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Beenish Faheem
St Joseph's University Medical Center, Paterson, NJ, beenishfaheem@students.aucmed.edu

Sarah Ayad
Trinitas Regional Medical Center, Elizabeth, NJ, USA

Leena Bondili
St Joseph's University Medical Center, Paterson, NJ, USA

Michael Maroules
St Joseph's University Medical Center, Paterson, NJ, USA

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CASE REPORT

Multiple Myeloma with CNS Involvement in the Form of Leptomeningeal Carcinomatosis Presenting as Vitamin B12 Deficiency

Beenish Faheem [a,*], Sarah Ayad [b], Leena Singh [a], Michael Maroules [a]

[a] St. Joseph's University Medical Center, United States
[b] Trinitas Regional Medical Center, United States

Abstract

A 75-year-old male presented with lower back pain, bilateral lower extremity weakness, decreased sensation to vibration and proprioception in lower extremities, anemia, and vitamin B12 deficiency. The MRI of the lumbar spine revealed extensive leptomeningeal carcinomatosis. Subsequently, the patient was diagnosed with multiple myeloma (MM) and B12 deficiency with negative intrinsic factor antibodies. MM can present as extramedullary hematopoiesis (EM) to involve the central nervous system (CNS). CNS involvement is rare and develops in only around 1% of MM patients. It carries a poor prognosis with less than 6 months survival. MM is thought to be associated with both B12 deficiency and pernicious anemia. Some studies have even suggested B12 deficiency as a possible marker for worsening disease and a prognostic factor. In our patient's case, he had extensive CNS involvement at diagnosis of MM with very low B12 levels. The extent of his disease with extensive CNS involvement, which carries a poor prognosis, could possibly explain the very low levels of B12. This is the first reported case of a patient presenting with B12 deficiency found to have MM with leptomeningeal carcinomatosis at diagnosis. To the author's knowledge, there is no literature investigating association between B12 deficiency at the time of diagnosis of MM with CNS complications. Furthermore, there are no established guidelines on treatment for leptomeningeal myelomatosis. We present this case with the effort to learn more about this disease in terms of response and overall survival.

Keywords: Multiple myeloma, Vitamin B12, Vitamin B12 deficiency, CNS involvement, Leptomeningeal myelomatosis, Leptomeningeal carcinomatosis

1. Introduction

Multiple Myeloma (MM) is a hematological neoplasm that constitutes about 1.6% of cancer cases reported in the United states and is associated with increased morbidity and mortality.[1] MM is mainly a disease of the elderly with median age above 65 and is characterized by proliferation and infiltration of the bone marrow with clonal plasma cells and increase of abnormal monoclonal immunoglobulins in the serum or urine.[2] The clinical presentation and evaluation consist of non-specific symptoms of bone pain, weight loss, fatigue/generalized weakness while others may present with hypercalcemia, anemia, proteinuria, and renal involvement.[1] Multiple myeloma can present as discrete masses of monoclonal neoplastic plasma cells in bone, solid tissues, or central nervous system (CNS). This extramedullary myeloma (EM) is seen when plasma cells escape the bone marrow and infiltrate other tissues. There have been reports of skin, liver, pancreas, lungs, lymph nodes, and central nervous system involvement.[2] EM of CNS type is a more aggressive subtype of multiple myeloma with an unrelenting course and with poor prognosis with survival typically being less than 6 months. CNS involvement, presenting as either dural myeloma, intra parenchymal infiltration or leptomeningeal lesions, is rare and develops in only around 1% of MM patients.[2] In patients with CNS involvement symptoms may include focal

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* Corresponding author. St Joseph's University Medical Center, 703 Main Street Paterson, NJ, United States. Fax: +1 5163010748.
E-mail address: beenishfaheem@students.aucmed.edu (B. Faheem).

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neurological deficits, impaired mental state, or cognitive disability.[2] There has been literature suggesting that low vitamin B12 levels may represent prognostic significance and could function as a marker for worsening MM when CNS involvement has not yet been identified.

We report a 75-year-old male with history significant for sick sinus syndrome and hepatitis C who presented to the emergency department (ED) with bilateral lower extremity weakness of 6 months in duration. Patient was found to have MM (IgG Kappa) with leptomeningeal involvement presenting with B12 deficiency. There are no established guidelines on treatment for leptomeningeal myelomatosis. We present this case with the effort to learn more about this disease in terms of response and overall survival.

2. Case presentation

We report a case of a 75-year-old African American male with past medical history of Hepatitis C and sick sinus syndrome status post pacemaker placement who presented with progressively worsening bilateral lower extremity weakness of six months in duration. He states that his bilateral lower extremity weakness is associated with intermittent numbness causing unsteady gait, incurring frequent falls. Patient reported borrowing lower back pain that radiates down the back of his legs along with 40 pounds of weight loss. He denied any urinary or bowel incontinence, night sweat, fevers, chills, dizziness, headaches, blurry vision, shortness of breath, nausea, vomiting, any recent travels or sick contacts, syncope, seizures, speech changes. Patient is independent with all activities of daily living at his baseline. Patient has no history of alcohol or tobacco use disorder and no family history of malignancy, liver, or kidney disease.

On the physical exam the patient appeared frail and cachectic and in mild distress due to his lower back pain. His muscle strength was decreased at a three on a 5-point scale in bilateral lower extremities with diminished sensation to vibration, temperature, and light touch. There was no hepatosplenomegaly or lymphadenopathy detected. On the initial basic metabolic panel, the patient had a protein gap of 7.8 g/dL, with albumin 2.9 g/dL, total protein 10.7 g/dL, BUN 16 mg/dL, and creatinine 1.09 mg/dL. His folate level was 16 ng/dL and vitamin B12 124 pg/mL. Patient's complete blood count was significant for macrocytic anemia with hemoglobin 8.9 g/dL, hematocrit 26.8 g/dL, mean corpuscular volume (MCV) 101.5 fL, Red cell distribution width (RDW) 13.4%, platelets 166,000 mm^3, white blood cells 5.5 $\times$ $10^3/mm^3$ with an absolute neutrophil count (ANC) 3.71 $\times$ $10^3/mm^3$. His anemia profile revealed iron 94 mcg/dL, TIBC 234 mcg/dL, Ferritin 327 ng/mL, erythrocyte sedimentation rate (ESR) 70 mm/h. A complete pernicious anemia work up was done that was unremarkable. Patient was treated for vitamin b12 deficiency.

On magnetic resolution imaging (MRI) of the lumbar spine demonstrated a pathological fracture at the level of L5 vertebral body. There was a lesion in the left L1 vertebral body extending into the pedicle and a left L3 vertebral body lesion with enhancement. There was a nodular enhancement along the conus medullaris in the leptomeninges compatible with leptomeningeal carcinomatosis. There was a fusiform mass along the right L3-4 neural foramen, along the bilateral L4-5 neural foramen, bilateral L5-S1 neural foramen and along the S1 to S3 neural foramina bilaterally with enhancement. There was also an enhancement along the T12-L1, L1-2 and L2-3 neural foramen. A compression fracture of L5 was noted leading to marked central stenosis with lateral recess stenosis bilaterally. A computed tomography (CT) scan of the head/brain was unremarkable. A CT scan of the chest, abdomen, and pelvis was unremarkable, without any evidence of adenopathy, ascites, or inflammatory changes (see Fig. 1).

There were concerns for Multiple Myeloma (MM) and further workup was undertaken. Patient's labs revealed a monoclonal gammopathy with IgG 7113 mg/dL, IgM <20 mg/dL, IgA 33 mg/dL, M spike 5.7 g/dL, beta-2 microglobulin 2.5 mg/L, free kappa light chains 416.3 mg/L, with a kappa/lambda ratio 154 (normal: 0.26–1.65), with an LDH 109 unit/L, and uric acid 4.7 mg/dL.

Immunofixation showed IgG monoclonal protein with kappa light chain specificity. The bone marrow aspirate smears showed markedly increased plasma cells, focally approximately 79% of the total number of cells, consistent with plasma cell myeloma. The flow cytometry analysis demonstrated monoclonal IgG kappa plasma cells. The Fluorescence in-situ hybridization (FISH) confirmed Multiple Myeloma and the cytogenetic analysis showed no evidence of chromosomal abnormalities.

Taken together with the laboratory findings, physical examination, imaging along with the bone marrow pathology report, the patient was diagnosed with advanced multiple myeloma with an initial presentation of vitamin b12 deficiency and CNS involvement manifesting in gait abnormalities. There are studies that have shown a correlation between vitamin b12 deficiency and multiple myeloma as a marker of disease severity. Our case is

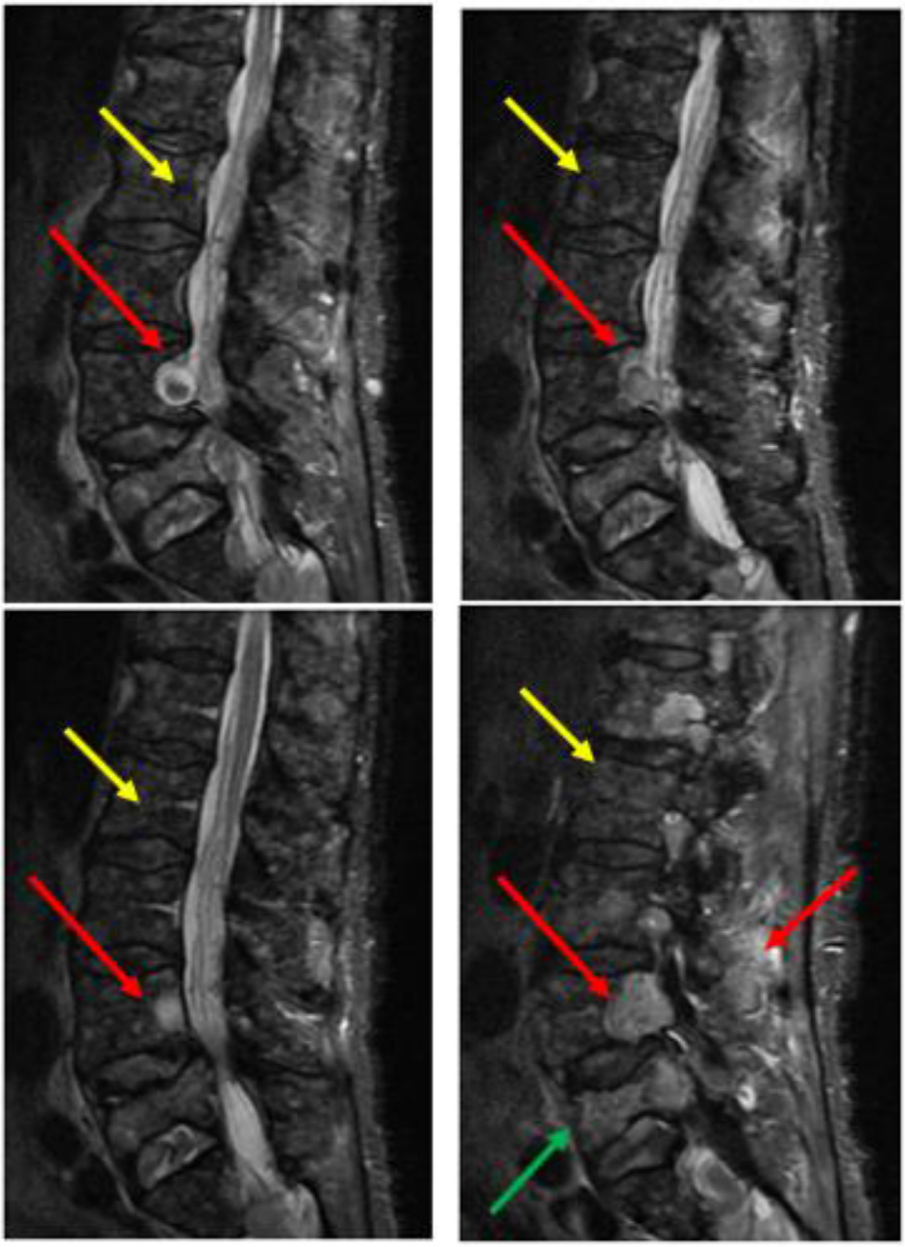

Fig. 1. There is heterogeneity of marrow signal with multiple foci of STIR hyperintensity and enhancement compatible with diffuse osseous metastases (yellow arrow). There is a probable pathologic compression fracture of the L5 vertebral body with concavity of the superior and inferior endplates and marrow edema (green arrow). There is nodular enhancement along the conus medullaris in the leptomeninges compatible with leptomeningeal carcinomatosis (red arrow). There is a fusiform mass along the right L3-4 neural foramen, along the bilateral L4-5 neural foramen, bilateral L5-S1 neural foramen and along the S1 to S3 neural foramen bilaterally with enhancement (red arrow). There is also enhancement along the T12-L1, L1-2 and L2-3 neural foramen.

unique in that the patient presented with intramedullary lesions in the central nervous system (CNS) as an extremely rare complication of multiple myeloma in the setting of vitamin b12 deficiency.

3. Discussion

Multiple myeloma (MM) is a bone marrow-derived clonal plasma cell neoplasm that is characterized by the overproduction of monoclonal antibodies.[3] MM is a devastating disease where patients may develop renal failure, cytopenia, infections because of immunoparesis, electrolyte abnormalities like hypercalcemia, and lytic bone lesions manifesting as skeletal symptoms with back pain and vertebral fractures.[4] Extramedullary dissemination, a rare event, has also been noted with MM and carries a poor prognosis. Among the

locations for extramedullary hematopoiesis, the central nervous system (CNS) involvement is particularly devastating with an even worse prognosis.[5] MM involving the CNS is a rare complication of MM occurring in roughly 1% of MM patients with an overall survival of less than 6 months.[5] Based on a review by Dispenzieri and Kyle, intracranial plasmacytomas or myelomas can be classified into four groups:[1] lesions extending from the skull and pressing inward,[2] lesions growing from the dura mater or the leptomeninges,[3] lesions from the mucous membranes of a nasopharyngeal plasmacytoma, and[4] intraparenchymal lesions not arising from any of these other sites.[6] Leptomeningeal involvement is the most common form, often leading to nerve root infiltration and cerebral nerve palsies.[6] Leptomeningeal metastasis can be diagnosed by either magnetic resonance imaging (MRI) and/or evidence of malignant cells in CSF cytology.[6]

Vitamin B12 deficiency has been associated with MM through various postulated mechanisms that are still not completely understood.[7,8] Some of the mechanisms of B12 deficiency described are development of specific autoantibodies, possible IgM paraprotein with inherent anti-intrinsic-factor-like activity, or renal dysfunction hindering appropriate B12 absorption.[3] Pernicious anemia has been associated with IgG and IgM kappa type of paraproteinemia along with IgA myeloma.[3] Furthermore, Seegobin et al. described worsening of MM in association with B12 deficiency and pernicious anemia. They found worsening pancytopenia along with increasing monoclonal paraprotein levels with a simultaneous decrease in B12 levels.[3] They concluded that B12 deficiency could possibly behave as a marker of worsening MM and overall disease activity. Yikilmaz et al. retrospectively investigated an association between B12 deficiency and MM and concluded that vitamin B12 may carry prognostic significance in disease course. They recorded B12 levels at diagnosis of MM along with complications such as hypercalcemia and fracture.[4] They found B12 deficiency in approximately 20% of patients with MM at the time of diagnosis which correlated with an increased frequency of hypercalcemia and bone fracture.[4]

This is the first reported case of a patient presenting with B12 deficiency found to have MM with leptomeningeal involvement. His lower back pain with gait abnormalities due to decreased sensation of vibration and proprioception, prompted checking folate and B12 levels along with imaging by MRI of the thoracic and lumbar spine. His B12 levels were significantly low at 126 mg/dL. The imaging revealed leptomeningeal carcinomatosis and diffuse vertebral osteolytic lesions. Patient's labs were concerning for renal failure and pancytopenia. Our patient's work-up for pernicious anemia was unremarkable. Taken together these findings prompted MM work-up that confirmed the diagnosis. This patient's presentation poses a unique scenario of differentiating whether the neurological symptoms were due to the B12 deficiency, leptomeningeal involvement, or a combination of both. It will be imperative to follow the patient to assess for symptom resolution status post B12 supplementation or whether his symptoms continue until he is treated for leptomeningeal carcinomatosis.

In retrospect, this corroborates the finding that low levels of vitamin B12 may help indicate the disease severity. The question becomes if B12 deficiency was predictive of this patient's advanced disease with CNS involvement or if the two factors were an independent and rare combination. The previous studies and cases reported with MM and CNS involvement did not report B12 deficiencies. It is unclear whether these patient's B12 levels were measured. To the author's knowledge, there is no literature investigating association between B12 deficiency at the time of diagnosis of MM with CNS complications of leptomeningeal carcinomatosis. Further investigation and research into the relationship between B12 deficiency and CNS involvement in MM is needed to demonstrate the usefulness of B12 levels as a marker for worsening MM, disease activity, and/or a prognostic factor.

4. Conclusion

Multiple myeloma is an incurable neoplasm of monoclonal plasma cells that makes up approximately 1.6% of cancer cases. MM can have extramedullary involvement and rarely can occur in the CNS, manifesting as leptomeningeal carcinomatosis. The prognosis is extremely poor with overall survival being less than 6 months. Furthermore, there may be an association between MM and vitamin B12 levels. Patients with vitamin B12 deficiency at diagnosis of MM may serve as a prognostic factor or a marker for worsening disease as our patient was then found to have CNS involvement. Treatment guidelines are lacking in MM with CNS involvement and particularly the role of B12 deficiency in the understanding of MM.

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Conflict of interest

All authors declare that there are no conflicts of interest.

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