arisen independently as a second primary malignancy. Thus, the tissue diagnosis is important in order to rule out SM which is often associated with advanced MM. It is not unusual, since the prognosis of patients with MM has improved over the last couple of decades. With increased survival, continuous anti-myeloma therapy, and secondary immunodeficiency, the incidence of SMs is increasing. SMs currently affect 5–7% of MM patients [11]. Also, alkylating agents (melphalan) and immunomodulators (lenalidomide) used for maintenance therapy may contribute to the emergence of the extramedullary plasmacytoma among other factors [11].

Conclusion

NSMM relapse should be suspected in patients with relapsed refractory disease. It usually happens late in the course of the disease and is associated with clonal evolution and escape from anti-myeloma therapy. Relapse should be confirmed by a tissue biopsy, and SMs should be ruled out. Radiotherapy is an excellent option to treat localized relapse and preserve the current line of systemic anti-myeloma therapy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536675).

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This case report does not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The completed consent form is available to the editor if requested.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no research support for this study.

Author Contributions

D.D., S.K., and R.K. wrote and reviewed the manuscript. All authors approved the final version to be published and agreed to act as guarantors of the work.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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