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CASE REPORT

A Very Rare Relaps Type in Multiple Myeloma: Leptomenıngeal and Cranial Involvement

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Abstract

Multiple myeloma is a hematological malignancy that develops as a result of clonal proliferation of plasma cells and progresses with remissions and relapses. It is clinically characterized by many symptoms and signs such as osteolytic bone lesions, hypercalcemia, renal dysfunction, hypergammaglobulinemia and anemia. However, involvement of the central nervous system, especially the leptomeningeal/cranial region, is a rare and prognostically important form of relapse of the disease. This case report discusses this rare clinical presentation, diagnostic approach, and treatment strategies of extramedullary involvement of multiple myeloma.

Keywords: *Multipl Myeloma, Cranial involvement, Leptomeningeal involvement*

Introduction

Multiple myeloma (MM) is a B cell malignancy characterized by clonal proliferation of plasma cells. One of the most distinctive features of MM is abnormal plasma cell accumulation in the bone marrow and high levels of monoclonal immunoglobulin (M protein) accumulation in the serum[1]. At the genetic and molecular level, critical chromosomal changes play a role in the development and progression of MM. Specific chromosomal translocations and deletions, especially t(11;14), t(4;14) and del(17p), are important in the pathogenesis of this disease[2]. The interactions of MM in the bone marrow microenvironment, especially its interactions with bone marrow stromal cells, are critical for the development of the disease. Interactions between MM cells and bone marrow stromal cells trigger the release of various cytokines and growth factors. Cytokines, especially IL-6, Vascular Endothelial Growth Factor (VEGF) and Tumor Necrosis Factor alpha (TNF-α), while supporting the proliferation and differentiation of MM cells, may also contribute to the development of resistance to protease inhibitors[3]. The bone marrow

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microenvironment of MM stimulates osteoclast activity while inhibiting osteoblast activity. The interaction of MM cells with bone marrow stromal cells stimulates the production of RANKL (receptor activator of nuclear factor kappa-B ligand). This stimulates osteoclastogenesis by activating osteoclast precursor cells bearing the RANK receptor[4]. At the same time, MM cells can inhibit the production of osteoprotegerin (OPG), a molecule that antagonizes the effects of RANKL. This imbalance causes increased osteoclast activation and bone resorption[5].

MM has a prevalence rate of 1-2% among hematological malignancies[6]. An increased incidence has been observed in the population aged 65 and over, with approximately 6 new cases per 100,000 people reported annually in western societies[7]. It has been stated that the incidence of MM is higher in men and individuals of African origin than in women and individuals of Caucasian origin[8]. MM has a significant impact on the skeletal system, especially due to osteolytic lesions, pathological fractures and osteoporosis[9]. Renal involvement can occur both by the direct nephrotoxic effects of monoclonal light chain accumulation and by the combination of other factors such as hypercalcemia, dehydration and nephrotoxic drug use[10]. Additional organ involvement such as cardiomyopathy, amyloidosis and pulmonary complications can also be observed in MM patients[11].

Although MM is primarily known as the malignant proliferation of plasma cells within the bone marrow, extramedullary involvement can also be frequently observed in the later stages of the disease. While the incidence of extramedullary involvement varies between 7-18% at the time of diagnosis, it has been reported that this rate can increase to 20-40% in the later stages of the disease [12].

Nervous system involvement, seen as exramedullary involvement in MM, is a condition that should be taken into consideration both clinically and prognostically. Among the neurological complications of MM, such as radiculopathy, peripheral neuropathy and spinal cord compression are frequently observed clinical findings. However, although leptomeningeal involvement in central nervous system complications is relatively rare, it is of critical importance in terms of clinical course and treatment strategies[13]. Leptomeningeal involvement is characterized by the infiltration of malignant plasma cells into the subarachnoid space. This can occur independently of the classic MM symptoms of Bence Jones proteinuria, hypercalcemia, anemia, and bone lesions. This involvement can include a wide clinical spectrum, such as signs of meningeal irritation, neurological deficits, and cranial nerve palsies. Early diagnosis and management of leptomeningeal involvement has a decisive role on the clinical outcomes of the patient. Therefore, in addition to clinical and radiological evaluations, cerebrospinal fluid analysis is recommended in MM patients

with suspected involvement of leptomeninges. Intrathecal treatment and radiotherapy are among the potentially effective methods in the treatment of these patients[14].

Cranial involvement is an advanced-stage complication that can be observed in MM patients, and this condition poses significant challenges for both diagnostic and therapeutic approaches. Cranial involvement associated with MM usually occurs through osteolytic lesions or, more rarely, through direct invasion into the central nervous system (CNS)[4]. Clinically, this involvement can lead to various symptoms such as headache, neurological deficits and cranial nerve palsies[7].

Magnetic resonance imaging (MRI) is particularly valuable in the diagnosis of cranial involvement. MRI allows detailed evaluation of intracranial structure, as well as lesions within the skull and meninges, and plays a critical role in monitoring treatment response[4]. Treatment usually involves a combination of systemic chemotherapy regimens and regional radiotherapy. As in leptomeningeal involvement, the potential benefits of intrathecal chemotherapy and molecular targeted therapies in the treatment of cranial involvement are being investigated[14].

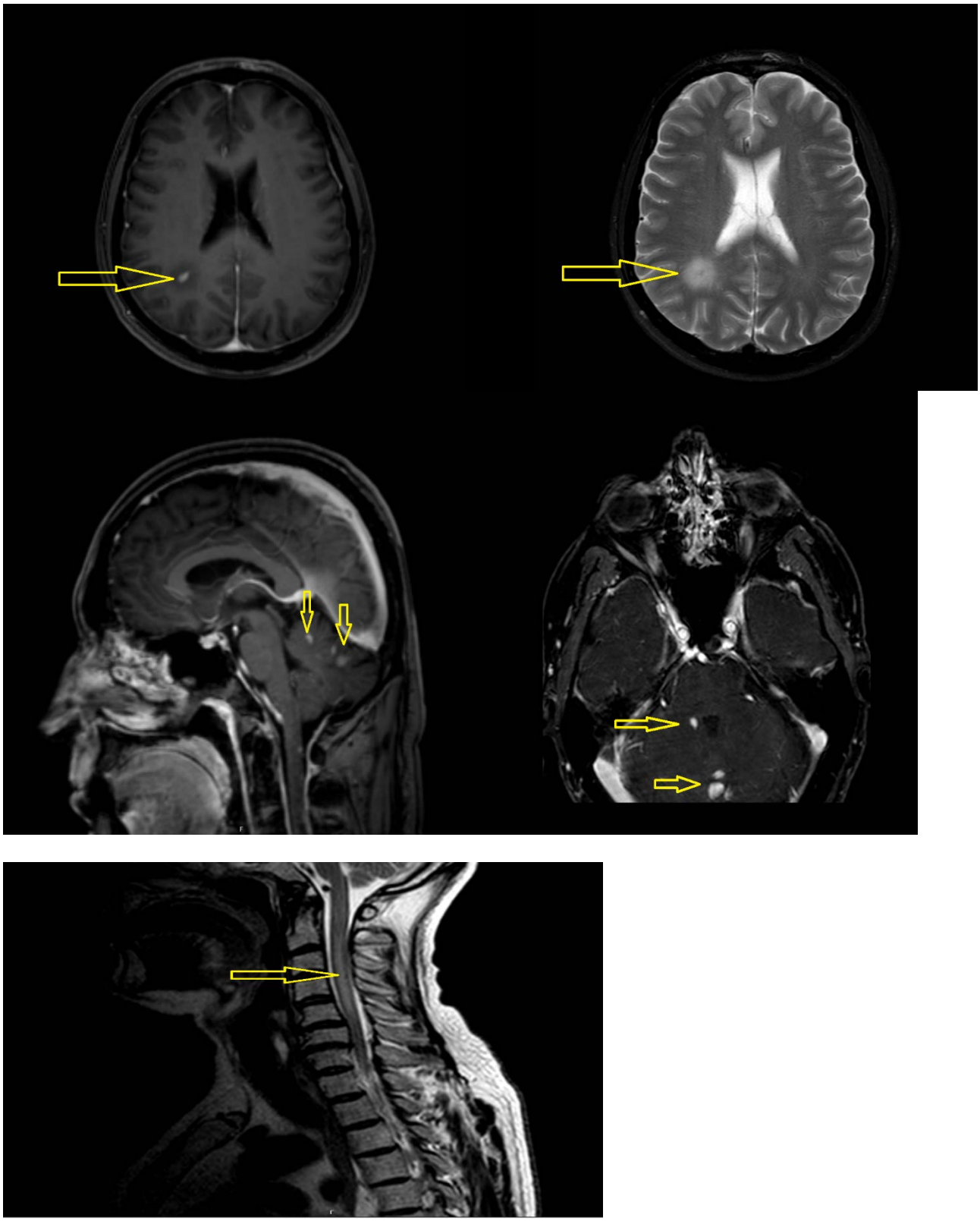
In conclusion, both leptomeningeal and cranial involvements of multiple myeloma are serious complications seen in aggressive and advanced forms of the disease. Early diagnosis and effective management of these complications can significantly improve patients' quality of life and potentially prolong survival. Therefore, it is recommended to carefully evaluate neurological symptoms in MM patients and apply aggressive treatment strategies in the early period when necessary.

CASE REPORT:

53-year-old male patient, no known chronic disease or medication use. The patient applied with the complaint of double vision in 2020. As a result of the cranial imaging, a diagnosis of meningioma was made and accordingly, the patient received cranial gamma knife radiotherapy (RT) in March 2020. In the same year, in the additional evaluations made for the patient who re-applied with complaints of pain in the low back and left hip area, a biopsy of the mass located in the subtrochantiric region of the left femur was taken on October 13, 2020. The biopsy result was reported as plasma cell myeloma of bone. According to the results of the bone marrow aspiration biopsy performed on November 2, 2020, the patient was diagnosed with multiple myeloma. At diagnosis, the patient exhibits findings compatible with only "B" of the CRAB criteria of multiple myeloma, that is, a bone lesion. Anemia, hypercalcemia and renal dysfunction were not observed in this patient. Immunoglobulin values (IgA, IgG, IgM) were found to be within normal limits.

However, the presence of lambda light chains as a result of serum immunofixation was considered a sign of MM. Immediately after the diagnosis of multiple myeloma, the patient received palliative radiotherapy (RT) for the lesion detected in the left femur. In November 2020, a course of chemotherapy with a combination of cyclophosphamide, velcade, and dexamethasone (CyBorD) was started. Autologous peripheral stem cell transplantation (APSCT) was performed in February 2021. After the transplantation, the patient was followed up with Lenalidomide maintenance. While the patient was being followed up with a full response under maintenance treatment, he applied with complaints of vision loss in the left eye and severe neck pain in June 2023. Cranial computed tomography (CT) examination was performed after the patient presented with complaints of vision loss in the left eye and neck pain. No abnormal findings were detected in this examination. However, for a more detailed examination, contrast-enhanced cranial and cervical magnetic resonance imaging (MRI) was performed. In MR imaging, lesions showing contrast enhancement after intravenous contrast material (IVCM) were seen in the right parietal region at the corona radiata level, in the right middle cerebellum peduncle, in the cerebellar vermis and in the left cerebellar hemisphere, and increased contrast enhancement was detected in the cerebellar folia. Two nodular lesions with meningeal contrast enhancement were observed in the cervical spinal cord. Edema was detected in the spinal cord between the C2-6 vertebral levels [Figure 1-5]. Visual field examination revealed papilledema and vision loss in the left eye [Figure 6-7]. Following the observed radiological findings, cerebrospinal fluid (CSF) examination was performed to determine neurological involvement. In this examination, the presence of diffuse plasma cells was detected and these findings were evaluated as leptomeningeal involvement [Figure 8].

In June 2023, DR-PACE (Dexamethasone, Lenalidomide, Cisplatin, Etoposide, Cyclophosphamide, Doxorubicin) chemotherapy protocol and cranial RT were applied, and in addition to this protocol, intrathecal treatment was also performed. Following this treatment approach, a significant regression was detected in the patient's complaints, his life comfort improved, and a clinical improvement was observed in the visual function of his left eye. It was reported that he passed away in the intensive care unit where he was hospitalized due to pneumonia in the city where he lived, although his hematological parameters were good.



Figures-1-5: Cranial MR Findings

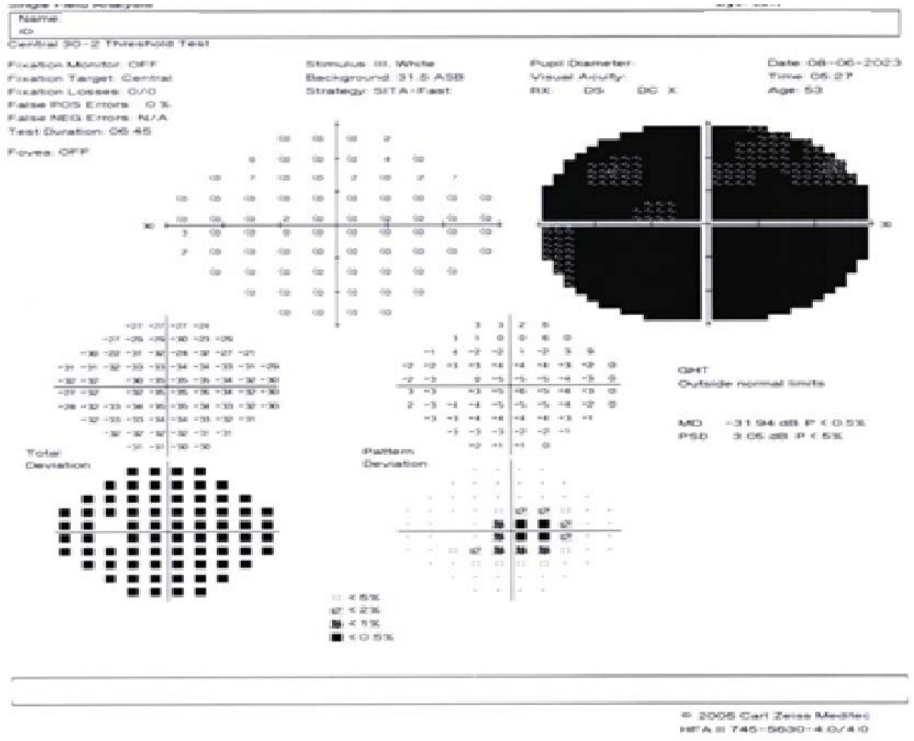


Figure-6: Left eye visual field

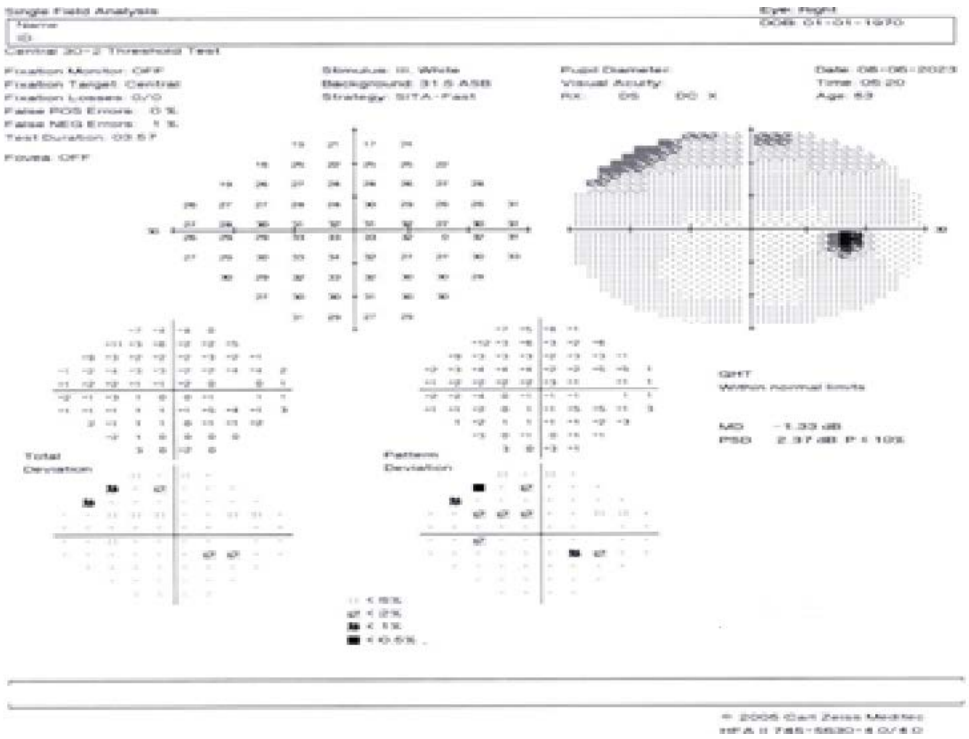


Figure-7: Right eye visual field

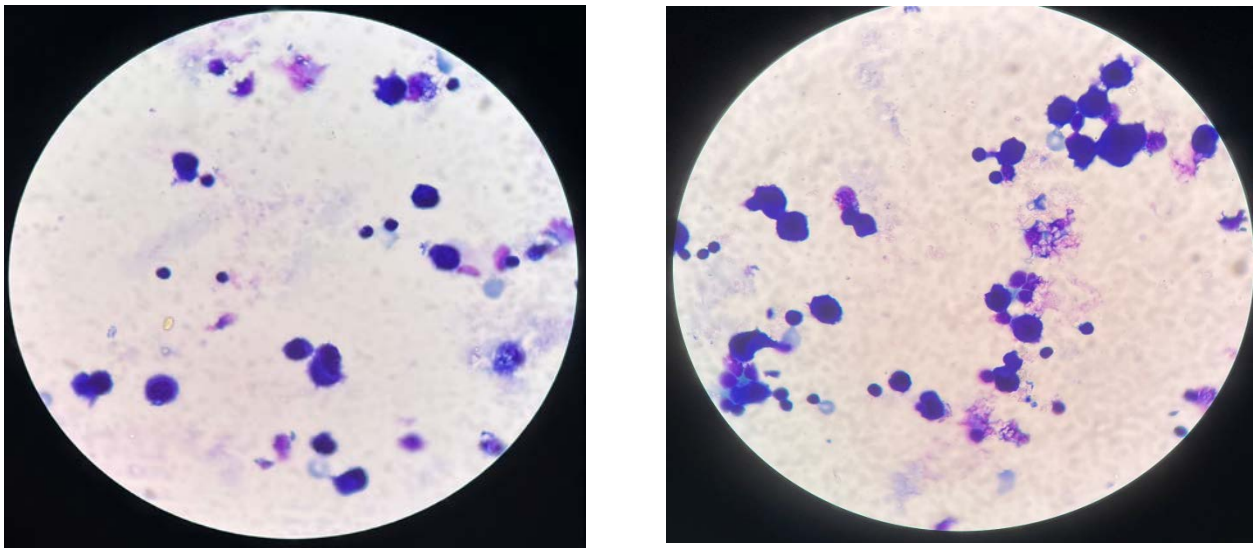


Figure-8: Plasma cells in cerebrospinal fluid

Discussion

Multiple myeloma (MM) is a hematological malignancy that develops due to malignant proliferation of plasma cells and is characterized mainly by involvement in the bone marrow. However, there is also the potential for spread to extramedullary regions in the course of the disease. Leptomeningeal involvement, which is among the neurological complications of MM and has been reported in a limited number of cases in the literature, has been brought to the fore once again with this case. Extramedullary involvements of MM are generally observed in the advanced stages of the disease or in case of relapse, and can sometimes be observed at initial presentation. The main reasons for these involvements include worsening of the patient's general condition, development of resistance to treatment, and the presence of some genetic mutations. Such complications often indicate aggressive forms of MM and require re-evaluation of treatment strategies. Neurological involvements occur especially as a result of the infiltration of plasma cells in neural tissues. This situation can both negatively affect the patient's quality of life and be a negative indicator for prognosis. Leptomeningeal involvement is a rare neurological complication of MM and often negatively affects prognosis. Management of leptomeningeal involvement requires early diagnosis and aggressive treatment strategies because this condition often occurs in advanced stages of the disease and can have serious clinical consequences. In the literature, studies addressing leptomeningeal involvement of MM emphasize the importance of this complication, despite its rarity, and the difficulties of response to treatment. In one study, Gozzetti et al. (2012) stated that intracranial and leptomeningeal involvements of MM may require different treatment approaches compared to standard MM treatments[14]. This study showed that intrathecal chemotherapy and radiotherapy may be effective in the management of leptomeningeal

involvement14. Additionally, research on the genetic and molecular mechanisms associated with the neurological manifestations of MM allows personalization of treatment strategies. Fonseca et al. Genetic and cytogenetic analyzes conducted by (2004) showed that certain chromosomal changes and mutations play an important role in the aggressiveness of MM and response to treatment[2]. In conclusion, leptomeningeal and cranial involvements of MM may have a significant impact on the course of the disease and response to treatment. Management of these complications requires a multidisciplinary approach and personalized treatment strategies based on the genetic and molecular characteristics of the disease.

This case report aims to draw attention to the rare neurological involvements of MM. It reminds us of the need to evaluate such rare complications in MM patients presenting with atypical neurological symptoms. Early diagnosis of the underlying causes of atypical symptoms, especially those encountered in the clinic, is essential in determining the prognosis and planning the most appropriate treatment approach for patients.

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