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Case Report
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# Managing Extramedullary Disease in Multiple Myeloma: A Clinical Case Paradigm

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## Abstract

Extramedullary Disease (EMD) in Multiple Myeloma (MM) poses a unique clinical challenge, with uncommon manifestations beyond the bone marrow and a dismal prognosis. This rare disease variant can impact multiple anatomical areas, complicating therapeutic strategies. This case report explores a complex manifestation of multiple myeloma with extramedullary involvement, particularly affecting the head and neck region. Despite receiving radiation therapy and many lines of therapy, the disease continued to advance aggressively, resulting in the development of lumps in the neck and visible lesions on the chest wall. The disease showed resistance to daratumumab, indicating anti-CD38 refractory disease, a condition that is becoming more acknowledged in the field of myeloma management. The limited effectiveness of new immunotherapies in patients with advanced extramedullary disease reflects the clinical and biological diversity of this entity.

## Introduction

Multiple Myeloma (MM) is an incurable plasma cell neoplasm that is characterized by significant biological and clinical heterogeneity. The Overall Survival (OS) rate varies, spanning over ten years for patients with a standard-risk disease while decreasing significantly for individuals presenting high-risk characteristics [1]. The existing staging system, which utilizes basic biological markers to categorize patients into different risk groups, might occasionally be inadequate for identifying patients with a high risk of adverse outcomes [2]. This phenomenon becomes notably apparent when analyzing the cohort of individuals who exhibited extramedullary disease. These patients do not consistently exhibit high-risk characteristics at baseline; however, they are commonly resistant to therapeutic interventions or experience a relapse shortly after treatment initiation. Plasmacytomas are recognized as solid tumors that arise from the aberrant expansion and uncontrolled proliferation of neoplastic plasma cells [3,4]. The most recent consensus on plasmacytomas published in 2021 classifies them into two distinct categories: Extramedullary Disease (EMD) and Paraskeletal (PS) types [5]. EMD refers to soft tissue involvement developed outside of the bone. Plasma cell migration through the bloodstream can trigger the appearance of such a condition in different areas of the body. Conversely, the PS type involves the presence of soft tissue masses that emerge directly from the bones. Solitary plasmacytomas, which can be present in the extramedullary or bony part of the body, are a rare type of plasma cell neoplasm that is limited or not present in the bone marrow [6]. The prevalence of PS appears relatively consistent, ranging from 7% to 34% at initial diagnosis and from 6% to 34% in the relapse setting [5,7]. An increasing trend in the incidence between diagnosis and relapse is present in the EMD setting, starting from 0.5% to 5% at diagnosis and reaching 8% at relapse, with several studies reporting even higher frequencies [5,8-10]. They frequently manifest in the craniofacial region, including the nasal cavity, sinuses, and nasopharynx, as well as in the larynx [11,12]. These tumors may be confused with more common forms of head and neck malignancies, such as squamous cell carcinoma, the most prevalent form of malignant laryngeal tumor [13], based on clinical presentation and imaging findings. The prognosis for patients with EMD remains unfavorable, even when innovative treatments are employed. The timely recognition and efficient treatment of this particular cohort of patients constitute an unmet medical need. Here, we present a case of a patient who was diagnosed with an unusually extensive extramedullary plasmacytoma that primarily affected the base of the skull and facial area and, later, the cervical region and the chest wall. In addition, we performed an extensive review of the diagnostic and therapeutic challenges associated with the management of this condition.

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## Case Presentation

A 63-year-old man who was referred to us for evaluation of anemia and hyperglobulinemia was diagnosed with MM in 2014. He also reported a recent onset of back pain. The serum IgG level was 61 g/L. Serum immunoelectrophoresis showed a monoclonal IgG-κ. Multiple lytic lesions were seen across his axial skeleton. A bone marrow biopsy demonstrated plasma cells with kappa light chain restriction at 65% cellularity. The diagnosis of an MM, IgG-κ, stage I, based on the International Staging System (ISS), was made. Normal results were obtained from cytogenetic tests and interphase fluorescence in situ hybridization for translocation t (4;14) and 17p deletion.

The patient had no comorbidities and an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Treatment was started with a Combination of Bortezomib, Cyclophosphamide, Dexamethasone (CyBorD), and monthly zoledronic acid infusions. The patient achieved a Very Good Partial Response (VGPR) after 4 cycles of the CyBorD regimen. He Denied stem cell Mobilization and Autologous Stem Cell Transplantation (HDM-ASCT) and continued on CyBorD for up to 8 cycles. Six months after the end of the induction regimen, a biochemical relapse with an increase in serum monoclonal protein levels manifested. A second-line treatment with lenalidomide and dexamethasone (Rd) was started, which was not administered adequately due to prolonged respiratory infections that caused delays. However, the patient progressed after 7 months on this regimen. He started experiencing loss of vision in the left eye, along with vomiting, nausea, dizziness, and a burning sensation in the left cheek area. Upon physical examination, there was facial edema in the left zygomatic and infraorbital regions and mydriasis in the left eye, coupled with ptosis of the eyelid. An MRI of the brain and viscerocranium showed that the sphenoid sinuses and a large part of the posterior half of the ethmoid sinuses were completely occupied. The lesion extended to a significant part of the skull base and the clivus, with direct extension to the left sphenoid sinus up to the optic canal on the same side. Additionally, there was penetration of the med Hematology Unit, 1st Department of Internal Medicine, Aristotle University School of Medicine, AHEPA University Hospital, Thessaloniki, Greece l rectus muscle in the left eye orbit and marginal expansion to the optic chiasm. The patient's clinical and imaging picture was highly indicative of the development of extramedullary plasmacytomas.

High doses of cyclophosphamide (3 g/m$^2$) and dexamethasone were administered as a salvage treatment, which led to relief and regression of the symptoms. Subsequently, the involved area received palliative radiation therapy with a fractioned total dose of 30 Gy. Unfortunately, following the initial improvement, the patient's condition gradually deteriorated, with a worsening of symptoms and an enlargement of the mass to encompass the left side of the face. Because of this, the treatment plan was changed, and a V-DCEP-intensive chemotherapy regimen with bortezomib, dexamethasone, cyclophosphamide, etoposide, and cisplatin was started. An MRI scan done after treatment (Figure 1) showed the growth of new lesions that looked like abnormal tissue masses and spread to the patient's chest wall, the submandibular gland, and the mandible and maxilla. These masses were most likely plasmacytomas. The histology of the chest mass confirmed the presence of extramedullary plasmacytomas.

After this, the patient received several types of therapy, including the combination of daratumumab, carfilzomib, and dexamethasone, as well as an intermediate dose of melphalan (70 mg/m$^2$) and the combination of VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide). Nevertheless, these regimens failed to elicit any response. The gradual growth in the size of the masses on the patient's face, neck, and chest indicated the progressive nature of the disease. The facial mass continued to grow, causing the displacement of the nose and palate (Figure 2). The patient also experienced spontaneous bleeding within the lesion next to the nose, as well as bleeding inside the mouth. This required frequent assistance from Ear, Nose, and Throat (ENT) specialists to manage the recurring bleeding episodes. Due to the pressure from the expanding mass, the left corner of the mouth also descended (Figure 2). The neck mass extended to involve the clavicle. In addition, the skin that was affected leaked a yellow serous fluid and had cutaneous

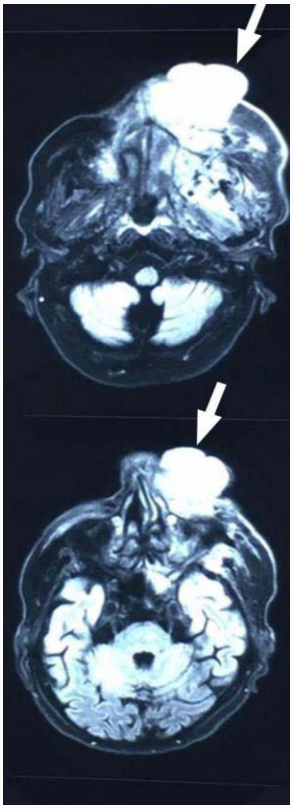

**Figure 1:** Axial T1-weighted Magnetic Resonance Imaging (MRI) scan of the viscerocranium, highlighting the specific compression of nasal structures and the intracranial expansion of the mass within the viscerocranium.

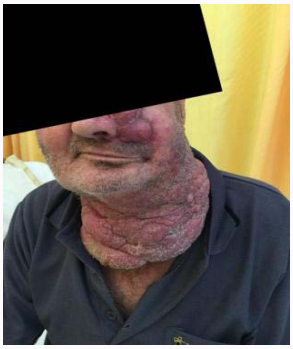

**Figure 2:** Extramedullary disease with extensive involvement of the facial and cervical regions.

erosions that looked like blisters or vesicles (Figure 2). The last CT imaging performed before the patient's death revealed a large tumor mass arising from the left side of the nose's root, which caused considerable disruption to the structures of the viscerocranium. The mass grew and connected with a similar lesion in the left cervical region, descending to the sternum and causing displacement of the structures within the larynx and trachea. Additionally, the mass exerted pressure on the left jugular vein. The patient died 12 months after the appearance of plasmacytomas in the viscerocranium, which caused extensive facial involvement, an inability to eat, episodes of bleeding, and difficulty breathing.

## Discussion

Multiple myeloma, the second-most common hematologic malignancy, is currently not curable. Although the current treatments have demonstrated great efficacy in achieving deep remissions, multiple myeloma often relapses, necessitating frequent therapeutic intervention to keep the disease under control. Despite efforts to classify patient risk using the Revised International Staging System (R-ISS), the variability in disease progression and treatment response highlights the unpredictable and complex nature of the disease. Extramedullary involvement signifies a highly aggressive type of MM. It develops as a result of a clone's and/or subclone's ability to migrate and proliferate independently of the supporting milieu of the bone marrow microenvironment. Advancements in imaging techniques, like the Positron Emission Tomography-Computed Tomography (PET-CT) scan, have greatly improved the ability to detect and diagnose plasmacytomas.

Plasmacytomas of the head and neck are rare, accounting for only about 1% of malignancies in this region. They usually arise as submucosal masses in the nasal cavity, paranasal sinuses,

nasopharynx, and larynx, mostly in patients over the age of 50 [14,15]. This patient's case is extremely important considering the increasing concerns about resistance to anti-CD38 antibodies. It emphasizes the urgent need to understand the mechanisms behind this resistance and develop new immunotherapies to improve the prognosis [16,17]. It is well known that EMD exhibits remarkable resistance to all treatment options and is an adverse prognostic factor that heralds an unfavorable outcome. According to a meta-analysis of eight clinical trials, the presence of plasmacytomas was found to be a significant predictor of shorter OS in a multivariable setting. However, it did not have a significant impact on Progression-Free Survival (PFS) [7]. A large study by Varetonni et al. used a time-dependent analysis to show that patients with plasmacytomas had a shorter OS and PFS than patients with bone marrow involvement alone, even when age, gender, and disease stage were taken into account [18]. It also appears that EMD, which indicates the spread of the disease through the bloodstream, has a worse prognosis than just the expansion of the bone. Two retrospective cohort studies observed a lower OS in the EMD group compared to the PS group, as well as in patients without plasmacytomas [19,20].

Solitary plasmacytomas, including those located in the head, neck, and skull base, are highly radiosensitive, and radiotherapy with a total dose within the range of 40 Gy to 50 Gy is recommended as the optimal therapeutic approach [21-27]. According to Creach et al., in cases of nasal and paranasal sinuses plasmacytomas, the field of irradiation should not be limited merely on the tumor mass, but should be extended for better outcomes [22]. Conventional therapies encounter difficulties in targeting myeloma disease that extends beyond the bone marrow, whereas novel agents provide the potential for increased effectiveness and accuracy. However, the existence of EMD remains a challenge for novel immunotherapies such as CAR T-cell therapy and Bispecific Antibodies (BsAbs). Preclinical studies suggest that the efficacy of immunotherapy may be hindered at extramedullary myeloma sites due to inhibitory mechanisms influenced by the microenvironment [28]. Teclistamab, a bispecific antibody that targets both CD3 receptors on T cells and BCMA receptors on myeloma cells, showed less efficacy in patients with EMD in both types of studies: A real-world German study involving 123 patients and the MajesTEC-1 clinical trial. In the real-world analysis, patients with EMD had a significantly reduced overall response rate and PFS compared to those without EMD. The MajesTEC-1 trial similarly reported less efficacy of Teclistamab among patients with EMD [29,30]. The combination of teclistamab and talquetamab, a bispecific antibody that targets the myeloma protein GPRC5D, showed better outcomes. Specifically, the EMD subgroup demonstrated an impressive overall response rate of 83% to this treatment combination [31]. Finally, a study of 134 patients who underwent CAR T-cell therapy for relapsed/refractory multiple myeloma, including EMD, revealed that EMD was an adverse prognostic indicator, with the outcomes for those with EMD being significantly worse than those with PS [32].

Recognizing and managing extramedullary manifestations early in the myeloma disease course is crucial for optimizing treatment strategies and improving patient outcomes. Radiation and systemic anti-myeloma treatment might be better used together to treat EMD because they provide both localized disease control and a reduction in myeloma burden. Furthermore, this approach recognizes the changing nature of relapsed myeloma, which involves both local and systemic aspects of the disease.

## Conclusion

This case report provides valuable insights by documenting the clinical course, radiographic findings, and treatment outcomes in a patient with extramedullary disease affecting the head and neck. EMD in this area can compress or obstruct vital tissues, organs, and the respiratory tract, posing significant risks. As MM experiences relapse, especially with EMD, it becomes more resistant to the available treatments. This leads to shorter periods of remission, and eventually, the majority of patients succumb to problems caused by the refractory disease. There are several unmet needs in this field, including the limited effectiveness of novel, approved immunotherapies in this specific patient population, such as those with advanced EMD.

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