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A case of incidental multiple myeloma presenting with pathologically proven large frontal skull plasmacytoma and review of therapeutic targets: Case report

Gogo-Ogute E Ibodeng, Ayotola Fatola, Jose Galeas

ABSTRACT

Introduction: Multiple myeloma and plasmacytoma are both plasma cell malignancies that belong to the family of blood dyscrasias. They are thought to be different entities but can occur simultaneously in some patients.

Case Report: We present a unique case of a large plasmacytoma heralding the diagnosis of multiple myeloma with a preceding history of trauma which makes this case peculiar as this is an important addition to the limited existing scientific literature. The index patient was largely asymptomatic despite having a massive frontal skull/lobe lesion measuring approximately 8 × 6 cm in size alongside a chest wall mass involving the anterior left 6th rib, and a mildly displaced acute pathological fracture of the left clavicle. A primary diagnosis of multiple myeloma was made following serum protein electrophoresis with pathological confirmation of frontal skull plasmacytoma. After multidisciplinary discussion, radiotherapy was administered for plasmacytoma with complete resolution of the frontal skull mass without the need for resection and chemotherapy for multiple myeloma with daratumumab in combination with lenalidomide-dexamethasone—chosen due to anticipated poor outcome at the time of diagnosis. Autologous stem cell transplantation was subsequently instituted for multiple myeloma with a good outcome to date.

Conclusion: Solitary plasmacytoma can co-exist with multiple myeloma and the prognosis remains poor in such circumstance. Patients should be followed up closely with yearly imaging—magnetic resonance imaging (MRI)/computed tomography (CT), and positron emission tomography (PET) scans. A pivotal lesson from this case report emphasizes the atypical presentation of plasmacytoma and multiple myeloma with the peculiarity of a prior history of trauma which is believed to be associated with plasma dyscrasias. Over the last decade, novel therapeutic agents such as chimeric antigen receptor T-cell therapy, which is the first approved cell-based therapy for multiple myeloma, antibody-drug conjugates, and a dozen of bi-specific antibodies/immunotherapy have been developed and shows promising outcome in the future, especially for refractory cases of multiple myeloma.

Keywords: Head trauma, Immunohistochemistry, Multiple myeloma, Plasmacytoma

Gogo-Ogute E Ibodeng[1], MD, Ayotola Fatola[2], MD Jose Galeas, MD[3]

Affiliations: [1]Department of Internal Medicine, Thomas Hospital, 750 Morphy Avenue, Fairhope, Alabama 36532, USA; [2]Department of Internal Medicine, Johns Hopkins Hospital, Baltimore, Maryland 21287, USA; [3]Infirmary Cancer Care, Mobile, Alabama 36604, USA.

Corresponding Author: Gogo-Ogute E Ibodeng, Department of Internal Medicine, Thomas Hospital, 750 Morphy Avenue, Fairhope, Alabama 36532, USA; Email; gogo.ibodeng@infirmaryhealth.org

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INTRODUCTION

Multiple myeloma and solitary plasmacytoma are both plasma cell malignancies that belong to the family of blood dyscrasias. Multiple myeloma is characterized by the proliferation of monoclonal plasma

cells that proliferate in the bone marrow leading to an overabundance of monoclonal paraprotein (M protein) while plasmacytoma is a discrete proliferation of neoplastic monoclonal plasma cells without the abundance of M protein. They are thought to be different entities but can occur simultaneously in some patients. In the United States, multiple myeloma accounts for 1.8% of all cancer diagnoses with an estimated incidence rate of 7.0/100,000 [1]. Solitary plasmacytomas are rare accounting for only 3% of all plasma cell neoplasms [2]. Aside from the rarity of the tumor itself, the location of the lesion in our patient is even more uncommon creating a unique platform for closer examination. Our patient is an extraordinary example of a pathologically proven large plasmacytoma occurring concurrently with multiple myeloma. This is a rare presentation and can be diagnostically challenging. Other studies which have clearly demonstrated difficulties in establishing diagnosis include skull metastasis from uterine leiomyosarcoma by Alessandro Rizzo and colleagues [3], sarcoidosis after chemoradiation for head and neck cancer by Min Yao and colleagues [4].

CASE REPORT

A 63-year-old Caucasian female presented to the emergency department with complaints of frontal headache and some personality changes following head trauma sustained during a fall in the bathtub earlier that evening. She also complained of left rib pain present since undergoing a breast MRI two years prior due to her increased risk for breast cancer as her family history was positive for cancers of the breast, lung, and prostate. Medical history was significant for hypothyroidism, hysterectomy, appendectomy, and cholecystectomy but no history of smoking. She was involved in a motor vehicle accident six months prior; she was struck on the right side of her vehicle without serious injury or head trauma; however, she had reported possibly hurting her head during the impact.

On examination, her vitals were stable and her laboratory work-up revealed mild normocytic anemia with hemoglobin of 11.2 g/dL but normal creatinine and calcium levels. A physical examination revealed a right frontoparietal swelling approximately 8 × 6 cm in size. Computed tomography of the head was most concerning, showing a large expansile heterogenous right frontal mass eroding the skull and protruding outward (Figures 1–3). There was frontal vasogenic edema, mass effect, generalized cerebral sulcal effacement, as well as effacement of the frontal horns of the lateral ventricles and suprasellar cistern. Additionally, scattered sub-centimeter calvaria lytic foci were noted.

Computed tomography of the chest showed a large metastatic mass located in the anterior left pericardial region with associated osseous expansion and destruction of the adjacent anterior lateral left 6th rib. X-ray of the left shoulder showed a mildly displaced acute pathological fracture of the left clavicle.

The patient was admitted for further workup with consults to oncology, orthopedic surgery, and neurosurgery. A core biopsy of the chest mass demonstrated hypercellular proliferation of plasma cells arranged in a sheet-like configuration with the cells demonstrating immunoreactivity for CD138 and lambda light chain restriction. Flow cytometry of the biopsy sample revealed approximately 2% abnormal and monoclonal plasma cells. Biopsy of the left chest mass was also positive for CD56 with an elevated lambda cytoplasmic light chain ratio of 305. Serum protein electrophoresis (SPEP) with immunofixation confirmed IgG lambda monoclonal protein of 3.3 g/dL concerning for multiple myeloma. At that time, a diagnosis of IgG lambda multiple myeloma and plasmacytoma of the right frontal cranium was made. Additional imaging was obtained for staging which included a whole-body PET, CT, MRI of the thorax, and MRI of the lumbar spine—all consistent with active multiple myeloma. She was immediately started on decadron, evaluated for a bone marrow transplant, and started on radiation therapy targeting the frontal lobe lesion.

Overall, she underwent radiotherapy with a total of 3000 cGy (30 Gy) in 15 fractions to the skull. Following radiation, there was a significant reduction in the size of the brain lesion. Cytogenetics revealed gain at chromosomes 7, 9, and 15, as well as gain of 1q on myeloma fluorescence in situ hybridization (FISH)—a poor prognostic marker indicating high-risk myeloma.

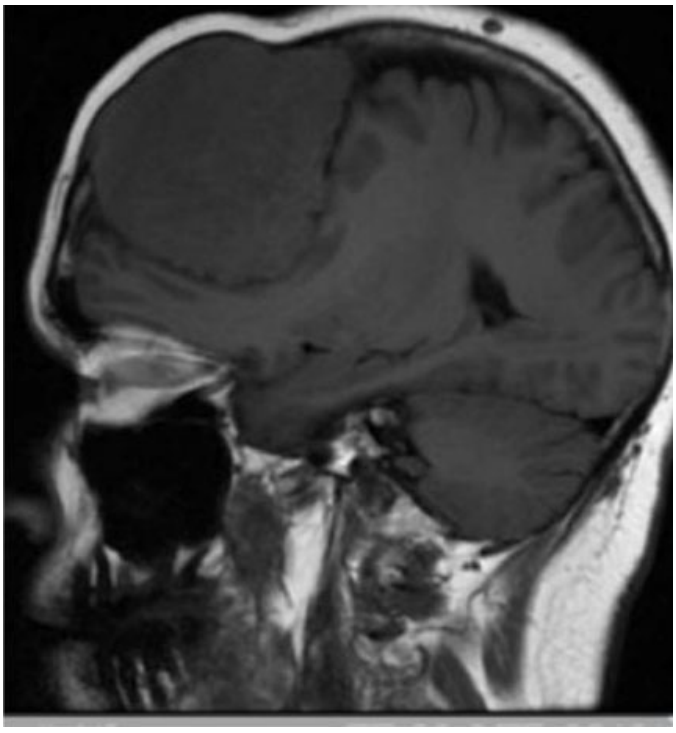

Figure 1: Sagittal T1 view demonstrates some extra-axial mass with mass effect upon the frontal lobe cortex isointense to grey matter on the T1 series.

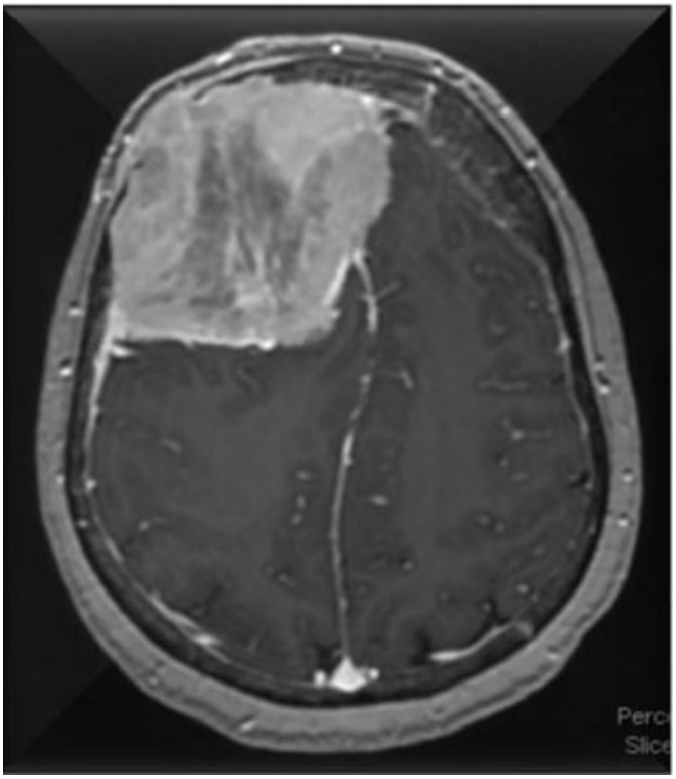

Figure 2: Axial T1 view showing heterogeneous enhancement and leftward displacement of the falx. There is some destruction of the overlying right frontal calvarium.

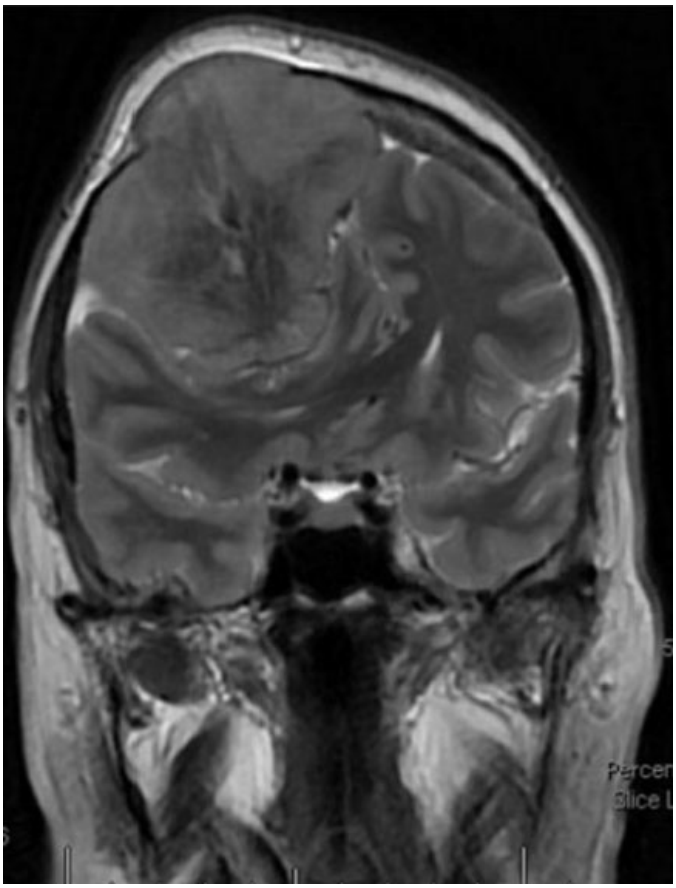

Figure 3: Coronal view T2; features showing heterogeneous enhancement and leftward displacement of the falx. There is some destruction of the overlying right frontal calvarium.

Post-radiation, reconstructive surgery was planned, and a port was placed to begin therapy for multiple myeloma. She was subsequently initiated on a Dara-Rd regimen (daratumumab in combination with lenalidomide-dexamethasone) which is a first-line treatment option for transplant-eligible patients, although not the preferred first-line combination chemotherapy and she received a total of 4 cycles. Afterward, she had melphalan 200 mg/m^2 and autologous bone marrow stem cell transplantation for Multiple myeloma. Her post-transplantation course was complicated with nausea, vomiting, diarrhea, and electrolyte imbalance which were managed supportively. Her frontal skull plasmacytoma resolved completely without any further need for reconstructive surgery. She is 18 months post-initial diagnosis and 1-year post-bone marrow transplantation in clinical remission and she continues to show a good response to therapy with regular follow-up visits to date.

DISCUSSION

Solitary plasmacytomas present an interesting and unique field for study because of their very infrequent occurrence. Solitary plasmacytomas are a rare subset of plasma neoplasms accounting for approximately 5–10% which manifest either in bone (osseous/solitary plasmacytoma of bone—SBP) or extraosseous (extramedullary plasmacytoma—EMP) with a low risk of progression to myeloma in the extramedullary lesion [5]. Extramedullary plasmacytomas are rare at diagnosis of multiple myeloma. Kyle and his colleagues reported only 4 out of 1027 patients with new-onset multiple myeloma as having EMP in a 13-year retrospective study of 1027 newly diagnosed patients with multiple myeloma at Mayo Clinic [6]. This, in turn, limits knowledge of the disease, treatments, and prognosis. Multiple myeloma (MM) on the other hand is more common and is typically associated with distinct clinical entities, typically identified as CRAB (hypercalcemia, renal insufficiency, anemia, and bone lesions).

There is a slightly more male-to-female predominance of plasmacytomas with a ratio of 2:1 and a median age of 55–60 years [7]. Our patient is female and 63 years of age, which is slightly outside the typical demographics but may explain the co-existing disease, as the average age at diagnosis of MM is approximately 65. By strict definition, the incidence of EMP at diagnosis was found to be 2% and the rate of EMP in the first three years following diagnosis of plasma cell myeloma was 3% [8]. Using a broader definition of EMP, the incidence of EMP at diagnosis of multiple myeloma is 15–20% with an additional 15% occurring during the course of multiple myeloma indicative of relapse or refractory disease as elaborated by other series [9].

Little is known as to why these B-cell plasma dyscrasias develop though there is speculation that localized trauma or surgery may play an activating role that cannot be

completely ruled out; in our patient's case, she presented a few months after an initial traumatic episode. In a study by Hussein and colleagues, it was postulated that trauma causes enhanced release of cytokine resulting in increased proliferation of plasma cells and stromal cells in the bone [10]. Another study observed an increased quantity of BCL-2, an antiapoptotic protein, in plasmacytomas. BCL-2-like gene encodes BCL-XL as a transcriptional target of IL-6 which is a well-known inflammatory cytokine that promotes B cell proliferation [11]. Although the study was done in mice, mice with dysregulated IL-6 and MYC expression developed plasma cell tumors that expressed BCL-2 and BCL-XL respectively. While no direct correlation between trauma and plasma dyscrasias has been established in humans, Hussein and his colleagues reported a diagnosis of plasma dyscrasias in about 8 patients who stated a history of trauma to the site where plasma cell neoplasms were later diagnosed [10]. Initial workup in our patient with tissue biopsy of the chest wall mass confirmed plasmacytoma and clonal plasma cell of 2% suggesting possible plasmacytoma with minimal bone marrow involvement. This technically does not meet the criteria for myeloma as >10% of clonal plasma cells are in favor of the diagnosis of multiple myeloma. However, further myeloma work-up; SPEP with immunofixation confirmed IgG lambda monoclonal protein of 3.3 g/dL alongside lytic lesion of the 6th rib consistent with multiple myeloma. Immunohistochemistry is very helpful in distinguishing both conditions as extramedullary plasmacytomas present with an absence of cyclin D1 and infrequent expression of CD56 [12]. Immunophenotyping in our patient was positive for CD56 which offers a slightly favorable prognosis in patients with plasmacytoma coexisting with multiple myeloma but myeloma FISH studies revealed hyperdiploidy and gain of 1q—a poor prognostic marker indicating high-risk myeloma. Serum-free light chain assay and plasma cell FISH for del 13, del 17p13, t(4;14), t(11;14), 1p deletion, and 1q amplification/gain, have been strongly recommended by the National Comprehensive Cancer Network (NCCN) guidelines as part of initial diagnostic work as it may help identify ultra-high risk multiple myeloma as well as immunohistochemical analysis for CD138 positivity which is strongly expressed in neoplastic monoclonal plasma cells and plasmacytoma as was seen in our case.

Positron emission tomography/computed tomography scans at diagnosis and follow-up of multiple myeloma have been recommended by the international myeloma working group since early detection of EMP lesions may lead to better survival. Additionally, it is mandatory, to confirm a diagnosis of solitary plasmacytoma [13]. Localized radiation therapy is the definitive treatment for plasmacytoma as it provides excellent outcomes. Chemotherapy and surgical interventions are sometimes required in certain patients but most commonly are adjunct therapy.

Although surgery was initially planned considering the size of the frontal skull lesion at the time of diagnosis, our patient underwent localized radiation therapy to the frontal skull mass with excellent response, and complete resolution of mass, without any need for surgical intervention. Most clinicians recommend a minimum dose of radiation treatment regardless of tumor size as published by the International myeloma working group, however, our patient received 30 Gy with a good outcome despite the large size of the mass, which may in part, be explained by the patient's good performance status before commencing therapy [13].

The choice of systemic chemotherapy with Dara-Rd was made based on the high-risk disease burden, especially with the gain of chromosome 1q, and anticipated poor prognosis based on dual disease state at the time of diagnosis. She subsequently had autologous stem cell transplantation for multiple myeloma with good recovery to date. We believe this patient showed a prompt response to therapy possibly because her condition was managed aggressively and non-conventionally; the use of Dara-Rd as opposed to the preferred first-line therapy for multiple myeloma—Bortezomib/Lenalidomide/Dexamethasone, for transplant eligible candidates.

Older age has been shown to have a poor prognosis and patients beyond the age of 60 demonstrate significantly reduced overall survival in both plasmacytoma and multiple myeloma but were slightly more favorable for solitary plasmacytoma than multiple myeloma [14]. In a Spanish registry study, relapse after autologous stem cell transplant occurred in the form of EMP which accounted for about 14% of the cases [15].

Solitary plasmacytoma has a slightly better prognosis than multiple myeloma when occurring independently. Over the last decade, several therapeutic advances have been developed for patients with multiple myeloma as the disease remains largely incurable. Chimeric antigen receptor T (CAR-T) cell therapy has demonstrated an objective response in patients with refractory multiple myeloma. Studies identifying CAR-T cell target antigens are believed to yield some effect by delaying the onset of relapsed disease [16, 17]. Other new therapeutic targets being developed include immunotherapy such as Teclistamab which is a novel human IgG4 B-cell maturation antigen and CD3-directed bispecific monoclonal antibody with silenced Fc function [17].

There is a need for robust prospective studies to focus on early diagnostic modalities to exclude occult multiple myeloma in the evaluation of plasmacytomas. In the next five years, we suspect this area will continue to unfold with a particular focus on the early diagnosis of occult multiple myeloma using molecular and epigenetic studies as biomarkers. The limitation of this study mainly revolves around the difficulty of identifying occult myeloma early enough as the patient only presented after a preceding traumatic incident. It would also be challenging to identify occult multiple myeloma in an early plasmacytoma disease due to the paucity of literature regarding the early identification of occult multiple myeloma. However, a close follow-up of patients with plasmacytoma would be

beneficial in early diagnosis and effective management of multiple myeloma.

This study will help facilitate early investigation of multiple myeloma in patients with extramedullary plasmacytoma as well as add to the limited existing literature on similar cases. More so, the treatment modalities instituted in the case of our patient can help guide other physicians faced with similar clinical dilemmas especially if the patient does not tolerate the first-line regimen. The prognosis of extramedullary plasmacytoma and multiple myeloma especially when occurring concurrently appears to be very poor, however, our patient is currently free of any disease at this time. We will continue to follow this patient closely in the future with aim to monitor for full remission.

CONCLUSION

Plasmacytoma and multiple myeloma belong to the family of plasma dyscrasias with different treatment approaches. Plasmacytoma can occur with occult multiple myeloma and should be thoroughly investigated when identified as co-existing diseases have poor outcomes. Novel therapeutic agents such as chimeric antigen receptor T-cell therapy, antibody-drug conjugates, and a dozen of bi-specific antibodies/immunotherapy have been developed and shows promising outcome in the future, especially for refractory cases of multiple myeloma. Further studies are needed to analyze the relationship between cytogenetics in these malignancies and possible outcomes as well as treatment with novel systemic agents in the nearest future.

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Author Contributions

Gogo-Ogute E Ibodeng – Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ayotola Fatola – Design of the work, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jose Galeas – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

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Consent Statement
Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.