Case report

Raised β2-Microglobulin as a Surrogate Marker in Non-Secretory Multiple Myeloma

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Abstract:
Multiple myeloma is a neoplasm of plasma cells in the bone marrow. It is characterised by lytic lesions in the bones, marrow plasmacytosis and presence of M protein in serum and/or urine. Serum β2 microglobulin is also raised and can be used for classification and prognostication of the disease. In the absence of M protein, the disease is known as non-secretory myeloma. It is proposed that raised β2 microglobulin can be used for diagnosis and therapeutic guidance in the absence of M protein. A rare case of nonsecretory myeloma with neurocognitive impairment along with review of literature is being presented. The patient had multiple lytic lesions in bones with marked increase in plasma cells in bone marrow. M protein was not detectable in serum or urine but serum β2 microglobulin was much elevated.

Key words: nonsecretory myeloma, neurocognitive impairment, β2 microglobulin

Introduction:
Multiple myeloma is a monoclonal neoplasm of plasma cells in the bone marrow characterised by the presence of monoclonal immunoglobulin (Ig) or Ig fragments in the serum and/or urine. It is a disease of the elderly and median age at diagnosis is 68 years. Important symptomatology of this neoplasm ranges over the hematological (anaemia, occasionally clotting abnormalities, manifestations of hyper viscosity, susceptibility to infections), skeletal (bony pains or fractures), renal and neurological manifestations. The triad of symptoms which is a strong indicator of multiple myeloma includes marrow plasmacytosis (>10%), lytic bone lesions and serum and/or urine M component. M component is found in majority of cases by IgG (55%), followed by IgA (9%) and rarely by IgM, IgD and IgE. Detection of free light chains in urine in the form of Bence-Jones protein also serves as a useful tool in diagnosis of myeloma. However, in around 1-5% of cases serum and/or urine M spike is not seen and such myelomas are known as non-secretory multiple myeloma. Hence, absence of M protein does not completely rule out the diagnosis. Besides M protein, beta 2 microglobulin (β2M) is also elevated in multiple myeloma. β2M is a light chain protein (11.8 kDa in size) present on cell surface. Raised level of β2M reflects increased cell turnover. It may also be elevated in other lymphoproliferative and myeloproliferative disorders. It is also used in staging and prognostication of multiple myeloma. A patient who presented with impaired sensorium was found to have multiple lytic lesions in the bones and marrow plasmacytosis. M protein was not detectable in serum protein electrophoresis. The patient was diagnosed as a case of nonsecretory myeloma associated with very high serum β2M level.

Case Presentation:
A 60- year old male presented with complaints of fever for 1month and altered mental status for 20 days. Fever was documented at home to be...
intermittent and low grade and reported to be relieved with medication but to recur on and off. There were no associated chills, rigor, or diurnal variation and night sweats. The patient did not give the history of symptoms associated with respiratory, urinary, or eye, ear, nose and skin infection. The family members gave a history of diminished responsiveness to oral commands, lethargic with decreased personal care and decreased oral intake for the past 20 days. Patient was a vegetarian, non-smoker, non-alcoholic, non-diabetic, non-hypertensive, non epileptic with normal bladder and bowel habits. There was no history of substance abuse. On examination patient was drowsy but arousable with Glasgow coma scale 10/15. The vital signs showed normal blood pressure (114/72 mm of Hg), pulse rate (94/minute, regular) and respiratory rate (22/min). The patient was febrile on presentation with temperature of 100°F. On general physical examination the BMI was 22.22 kg/m² (weight and height were 72 kgs and 1.80 m respectively) and patient was pale. A detailed neurological examination was performed which revealed severe cognitive impairment with Mini mental state examination score: 16 and Abbreviated mental test score: 5 (≤7/10 suggests cognitive impairment). Confusion assessment method was highly suggestive of delirium. Examination of cranial nerves, motor system, sensory system and cerebellar functions did not reveal any abnormality. Cardiovascular, respiratory, abdomen, musculoskeletal and genitourinary system examination was unremarkable.

Investigations revealed hemoglobin of 8.4 gm/dl, a total leukocyte count of 4400/mm³, ESR-24, platelet count was 1.5 lacs/mm³, peripheral blood film showed microcytic hypochromic anemia without any atypical cells or hemoparasite. The X-ray of chest, electrocardiogram, and fundus examination were normal. Liver function tests, random blood sugar, urine routine and microscopic examination, and thyroid function test were within normal range. Urine and blood culture were sterile. Blood Widal test, serum HBsAg, anti-HCV and HIV tests were negative. Renal functions were seen to be deranged with a blood urea of 98.97 mg/dL and creatinine of 4.36 mg/dL, serum calcium 10.82 mg/dL and uric acid 9.75 mg/dL. Ultrasonography of the abdomen revealed early acute renal parenchymal disease, X-ray skull lateral view revealed multiple lytic bone lesions (Figure 1). As delirium worsened MRI brain and lumbar puncture was done, in which cerebrospinal fluid(CSF) was normal for glucose, protein, total leukocyte count, differential leukocyte count, cytology, gram staining and adenosine deaminase, negative for AFB staining and CSF culture was sterile. The MRI report of brain was normal except for senile atrophy. Urine examination for Bence-Jones proteins was inconclusive. Serum and urine protein electrophoresis were normal with no M-spike. Serum beta microglobulin level was 21806.00 µg/L (normal range: 670-1310 µg/L). Bone marrow aspiration showed marked increase in plasma cells (60%) with many immature plasma cells which are binucleated to multinucleated and many plasmablasts which confirmed the diagnosis of multiple myeloma (Figure 2). A diagnosis of non-secretory multiple myeloma was made based on multiple lytic lesions in skull associated with marrow plasmacytosis, high β2-microglobulin and absence of M-spike in urine and serum protein electrophoresis. The patient was started on thalidomide and dexamethasone along with symptomatic therapy. The neurocognitive symptoms and hematological parameters improved initially but
later he developed severe coagulation derangements (i.e. hematuria) with significant prolongation of prothrombin time. Patient developed impaired sensorium and died on the 20th day of hospitalization.

**Discussion**

Multiple myeloma is a clonal proliferation of plasma cells. The interaction between abnormal plasma cells and stromal cells in bone marrow leads to increased IL-6 secretion and decreased apoptosis. Accumulation of plasma cells in bone marrow is a characteristic feature of multiple myeloma. In some countries such as United States multiple myeloma is seen to be accounting for 15% of all hematological malignancies. The disease is characterized by osteolytic bone lesions, M protein in serum and/or urine electrophoresis and marrow plasmacytosis. Non-secretory variant is rare and accounts for only 1-5% of all cases of myeloma. For simplicity non-secretory multiple myeloma can be considered as cases of multiple myeloma without identifiable M protein in serum and/or urine. Non-secretory multiple myeloma has been further divided into producers and non producers. In the producers, the plasma cells are producing immunoglobulin but they are not secreted out of the cells. According to some previous studies available in literature, most cases of non-secretory multiple myeloma are producers. Other studies proposed that even if the immunoglobulins are secreted, they are being rapidly degraded. More sensitive tests like immunoelectrophoresis, immunofixation may help in detecting M proteins leading to recategorizing of some of the non-secretory cases into typical multiple myeloma.

The patient had osteolytic bone lesions and >50% plasma cells in bone marrow. There was no M protein identifiable on serum protein electrophoresis but serum β2 microglobulin was grossly elevated. Considered in isolation, raised β2 microglobulin level may not be specific but in the presence of osteolytic bone lesion and marrow plasmacytosis it helps in staging and prognostication of the case. The patient had cognitive impairment but MRI of brain was normal except for minor diffuse cerebral atrophy. The cause of encephalopathy in our patient may be multifactorial including hyperviscosity, hypercalcemia and renal dysfunction. Fassas et al retrospectively reviewed 18 cases of multiple myeloma with neurological manifestation, out of which one was nonsecretory. Schulterman and Fassas et al further reviewed their case series of multiple myeloma with CNS involvement. They had studied 23 cases of multiple myeloma with central nervous system involvement. The median survival was only 1.5 months. Presence of plasma cell in CSF confirms the leptomeningeal involvement but plasma cell may be absent in some cases and sometime repeated CSF examination is required to confirm the diagnosis. CSF examination was performed only once in our case and plasma cells were not present. Coagulopathy was a terminal event in our patient. Intracerebral haemorrhage could be a contributory factor but could not be confirmed as brain imaging was not repeated.

There are different views about prognosis in non-secretory multiple myeloma. Drecier and Alexanian have studied 29 cases of non-secretory multiple myeloma and found that when tumour mass was low median survival was long. Rubio-felix et al reported early deaths in 2 out of 5 non-secretory multiple myeloma case they studied. The prognosis is extremely poor in patients of multiple myeloma with neurological involvement.

Batallie et al reported that serum β-2 microglobulin level decreased with response to chemotherapy and was comparable to that of fall in paraprotein levels. In our patient β-2 microglobulin was very high (21.8 mg/l), placing it in stage III as per international staging system for multiple myeloma (stage III β-2 microglobulin >5.5 mg/l). β-2 microglobulin has homology to the constant region of immunoglobulins and is increased in multiple myeloma and also in renal failure. Cassuto’s correction can be used to prognosticate for multiple myeloma in presence of renal failure, but medical research council’s working party on leukemia in adults have proposed that serum β-2 microglobulin, uncorrected for serum creatinine is a better prognostic indicator than corrected one.

In absence of M protein, the diagnosis of multiple myeloma requires demonstration of 30% of plasma cells in the bone marrow in patients with nonsecretory myeloma. The chemotherapy response becomes difficult to assess but β-2 microglobulin can be used for prognostication and sequential serum β2M level can be used in evaluating the therapeutic response in patients with non-secretory multiple myeloma. The short survival in our patient did not allow for any major therapeutic measures. However, the importance of β2M in the prognosis and follow-up of this condition should be kept in mind.
Raised β2-Microglobulin surrogate marker

References


