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

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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. 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. 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. 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. 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. In patients with CNS involvement symptoms may include focal...
neurological deficits, impaired mental state, or
cognitive disability. There has been literature sug-
gesting 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 signif-
icant 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 present-
ing with B12 deficiency. There are no established
guidelines on treatment for leptomeningeal myelo-
matosis. 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 Amer-
ican male with past medical history of Hepatitis C
and sick sinus syndrome status post pacemaker
placement who presented with progressively wors-
ening bilateral lower extremity weakness of six
months in duration. He states that his bilateral
lower extremity weakness is associated with inter-
mittent 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 his-
tory 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, tempera-
ture, and light touch. There was no hep-
atosplenomegaly or lymphadenopathy detected. On
the initial basic metabolic panel, the patient had a
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 dis-
tribution width (RDW) 13.4%, platelets 166,000 mm³,
white blood cells 5.5 \times 10^9/mm³ with an absolute
neutrophil count (ANC) 3.71 \times 10^9/mm³. 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 enhance-
ment. There was also an enhancement along the
T12-L1, L1-2 and L2-3 neural foramen. A compres-
sion fracture of L5 was noted leading to marked
central stenosis with lateral recess stenosis bilater-
ally. 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 inflamma-
tory 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
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. 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. 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.\textsuperscript{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.\textsuperscript{7} Based on a review by Dispenzieri and Kyle, intracranial plasmacytomas or myelomas can be classified into four groups:\textsuperscript{1} lesions extending from the skull and pressing inward,\textsuperscript{2} lesions growing from the dura mater or the leptomeninges,\textsuperscript{3} lesions from the mucous membranes of a nasopharyngeal plasmacytoma, and\textsuperscript{4} intraparenchymal lesions not arising from any of these other sites.\textsuperscript{6} Leptomeningeal involvement is the most common form, often leading to nerve root infiltration and cerebral nerve palsies.\textsuperscript{7} Leptomeningeal metastasis can be diagnosed by either magnetic resonance imaging (MRI) and/or evidence of malignant cells in CSF cytology.\textsuperscript{5}

Vitamin B12 deficiency has been associated with MM through various postulated mechanisms that are still not completely understood.\textsuperscript{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.\textsuperscript{3} Pernicious anemia has been associated with IgG and IgM kappa type of paraproteinemia along with IgA myeloma.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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