



CASE REPORT

A rare case of bifocal, extramedullary and hyposecretory relapse of multiple myeloma

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Abstract

We present a rare extramedullary, bifocal, and hyposecretory manifestation of relapsed MM that could be mistaken for an infection. We stress the importance of complex evaluation including serum, urine, and bone marrow assessment and whole-body imaging.

KEYWORDS

extramedullary, hyposecretory, imaging, multiple myeloma

1. **What is the new aspect of your work?** A very rare manifestation of multiple myeloma relapse, being all extramedullary, bifocal, and hyposecretory. Moreover, the activity of the disease did not behave as myeloma but rather as a different (infectious) condition.
2. **What is the central finding of your work?** We stress the importance of comprehensive examination including modern diagnostic tools to elucidate the diagnosis that goes behind routine criteria.
3. **What is (or could be) the specific clinical relevance of your work?** The key clinical points are following: Multiple myeloma manifestation can be really atypical and can be mistaken for a different condition. The approach to suspected relapse of multiple myeloma should not rely solely on routine monitoring but it should include complex

assessment including serum and urine tests, bone marrow assessment, and whole-body imaging. Extramedullary myeloma needs to be looked for using appropriate imaging techniques.

1 | INTRODUCTION

With prolonged survival of multiple myeloma (MM) patients due to the introduction of novel drugs, we encounter uncommon manifestations of the relapses. As the disease evolves, it becomes more aggressive, including secondary plasma cell leukemia, extramedullary plasmacytoma (EM), or central nervous system involvement. The latter relapses are often with lower M-protein, some patients might have

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TABLE 1 Patient characteristics and treatment outcomes

| Demographics | Male, 69 years |
|--------------------------|---|
| Diagnosis | MM IgA kappa, Durie-Salmon IIIA, ISS 2 |
| M-protein quantity | 40.6 g/L |
| Serum free light chains: | |
| Kappa | 237.15 mg/L |
| Lambda | 1.66 mg/L |
| Kappa/lambda ratio | 142.862 |
| Bone marrow involvement | 80% clonal plasma cells |
| Therapy | 9 cycles VMP (bortezomib, melphalan, and prednisone) |
| Best response | partial remission |
| M-protein quantity | 12 g/L |
| Serum free light chains | |
| Kappa | 77.91 mg/l |
| Lambda | 1.35 mg/L |
| kappa/lambda ratio | 57.756 mg/L |
| Time to progression | 16 months |
| Relapse #1 | |
| M-protein quantity | 20.72 g/L |
| Serum free light chains: | |
| Kappa | 94.98 mg/L |
| Lambda | 1.41 mg/L |
| Kappa/lambda ratio | 67.362 |
| Therapy | 28 cycles IRD (ixazomib, lenalidomide, and dexamethasone) |
| Best response | complete remission |
| M-protein quantity | 0 g/L (with negative immunofixation) |
| Serum free light chains | |
| Kappa | 15.22 mg/l |
| Lambda | 12.05 mg/L |
| Kappa/lambda ratio | 1.263 mg/L |
| Time to progression | 30 months |
| Relapse #2 | |
| M-protein quantity | 0 g/L (positive immunofixation)* |
| Serum free light chains | |
| Kappa | 44.93 mg/L |
| Lambda | 8.41 mg/L |
| Kappa/lambda ratio | 5.28 |

(Continues)

TABLE 1 (Continued)

| Demographics | Male, 69 years |
|-------------------------|---|
| Therapy | DVD (daratumumab, bortezomib, and dexamethasone), in course |
| Best response | complete remission |
| M-protein quantity | 0 g/L (with negative immunofixation) |
| Serum free light chains | |
| Kappa | 2.90 mg/l |
| Lambda | 1.01 mg/L |
| Kappa/lambda ratio | 2.87 mg/L |
| Time to progression | N/A at follow-up 18 months |

*Variable presence of small peak IgG kappa 0–1.27 g/L - probably due to monoclonal antibody therapy (daratumumab). Original M-protein (IgA kappa) was not detected.

“light-chain escape” or even become non-secretory. We present an unusual manifestation of a bifocal, hyposecretory, and extramedullary relapse of MM that was revealed due to thorough examination including the use of modern imaging techniques.

2 | CASE REPORT

A 69-year-old man was diagnosed with MM based on usual complaints (lower back pain with lytic bone involvement of the spine). The initial diagnosis was IgA kappa MM, stage IIIA (Durie-Salmon), ISS 2 (International Staging System), with hyperdiploidy (trisomy of chromosome 15) and t(4;14). The patient characteristics and therapy outcomes are in Table 1. Due to co-morbidities, he was transplant ineligible and started induction treatment with VMP regimen (bortezomib, melphalan, and prednisone). After 9 cycles, he reached partial remission (PR) with stable levels of M-protein (12 g/L) and was followed without therapy. 16 months after the diagnosis, he relapsed and started therapy with IRD regimen (ixazomib, lenalidomide, and dexamethasone). The therapy induced complete response.

Two years later, we noticed slight elevation of involved free light chain (FLC) kappa (up to 72.58 mg/L without clear dynamics, K/L up to 9.03) with inconstant presence of positive immunofixation, without measurable M-protein (Table 2). The patient was asymptomatic; therefore, we continued IRD treatment with careful observation as the results did not fulfill the IMWG (International Myeloma Working Group) criteria for progression.¹

Four months later, the patient had oral complaints (difficulty in biting) with a lesion on the upper left gum. As the

TABLE 2 Behavior of myeloma-specific parameters before and after the diagnosis of extramedullary relapse

| | Time before confirmed extramedullary progression of multiple myeloma | | | | | | | Time from treatment initiation | | | | |
|-------------------|--|----------|----------|----------|----------|----------|-----------------|--------------------------------|-----------|-----------|-----------|-----------|
| | 12 months | 6 months | 3 months | 2 months | 1 month | 0 months | Confirmed EM | 0 months | 1 month | 3 months | 6 months | 12 months |
| M-protein (g/L) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Immunofixation | Positive | Negative | Positive | Positive | Positive | Negative | Positive | Negative | Negative* | Negative* | Negative* | Negative* |
| FLC kappa (mg/L) | 13.23 | 15.22 | 21.16 | 72.58 | 23.73 | 35.60 | 44.43 | 77.32 | 4.21 | 9.23 | 3.22 | 2.90 |
| FLC lambda (mg/L) | 11.91 | 12.05 | 8.54 | 8.04 | 9.31 | 11.28 | 8.41 | 8.95 | 2.53 | 2.11 | 2.58 | 1.01 |
| K/L | 1.11 | 1.26 | 2.48 | 9.03 | 2.55 | 3.16 | 5.28 | 8.639 | 1.664 | 4.37 | 1.248 | 2.87 |
| UPEP (mg/24h) | — | — | — | — | — | — | Negative | — | — | — | — | — |

Abbreviations: EM, extramedullary myeloma; FLC, serum free light chains; UPEP, urine protein immunoelectrophoresis.

*small peak of IgG kappa (0–1.27 g/L) was detected, probably due to monoclonal antibody therapy (daratumumab). Original M-protein (IgA kappa) was not detected.

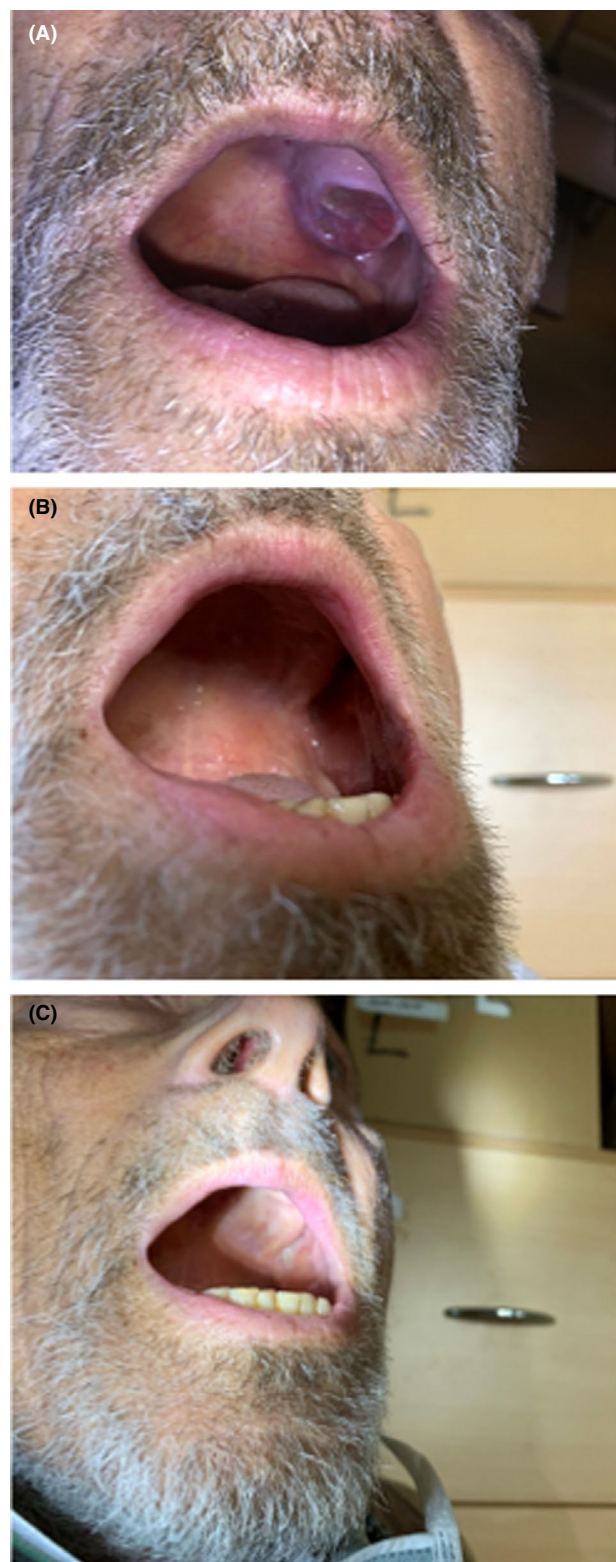


FIGURE 1 The lesion of left maxillary alveolus due to extramedullary progression of myeloma (A) initial finding; (B) and (C) improvement after 6 months of therapy

jaw was edentulous and there was a suspicion on a pressure damage from non-fitting dental prosthesis, the dentists started conservative therapy. However, the cultivation from

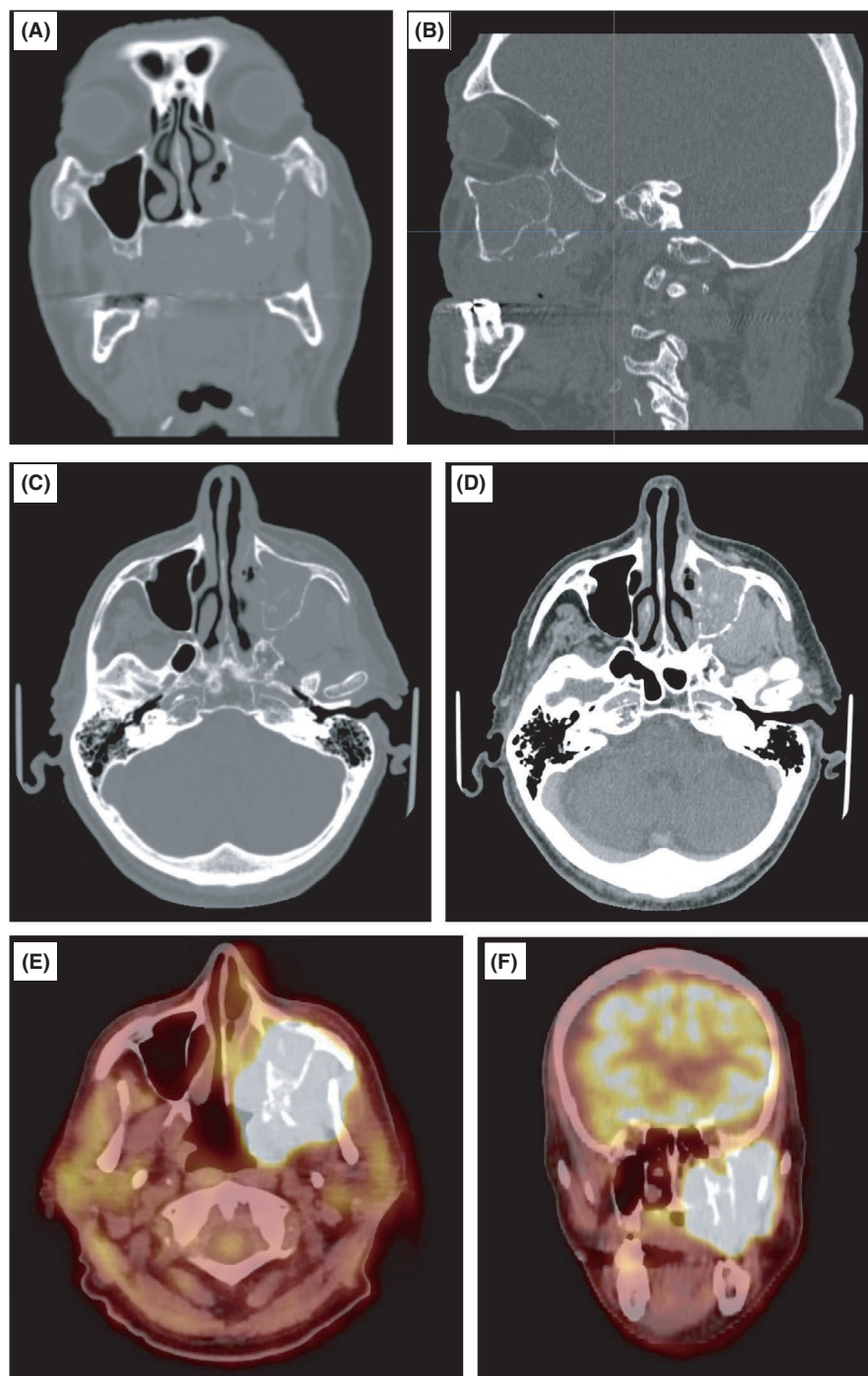


FIGURE 2 CT scan of a focal lesion of the left Highmore sinus. (A) coronary 2D reconstruction (B) sagittal 2D reconstruction (C) transversal scan (D) transversal scan aimed at soft tissues (E) PET/CT fusion transversal scan (F) PET/CT fusion coronary scan. Description: Paranasal sinuses are physiological except of left maxillary sinus. Significant tumorous infiltration of the skeletal wall of the left maxillary sinus, with a character of permeative osteolysis and destruction continuing to the alveolar part of the jaw. The cavity is completely filled with pathological content. Soft tissue masses cross the wall of the sinus to the infratemporal cavity and infiltrate fat tissue as well as pterygoid muscles. The infiltration continues through the alveolar protrusion into the hard palate and mouth cavity—locally infiltrating both buccal region and left part of the nasal cavity. The overall size is 55x50x35mm. In the center of maxillary cavity, there are smooth calcifications that might correspond to mycotic infection. The PET/CT scans show significant activity (standardized uptake value—SUV 36)

oral mucosa showed a presence of mucor, and laboratory testing revealed elevation of C-reactive protein (122.1 mg/L). The lesion was enlarged and painful (Figure 1A). Therefore, the patient was hospitalized with initiation of intravenous antimycotic therapy (amphotericin B lipid complex).

We performed CT scan that described a destruction of bone structures of the left maxillary sinus with soft tissue infiltration (Figure 2). The finding was suspicious of MM relapse with possible mycotic involvement in the center of the cavity. However, myeloma-specific parameters were as follows: M-protein 0 g/L with negative immunofixation, FLC

kappa 35.6 mg/L, lambda 11.28 mg/L, K/L 3.16, urine immunofixation negative (Table 2). Bone marrow aspiration did not find any clonal plasma cells.

Therefore, surgery was performed that removed most of the pathological masses. Histology of the bioptical sample confirmed infiltration by myeloma cells (Figure 3). Neither histology nor microbiology found fungal involvement. The reason might be due to only accidental finding or possibly due to initial course of anti-fungal therapy. There were no other signs of invasive mycosis, including repeatedly negative fungal cultures and galactomannan

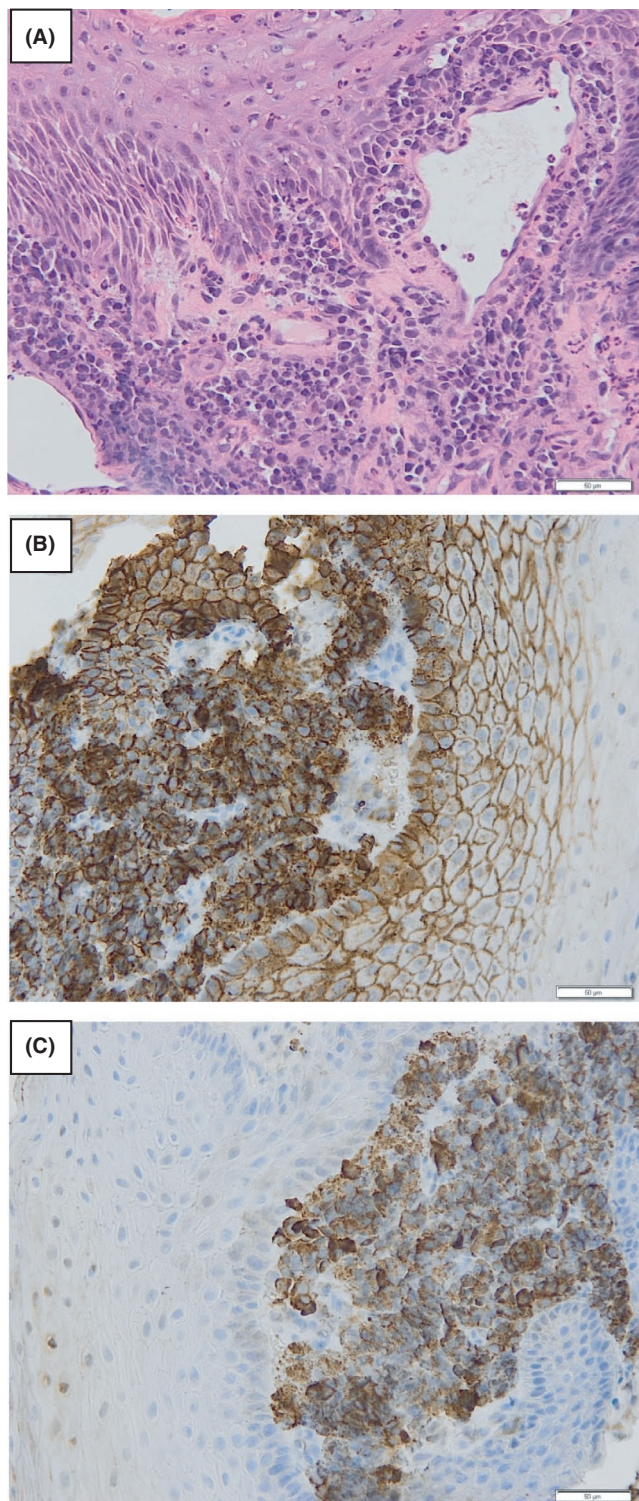


FIGURE 3 Histopathology of the focal lesion in Highmore sinus. (A) Hematoxylin-eosin stain, revealing plasma cell infiltration within the sinus epithelium. (B) CD138 stain, (C) Kappa positive stain (embedded by kappa negative epithelial cells)

assay. We performed PET/CT scan that described two focal lesions—one in the left maxillary sinus (standardized uptake values—SUV 36) and a second one in a soft tissue lesion behind the left kidney (SUV 37). The patient started

third-line therapy with DVD regimen (daratumumab, bortezomib, and dexamethasone) and palliative focal radiation. The myeloma-specific parameters during the therapy are summarized in Table 2. At present (18 months later), the patient is in remission with negative immunofixation and normal levels of FLC. The focal lesion of the left maxillary alveolus resolved completely (Figure 1B,C). Control PET/CT 6 months later confirmed complete regression of the lesion behind the left kidney, and significant regression of the lesion in the left maxillary sinus (SUV decrease: 36–2.2). The patient improved overall condition with no further complications.

3 | DISCUSSION

Our paper shows an example of a phenotypic clonal evolution of MM that presented as a complex of rare manifestations of the disease. At relapse, the disease became oligosecretory, extramedullary, and bifocal. Moreover, the manifestation was overshadowed by infectious symptoms with suspicion on invasive mycotic involvement.

The incidence of all these manifestations in one patient is uncommon. Up to 10% of MM patients undergo “light chain escape.” In most of them, the absolute increase of involved FLC is >100 mg/L, which is the recommended level for defining a relapse that requires treatment.² Only a few patients (1%–5%) are oligosecretory with very low levels of FLC or even non-secretory. Most of such patients, however, have significant bone marrow involvement by clonal plasma cells.

EM is a unique entity occurring in 6%–20% of patients in the course of MM.³ Both primary (at the time of MM diagnosis) and secondary EM (at MM relapse) can occur as bone-related or soft tissue-related usually in parenchymal organs or skin. With the introduction of more sensitive imaging methods (CT, magnetic resonance, PET/CT), the evidence of extramedullary involvement has become more frequent. Also, prolonged survival of MM patients due to novel drugs (such as immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies) has led to higher frequency of rare manifestations. There is, however, no direct connection between the therapy of any of these drugs and evolution of EM. Patients with EM are reckoned to be “high-risk” with poor prognosis and limited therapeutic response to both conventional chemotherapy as well as novel agents. Similar approaches as in the high-risk MM are recommended, with radiotherapy to improve disease control.⁴

Approximately 3%–5% of MM have bone marrow plasma cell infiltration $<10\%$. The reason might be due to inadequate tissue sampling, only a few of these are multiple plasmacytomas or lesions without generalized bone marrow

involvement. For such patients, repeated examination is needed or an image-guided biopsy of a bony or extramedullary lesion.⁵

We underline the importance of whole-body imaging. In our case, it revealed two distinct active EM despite no direct signs of systemic MM relapse. The diagnostics were quite fast due to the signs of MM instability (alternating positivity of immunofixation and slight elevation of iFLC). Nevertheless, the definitive diagnosis of relapse relied on histological verification of the extramedullary mass rather than on IMWG criteria. On the other hand, continuous measurement of FLC (despite low levels) was a contributive auxiliary tool for the disease assessment (Table 2).

We conclude that the biology and behavior of MM can be very heterogeneous. With the introduction of novel drugs, the patients live longer and may relapse with more uncommon manifestations. IMWG criteria should be always used as the gold standard but the biology may go beyond the criteria. Both clinical experience and routine examination are needed to set up a correct diagnostic approach. Modern diagnostic tools including imaging techniques as well as laboratory assessment are helpful and should be used appropriately also in patients with advanced disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JM wrote the paper. JM, TS, PK, TP, and JB treated the patient. JH and EB provided imaging techniques. JP provided biochemical panel and special tests. All co-authors critically reviewed and approved the paper.

ETHICAL STATEMENT

The patient provided informed consent with publication, and the paper was approved by the Ethical committee of the University Hospital Olomouc.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. Other relevant data are available from the corresponding author upon reasonable request.

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