MULTIPLE MYELOMA AND EXTRAMEDULLARY MANIFESTATIONS - A case Report

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Abstract:
Plasma cell myeloma is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin and usually presents with the classical CRAB (hyperCalcemia, Renal failure, Anemia, Bone lesions) symptoms. Extramedullary disease in plasma cell disorders can be either solitary plasmacytomas of bone (SBP) or multiple myeloma with extramedullary plasmacytomas (EPMM). We report the case of a 58 year old man who had a lesion in the patella followed by lesions in the pleura and lung, all of which were histopathologically confirmed to be myeloma. He also had the classical CRAB symptoms, though this was one of the latest manifestations. Extramedullary manifestations at diagnosis or during the course of multiple myeloma are rare with a cumulative incidence of 4.6 of multiple myeloma. Special characteristics, prognosis and treatment options are discussed here.

Keyword: multiple myeloma extramedullary manifestations

MULTIPLE MYELOMA AND EXTRAMEDULLARY MANIFESTATIONS

INTRODUCTION
Plasma cell myeloma is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin and usually presents with the classical CRAB symptoms. Extramedullary disease in plasma cell disorders can be either solitary plasmacytomas of bone (SBP) or multiple myeloma with extramedullary plasmacytomas (EP/MM). These are both uncommon presentations and can result in delay or misdiagnosis. We report one such case where a patient with multiple myeloma presented with multiple extramedullary lesions of the pleura and lung.

CASE REPORT
58 yr old male developed painful swelling and restriction of range of movements of the right knee eight months prior to presentation. He had no associated systemic symptoms. An MRI of the right knee was suggestive of patellar osteomyelitis. He underwent a curettage of the lesion and in view of conflicting
pathology reports the then treating surgeon went ahead with a patellectomy. He had an uneventful postoperative period and recovered to complete normalcy, independent for all activities of daily living, work and recreation.

Eight months later, he developed fever, high grade intermittent for a prolonged duration of one month. This was associated with severe fatigue, loss of appetite and significant weight loss. He also had pleuritic right sided chest pain with no cough, expectoration or haemoptysis. On clinical examination he was found to have pallor and tenderness in the right infra-axillary and infrascapular regions with normal breath sounds. Investigations revealed haemoglobin of 4.8 gm/dl, platelet count of 34,000/cu mm, normal total and differential count. S. Creatinine was 2.1 mg/dl. Chest X Ray showed a 3cm X 5cm pleural based nodule on the right side. He was transfused two pints of packed red cells and four platelet rich concentrates and was referred to our centre for further management.

At admission he had bicytopenia with renal failure and hypercalcemia. CT scan of the thorax revealed pleural based lesions on both left and right side of the chest (Figure 1).

**FIGURE 1**
Differentials considered were solid organ tumours like carcinoma lung with metastasis, lymphoproliferative malignancies or infections like tuberculosis lower down. Bone marrow examination was reported to have 99% plasma blasts (Figure 2).

**FIGURE 2**
Urine Bence Jones protein was positive and serum electrophoresis had a positive M band.
A diagnosis of multiple myeloma was made based on presence of classical “CRAB” symptoms of hypercalcemia, renal failure, anemia and bone involvement. CT guided biopsy of the pleural nodule was reported as syncitial sheets and solid growth of mature and immature plasma cells and blasts, consistent with myeloma. Hence a final diagnosis of multiple myeloma with extramedullary manifestations was made.
He was initiated on steroid and thalidomide based therapy with supportive conservative management of electrolyte imbalances and renal failure. His lab parameters normalized and he was discharged with the plan of initiating bortezumab based chemotherapy

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CASE DISCUSSION

Multiple myeloma (MM) is a B cell neoplasm of the bone marrow and accounts for 10%-15% of all hematologic malignancies, and 20% of deaths related to cancers of the blood and bone marrow (1).

Pathophysiology

Normally, ~5% of bone marrow cells are plasma cells; in multiple myeloma that level is elevated. There are different clones of plasma cells in the bone marrow, which make the numerous types of immunoglobulins (antibodies) needed for the immune system. In myeloma, the cancerous plasma cells are monoclonal and displace the bone marrow, causing some of the complications associated with the disease. These abnormal cancerous plasma cells make a similar immunoglobulin (monoclonal immunoglobulin, also called an M-protein). This can be of any type: IgG, IgA, IgD or IgE. IgG is, however, most common. Sometimes the cancerous plasma cells secrete only the light chains of the immunoglobulin, which are called monoclonal kappa and lambda light chains or Bence Jones proteins. Overall, approximately 70% of patients with myeloma will have elevated IgG, 20% IgA, and 5%-10% light chains only (Bence Jones protein). About 1% will have IgD, IgE, IgM or nonsecretory disease (cancerous plasma cells that do not secrete immunoglobulin). About 30% of the time there is an imbalance in the production of light and heavy chains, resulting in excess light chain production along with the monoclonal antibody. The underlying pathophysiological mechanisms include suppression of humoral and cell mediated immunity, elevation of IL-6, abnormalities of the bone marrow microenvironment, and increased osteoclastic activity.

Clinical presentation

Most patients with MM present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains. As an example, a retrospective analysis of 1027 sequential patients diagnosed with MM at a single institution found the following symptoms and signs at presentation(2):

- Anemia - 73 percent
- Bone pain - 58 percent
- Elevated creatinine - 48 percent
- Fatigue/generalized weakness - 32 percent
- Hypercalcemia - 28 percent
- Weight loss - 24 percent, one-half of whom had lost 9 kg

Although the typical clinical manifestations of multiple myeloma (MM) are summarized by the CRAB symptoms (hypercalcemia, renal insufficiency, anemia, and bone lesions), a significant proportion of patients with MM present with a variety of other clinical manifestations.

In a retrospective review of 170 patients with multiple myeloma, 74% presented with CRAB symptoms, 20% presented with non-CRAB manifestations, and 6% had both clinical features(3).

Ten categories of non-CRAB manifestations were found, in order of decreasing frequency:

- Neuropathy (because of spinal cord compression, nerve root compression, or peripheral neuropathy)
- Extramedullary involvement
- Hyperviscosity syndrome
- Concomitant amyloidosis (e.g., nephrotic syndrome or cardiomyopathy)
Hemorrhage/coagulopathy

Systemic symptoms (e.g., fever or weight loss)

Primary plasma cell leukaemia

Infections

Cryoglobulinemia

Secondary gout.

Extramedullary Manifestations

Extramedullary disease in plasma cell disorders can be either solitary plasmacytoma of bone or multiple myeloma with extramedullary plasmacytomas (EP, extraosseous plasmacytoma). Extramedullary (EM) localizations at diagnosis or during the course of multiple myeloma (MM) are rare with a cumulative incidence of 4.6% of MM (4). Multiple sites are usually involved. Commonly involved sites are liver, pleura, GI tract, lung, lymph nodes and skin. Most patients present with symptoms related to the location of the mass. Approximately 80 percent involve the upper respiratory tract (i.e., oronasopharynx and paranasal sinuses), producing epistaxis, nasal discharge (rhinorrhea), or nasal obstruction. Primary plasmacytoma of the lung often presents as a pulmonary nodule or hilar mass with or without hemoptysis (5). Regional lymph nodes may be involved.

Diagnosis

DIAGNOSTIC CRITERIA: ALL 3 REQUIRED (6)

[MC] Monoclonal plasma cells in the bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma

[MO] Monoclonal protein present in the serum and/or urine

Myeloma-related organ dysfunction (1 or more)

[C] Calcium elevation in the blood S. Calcium >10.5 mg/l or upper limit of normal

[R] Renal insufficiency S. Creatinine > 2 mg/dl

[A] Anemia Hemoglobin < 10 g/dl or 2 g < normal

[B] Lytic bone lesions or osteoporosis

Treatment

Autologous hematopoietic cell transplantation (HCT) either single or tandem is a standard treatment for patients with multiple myeloma, but a number of patients are not eligible for HCT due to poor performance status and/or the presence of comorbid conditions (7). Amongst patients not eligible for HCT, they are divided into symptomatic standard risk and symptomatic high risk and accordingly appropriate chemotherapeutic regimens are decided on. Preferred treatment for the standard risk group includes regimen consisting of melphalan, prednisone, and thalidomide (MPT) or bortezomib, melphalan, and prednisone (VMP) (8). Among patients with symptomatic high risk MM who are not candidates for autologous HCT, a bortezomib-containing regimen such as bortezomib, melphalan, and prednisone (VMP) or bortezomib, cyclophosphamide, dexamethasone (VCD) is recommended (9). Lenalidomide plus dexamethasone (len/dex) is the preferred initial therapy for patients who are candidates for HCT, since therapy is highly effective and well tolerated.
DIFFERENCE BETWEEN SOLITARY PLASMACYTOMA OF BONE AND MULTIPLE MYELOMA WITH EXTRAMEDULLARY MANIFESTATIONS

Extramedullary disease shows a poor response to chemotherapy with a very low response rate to thalidomide. The prognosis is very poor (10), especially when the diagnosis of EM tumour is concurrent with the diagnosis of MM (11). Solitary plasmacytomas of the bone on the other hand are localized plasma cell tumour of the bone in the absence of systemic features of multiple myeloma. Primary treatment is localized RT at curative doses of 40 to 50 GY. Surgery is indicated when there is bone instability or compression. Local response rate is 90% and overall survival is 10yrs but 85% (12) progress to MM by end of 10 yrs.

There is possibility of whether the use of high dose chemotherapy is responsible for increased incidence of extramedullary manifestations of multiple myeloma, but this has not been shown to be true in multiple studies and treatment for this aggressive disease remains high dose chemotherapy and biologicals in those not considering bone marrow transplantation.

CONCLUSION

Extramedullary manifestations of multiple myeloma are increasingly seen presentations of aggressive multiple myeloma. Such presentations are a deviation from the well described CRAB symptoms and hence diagnosis may be delayed as in our case and can result in advanced florid disease at the time of recognition. Hence multiple myeloma should be kept in the list of differentials in any bony lesion or soft tissue tumour especially in the elderly (13).

REFERENCES


