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Case Report

Relapsed IgA Multiple Myeloma as Testicular Plasmacytoma after Quadrable Novel Therapy and Autologous Stem Cell Transplant: A Rare Case Report and Literature Review

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Keywords
Multiple myeloma · Testicular neoplasms · Plasma cells

Abstract
Introduction: Multiple myeloma (MM) is a clonal neoplasm of plasma cells that may manifest as an extramedullary disease in rare cases. ***Case Report:*** In this case report, we present the rare occurrence of testicular relapse in a 39-year-old patient with IgA MM after 3 years of remission. We discuss the clinical course and management of this unusual presentation and provide a comprehensive literature review of testicular involvement by MM. ***Conclusion:*** Despite advances in MM treatment, relapse remains common, highlighting the importance of careful follow-up and timely detection of disease recurrence at atypical sites. This case highlights the need for further research to standardize the diagnosis and treatment of testicular MM.

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Introduction

Plasma cell (PC) diseases are clonal neoplasms of PCs that result in a spectrum of clinical conditions ranging from very early, asymptomatic states with minimal clonal expansion, monoclonal gammopathy of undetermined significance, to symptomatic disease states with associated end-organ damage (MM) [1]. In MM, extramedullary involvement (or extramedullary disease [EMD]) represents an aggressive form of MM characterized by the ability of a clone and/or subclone to thrive and grow independently of the bone marrow (BM) microenvironment [2]. The reported incidence of EMD varies considerably, and the differences in diagnostic approaches between studies likely contribute to this variability. In patients with newly diagnosed MM, the reported incidence ranges from 6% to 10% [3–5], while in relapsed or refractory MM, the reported incidence ranges from 3.4% to 14% [6].

Frontline treatment for MM consists of a combination of therapies, including immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and corticosteroids [7]. In addition, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is currently the standard of care after induction therapy [8]. There have been major breakthroughs in the field of MM treatment that have significantly improved the prognosis of patients. Despite these advances, the disease is still incurable, and relapses are common [9].

This case report describes a 39-year-old South Asian man with a history of MM who developed a rare testicular plasmacytoma 3 years after induction with novel therapy and ASCT. The rarity of this extramedullary manifestation and the subsequent management of this unusual case offer a valuable insight into our understanding of MM.

Case Report

A 39-year-old South Asian man presented in July 2020 with a 1-month history of back pain radiating to both thighs. Physical examination revealed lower thoracic spine tenderness and grade 3/5 lower limb weakness. Upon further evaluation, magnetic resonance imaging of the spine revealed evidence of lower thoracic spinal cord compression, so he underwent urgent posterior stabilization from T6 to L1 and decompression from T8 to T10, and he had a good neurological outcome. Further investigations, including serum protein electrophoresis and BM examination, revealed IgA MM. Unfortunately, cytogenetic analysis was not performed at diagnosis, and the patient was treated with daratumumab plus lenalidomide, bortezomib, and dexamethasone for six cycles. The treatment regimen was well tolerated, and he achieved complete remission. He then underwent ASCT as consolidation therapy for MM. The conditioning regimen was a melphalan-based regimen. He tolerated ASCT well and thereafter continued maintenance therapy with lenalidomide 10 mg daily for 21 days every 28 days. However, in August 2023 (almost 3 years after the MM diagnosis), during a routine physical examination, the patient reported a painless swelling of the left scrotum that had persisted for 2 months. A physical examination revealed an enlarged left testis measuring approximately 7 × 4 cm. Laboratory tests (Table 1), including complete blood count and renal function tests, were within normal limits. Serum protein electrophoresis showed a faint monoclonal band of free light-chain lambda (FLCL), while 24-h urine electrophoresis revealed an elevated FLCL level of 100 mg/24 h, serum free light-chain kappa of 16 mg/L, and FLCL of 191 mg/L with a kappa/lambda ratio of 0.08. Alpha-fetoprotein and beta-human chorionic gonadotropin were within normal limits.

An ultrasound examination of the testis showed an enlarged left testis with a maximum size of 7.2 × 3.9 cm. The testis had a heterogeneous tissue matrix, was predominantly hypoechoic, and had markedly increased vascularity (Fig. 1). In view of the concerned

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Table 1. Basic laboratory tests

Test	Result	Normal value
Hemoglobin	13.7 gm/dL	(13–17) gm/dL
WBCs	3.7 × 10^3/μL	(4–10) × 10^3/μL
Platelet	129 × 10^3/μL	(150–410) × 10^3/μL
Creatinine	80 μmol/L	(60–110) μmol/L
Calcium	2.27 mmol/L	(2.15–255) mmol/L
AFB	4 IU/mL	(0–6) IU/mL
B-hCG	Negative	<2 mIU/mL

WBCs, white blood cells; AFB, alpha-fetoprotein; B-hCG, beta-human chorionic gonadotropin.

ultrasound findings, a whole-body FDG positron emission tomography/computed tomography was performed. The results revealed heterogenous increased metabolic activity in the left testis, which was enlarged (Fig. 2). Histopathological examination of the testicular tissue (Fig. 3) showed infiltration of the testis with sheets of PCs (with plasmablastic morphology), which was positive for CD138 with aberrant expression of CD56 and showed lambda light-chain restriction.

The concurrent BM examination was negative for PC neoplasms with less than 1% polyclonal PCs. Based on the above findings, an MM relapse with testicular EMD was concluded. The patient received four cycles of the combination protocol: carfilzomib, daratumumab, and dexamethasone. Unfortunately, his myeloma was refractory, and he progressed with cutaneous nodules involving the scalp, trunk, and lower limbs. A new positron emission tomography scan revealed cutaneous infiltration, pathological retroperitoneal lymph nodes, and multiple new bony lesions, confirming disease progression.

Discussion

Multiple myeloma (MM) with testicular involvement is a remarkably rare event, with an incidence of 0.6–2.7% [10]. It was first described in the literature by Melicow et al. [11] in 1954. Subsequently, only 71 cases had been documented by 2008, as Wang et al. [12] noted in a review paper. Nevertheless, isolated testicular relapse after ASCT is even rarer. Wei et al. [13] reported only seven cases between 1998 and 2016. This rarity makes it difficult to study and conclude the clinicopathologic and prognostic data of testicular myeloma, as most information comes from single-case reports and small-case series.

Testicular EMD can occur synchronously with the primary MM diagnosis [14] or as an isolated testicular involvement in relapsed MM, as seen in our patient [15]. Ultrasound examination is often crucial for the diagnosis of MM [16], but a definitive diagnosis requires a tissue biopsy. To rule out other possible diagnoses, such as a germ cell tumor, an orchidectomy is usually performed.

Several studies have reported that MM with extramedullary plasmacytoma (EMP) has a poor prognosis [17]. Anghel and colleagues [18] reviewed the literature and found that the overall survival rate of patients with testicular plasmacytoma was poor. Most patients had a fatal outcome with progressive disease; some of them died very soon after diagnosis (9–36 days). The selection of appropriate treatments for testicular involvement in MM presents a unique challenge due to its extreme rarity and the presence of the blood-testicular barrier [19]. Surgical interventions such as radical orchiectomy can alleviate symptoms associated

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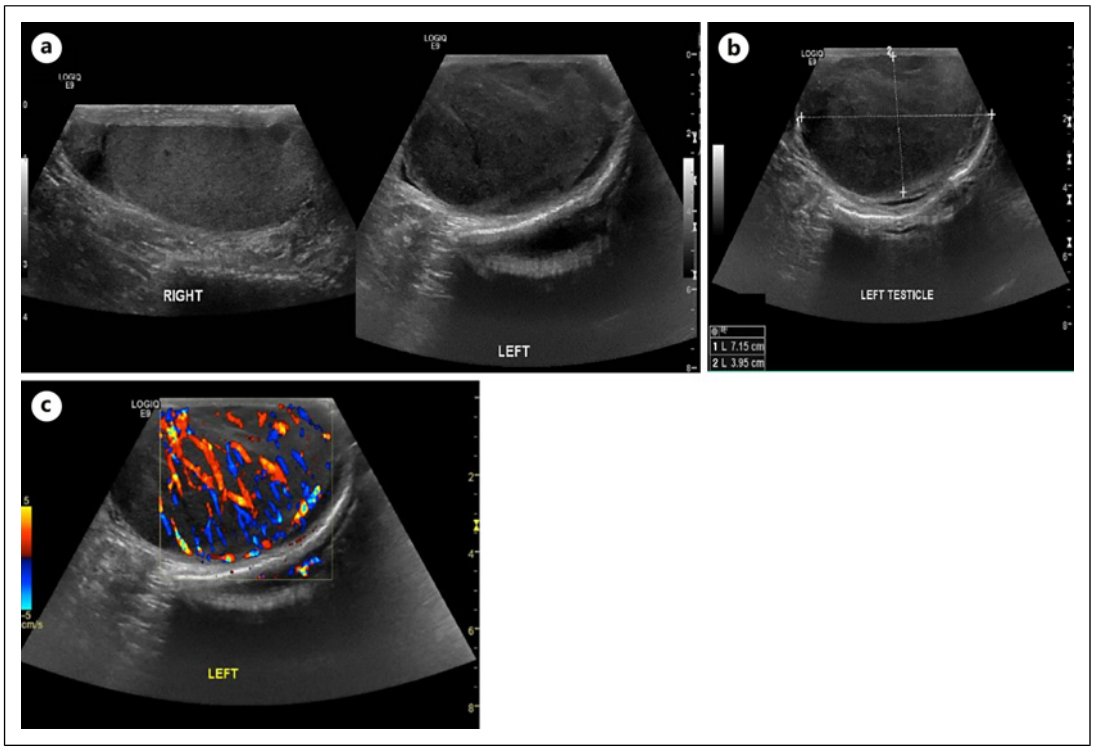

Fig. 1. a Ultrasound of the scrotum/left testis showing discrepancy in size and echogenicity of both testes with significantly enlarged left testis. The testis had a heterogeneous tissue matrix with predominantly hypoechoic with a maximum size of 7.2 × 3.9 cm (**b**) and had markedly increased vascularity on color Doppler study (**c**).

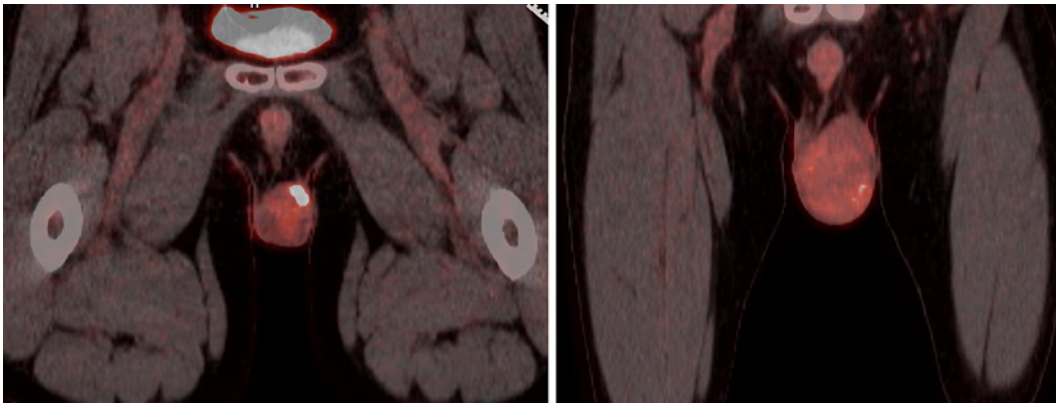

Fig. 2. ^{18}F FDG fused coronal FDG PET/CT images, which revealed heterogenous increased metabolic activity in enlarged left testis. PET, positron emission tomography; CT, computed tomography.

with testicular enlargement and are often performed to obtain tissue for histopathological analysis. However, systemic therapy is required to prolong the duration of remission [10]. Radiotherapy may have a synergistic effect with chemo-immune therapy when treating EMP.

Our patient with a history of IgA MM showed complete remission after initial treatment with daratumumab plus lenalidomide, bortezomib, and dexamethasone, followed by ASCT and lenalidomide maintenance. The subsequent development of testicular involvement raises

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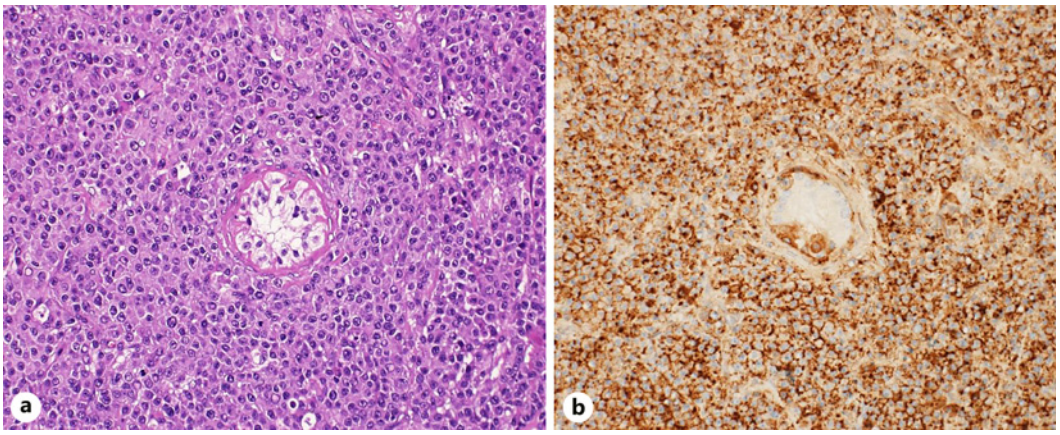

Fig. 3. Left testicular biopsy. H&E (×20): sheets of PCs with plasmablastic morphology (**a**). CD138 immunostain (×20), highlighted sheets of PCs (**b**).

the question of optimal treatment approaches for this unique relapse site. Our treatment approach for this patient consisted of carfilzomib-daratumumab induction therapy, followed by a second ASCT. Our patient underwent a diagnostic radical orchiectomy. We opted not to give radiotherapy as the benefit added to such a radical operation, together with systemic therapy, was not clearly evidence based.

Unfortunately, his myeloma was refractory to therapy, and he progressed with multiple new EMP. There is uncertainty about the treatment approach for patients who relapse with EMP after this quadrable combination. In addition, the data from MM with EMP treated with anti-BCMA T-cell engager and chimeric antigen receptor T cells are still limited, and extensive research is needed to expand our understanding of this condition [19–21]. The CARE Checklist has been completed by the authors for this case report, and it is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536512).

Conclusion

Testicular MM is a rare clinical entity; the literature on it is scarce and mainly made up of limited numbers of case studies. There is a wide variability in response to treatment, but generally, novel anti-myeloma agents have shown promising results. More studies are needed to standardize the diagnosis and treatment of this condition.

Statement of Ethics

This case was approved by the Hamad Medical Corporation's Medical Research Center, MRC 04-23-804. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

All authors contributed to manuscript conceptualization, drafting, or critical review for intellectual content, and approved the final version before submission. Mohammed Abdulgayom: writing manuscript, Dina Soliman: pathology findings reporting, Abbas Helmy and Athar Haroon: radiology findings reporting, Husam Telfah: details of histopathology, Rola Ghasoub and Hesham Elsabah: reviewing manuscript, Shehab Fareed: writing clinical details.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available on reasonable request from corresponding author.

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