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Non-Secretory Multiple Myeloma- A Diagnostic Dilemma: A Case Report

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ABSTRACT

Nonsecretory myeloma, which comprises 1-5% of all myelomas, is a variant of plasma cell myeloma. It is defined as symptomatic myeloma without detectable monoclonal immunoglobulin levels on serum or urine immunofixation electrophoresis. It often poses diagnostic dilemma with no clear features of the disease. Our case report examplifies such a diagnostic dilemma. We report a case of nonsecretory plasma cell myeloma that manifested as nonspecific backpain and lytic skull lesions. Due to the inability to detect monoclonal immunoglobulin on serum or urine immunofixation electrophoresis it was difficult to establish an early, accurate diagnosis. A high index of suspicion must be borne in mind when excluding multiple myeloma as a cause of pain, pathological fracture or osteolytic lesion. Misdiagnosing or mislabeling symptomatic myeloma patients results in the delay of their systemic treatment. Therefore, comprehensive imaging studies, the detection of free light chains, and histopathological confirmation from different sites and time points are necessary.

Keywords: Nonsecretory multiple myeloma; osteolytic lesions; plasma cell disorders; free light chains.

INTRODUCTION

According to the World Health Organization (WHO) classification system, the diagnosis of symptomatic myeloma is based on the pathological proof of plasmacytoma or the presence of bone marrow clonal plasma cells and end-organ damage, such as anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis, or recurrent infections. For patients that fulfill the above criteria, a minimum level of monoclonal proteins (M-protein) or percentage of bone marrow plasma cells is no longer necessary.

Symptomatic myeloma without detectable monoclonal immunoglobulin (Ig) levels on serum or urine immunofixation electrophoresis characterizes nonsecretory myeloma by the WHO definition. This diagnosis constitutes 1-5% of all myeloma patients.[1] By immunohistochemical analysis, 85% of patients with cytoplasmic M-protein are nonsecretors and the other 15% are nonproducers. Meanwhile, the detection of free light chains (FLC) has made true nonproducers even rarer than before.[2]

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The manifestations and survival outcomes of nonsecretory myeloma are similar to those of the secretory types, with the exceptions of improved hemoglobin levels, a less aggressive clinical evolution, lower incidences of renal insufficiency and hypercalcemia, improved Ig levels, and the decreased occurrence of osteolytic lesions.[3,4] A search for "non-secretory multiple myeloma" in the PubMed, yielded less than 80 case reports since 1972. These patients are often a diagnostic dilemma and a high index of suspicion should be borne in mind, especially in a patient with osteolytic lesions. This uncommon presentation may lead to delay in diagnosis if presented to medical specialist. We present a case report of a patient who presented to us with back pain and was subsequently diagnosed with nonsecretory multiple myeloma.

CASE REPORT

A 70 year female came to our outpatient department complaining of generalized body aches, low grade fever, weight loss and pain in right lumbosacral region. There was no history of trauma or history suggestive of any significant medical co-morbid conditions.

Examination revealed tenderness on the right side of the lumbosacral spine and right sacroiliac joint. There was para vertebral muscle spasm with loss of

lumbar lordosis. Hip movements were normal with no major disability. There were no root stretch signs and no neurological deficit was noted.

MRI screening of whole spine revealed minimal bulges of annulus of C3-4, C6-7, L3-4 and L5-S1 causing indentation on thecal sac. Other investigations revealed as Hemoglobin(Hb) 8.2gm %,total leukocyte counts of 4300/cumm, differential counts showing 58% polymorphonuclear cells,32% lymphocytes, 4% eosinophils, 4% monocytes,2% blast cells, platelet counts of 2,20,000/cumm. Peripheral smear revealed normochromic, normocytic red blood cells. Erythrocyte sedimentation rate(ESR) was 36mm/first hour, normal renal and liver profile with serum alkaline phosphate levels of 156 IU/L, Total serum proteins-6.0gm/dl,albumin-3.1gm%,and globulin-2.9gm%,S.calcium-10.9mg%,S. LDH-601 IU/L. Serology for Australia antigen, Anti-HCV IgM and HIV-1 and 2 were negative.

Considering nonspecific systemic complaints, backache, age of patient, normochromic normocytic anaemia, mild hypoalbuminemia and mild hypercalcemiam, myeloma screening was done which did not reveal presence of any abnormal compact bands in serum protein electrophoresis and there was no Bence-Jones proteinuria. X-ray skull showed small multiple lytic bony lesions. Serum beta 2 microglobulin levels were found to be raised with levels of 4129ng/ml (Reference value-609-2365 ng/dl). Hence the diagnosis of nonsecretory multiple myeloma was made.

Bone marrow aspiration showed normocellular marrow with mildly megaloblastic erythropoiesis with plasma cell 02%.Bone marrow biopsy revealed moderately hypercellular marrow with focal sheets of 6-9 atypical plasma cells, 12% intermediate atypical myeloma cells and no metastatic deposits. Kappa free light chain in serum were raised with a value of 62.4mg/l (Reference value-3.3-19 mg/L).Lambda free light chains in serum were of normal with a value of 19.9mg/l(Reference value 5.7-26.3mg/L) with increased Kappa/Lambda ratio of3.14(Reference value 0.62-1.62).

DISCUSSION

Western literature reveals that the incidence of multiple myeloma is 01% of all malignancies in the white population and 02% in blacks.[5] Among haematological-malignancies, it constitutes 10% of the tumours, second in frequency to non-hodgkin's lymphoma.[6] Among the varied presentation 10-40% is asymptomatic and 50-70% will have bony pain due to lytic lesions and pathological fractures.[7] A high index of suspicion should be kept in mind to avoid diagnostic delay.

Nonsecretory myeloma is a rare variant (1-5%) of multiple myeloma characterized by absence of detectable M protein in serum and urine.[1] Some researchers have further classified the nonsecretory myeloma based on the finding of intracytoplasmic immunoglobulin. They separated them into two types - nonproducer type (about 15%) where immunoglobulin was not found in plasma cells and in the remaining 85% called producer type the immunoglobulin is demonstrable in plasma cells but not in blood.[1,2]

Multiple myeloma is diagnosed on the basis of major and minor criteria comprising tissue diagnosis, monoclonal gammopathy, bone marrow plasmacytosis, lytic bone lesions, and suppressed uninvolved immunoglobulins.8 This system has drawbacks in that some patients with disease-related symptoms might not meet the criteria for myeloma because of a low marrow involvement and/or Monoclonal (M)-protein. More recently, International Staging System (ISS) for multiple myeloma has been established on the two of most powerful prognostic factors in multiple myeloma i.e. beta 2 microglobulin and serum albumin levels.[9] About 5 - 10% of symptomatic patients may have less than 10% of plasmacytosis.[8] The diagnostic dilemma may be resolved in such cases with tissue diagnosis, lytic bone lesions, sensitive serum free light chain assays and raised serum levels of beta 2 microglobulinemia (in the absence of renal failure).[10,11]

The presenting features of non-secretory myeloma, response to therapy and survival are similar to those of patients with measurable M-proteins.[4] However, there is bound to be some delay in diagnosis as they do not demonstrate the paraprotein in blood or urine which may shorten their survival This patient was symptomatic and was diagnosed with help of serum free light chain assay and hence was a producer but non-secretor. She responded very well to thalidomide and dexamethasone along with bisphosphonate with subjective improvement of her symptoms and lowering of serum levels of beta 2 microglobulin.

CONCLUSION

In conclusion, absence of paraprotein in the blood does not exclude multiple myeloma. Though doing a bone marrow biopsy routinely in all cases with suspected multiple myeloma can put extra strain on the hematology department, we recommend consultation with hematologist when diagnosis of multiple myeloma is strongly suspected, in the absence of any abnormal protein in blood and urine,and use of serum free light chains to avoid delay in diagnosis and treatment.

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