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Case Report

NON SECRETORY MULTIPLE MYELOMA – A CASE REPORT

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ABSTRACT
Multiple myeloma is characterized by clonal proliferation of plasma cells usually B cell type. The skeletal manifestations are usually osteolytic lesions whose differential diagnosis includes primary and secondary bone tumor or metabolic bone disorder. The tumor is characterized by the presence of abnormal paraprotein in blood and urine. However, one to five percent of the cases do not have protein. Hence they are termed non secretory. It often poses diagnostic dilemma with no clear features of the disease. Our case report exemplifies such a diagnostic dilemma. A high index of suspicion must be borne in mind when excluding multiple myeloma as a cause of pain, pathological fracture or osteolytic lesion.

Key Words: *Multiple Myeloma, Paraprotein, Plasma Cells.*

INTRODUCTION
Multiple myeloma is a malignant proliferation of plasma cells within the bone marrow with production of monoclonal immunoglobulins detectable in serum and/or urine. It is the most common primary tumor of the bone, about 27% of the biopsied tumors. Measurement of immunoglobulins has been the standard for the diagnosis, prognosis and management. However, in about one to five percent of the cases no protein can be detected and these patients are known to have non secretory type of myeloma (NSMM). A high index of suspicion must be borne in mind especially in patients with osteolytic lesions.
While some author consider NSMM as an entity that secretes neither entire immunoglobulin nor immunoglobulin light chains. Others assume that all the ones that do not have the M protein in electrophoresis can be classified as NSMM, in spite of having small elevations of monoclonal free light chains in serum and /or urine.
In some cases, plasma cell fail to produce or secrete an immunoglobulin, so there is no monoclonal spike. In other cases, there is lack of a detectable M protein because the cell does not produce entire immunogolbulin but a monoclonal free light chain peak detected in serum or urine, using techniques other than routine electrophoresis like immunoelectrophoresis or immunofixation.
Treatment of secretory and NSMM are similar and prognosis is also identical (Abd, 2002).

CASES
A 42 years old male presented with abdominal pain and vomiting for 3-4 months. Complained of pain in rib.

Radiological Findings
F18-FDG whole body PET CT scan report: Multifocal skeletal lesions suggestive of metastases with hypermetabolic focus at the gastroesophageal junction that needs to be investigated further to rule out the site of occult primary.
Bone scan showed multiple osteolytic lesions favoring Paget's disease. On investigation parathyroid hormone was normal and Paget's disease was excluded. Next suspicion was metastatic lesions.

Laboratory Findings
Hemogram: HB: 11.7 gm%; PCV: 34.8%; MCV: 82.9 fl; MCH: 27.8 pg; WBC: 7,100/cumm; Platelets: 2, 26, 000/cumm; PBS: Normochromic Normocytic; ESR: 62 mm/1 hour.

Biochemical Findings
Serum Calcium-14.6 mg/dl was high (normal 8.4-10.2 mg/dl); Phosphate-4.9 mg/dl (normal 2.5-5.0 mg/dl); Alkaline phosphatase-135 IU/L(normal 20-130 IU/L); PTH-13.4 pg/ml (normal 12-72 pg/ml);

Vitamin D-12.5 ng/ml(normal >40-100 ng/ml); Beta 2 microglobulin-16,479 ng/ml (normal 670-2143 ng/ml).

Protein Electrophoresis

M band- Monoclonal band not seen. Urine Bence Jones protein- not detected.

Quantitative Immunofixation

Total protein-7.7 gm/dl(normal- 6.4-8.2 gm/dl); Albumin-4.04 gm/dl (normal- 3.57-5.42 gm/dl); Alpha-1 globulin-0.36 gm/dl (normal 0.19-0.40gm/dl); Alpha 2 globulin- 1.09 gm/dl was mildly high(normal 0.45-0.96 gm/dl); Beta 1 globulin-0.41 gm/dl(normal 0.30-0.59 gm/dl); Beta 2 globulin-0.55 gm/dl was mildly high(normal 0.200.53 gm/dl); Gamma globulin-1.24 gm/dl (normal 0.71-1.54 gm/dl); A:G-1:1(normal 1.1-2.2).

Immunoglobulins

IgG-1280 mg/dl(normal- 700-1600 mg/dl); IgA- 241 mg/dl (normal 70-400 mg/dl); IgM-48.50 (normal 40-230 mg/dl); Free Kappa- light chain-120 mg/L was high(normal 3.3-19.4 mg/L); free Lambda light chain-14.30 (normal 5.71-26.3); Free Kappa/ Lamba ratio-8.39 (normal 0.26-1.65); Monoclonal band was not seen.

In view of bone pain, multiple bony lesions, multiple myeloma screen normal, PET CT scans report-hypermetabolic focus at the gastroesophageal junction that needs to be investigated further to rule out site of occult primary.

Endoscopy was done. No definite lesion identified but still stomach biopsy was taken from suspicious area- which was reported as – mild dysplasia, no evidence of malignancy. A bone marrow aspiration and trephine biopsy was taken from rib lesion.

Microscopy

Bone Marrow Aspiration: Normal marrow cells were replaced by atypical cells which appeared plasmablastic with bi- and multinucleate forms. Few erythroid, myeloid and megakaryocytic cells seen and all three series cells were suppressed.

Bone Marrow Trephine Biopsy: showed hypercellular marrow, with marked proliferation of plasmablastic atypical cells noted with presence of few erythroid, myeloid and megakaryocytic cells-which were relatively suppressed. Another focus with normal appearing haemopoiesis was also noted which explained the normal hemogram on presentation.

Immunohistochemistry was needed to confirm the diagnosis as metastatic tumor was also in the differential diagnosis. LCA, CD3 & CD20 showed background positivity. The atypical tumor cells were diffusely & strongly positive for CD138, confirmed with presence of plasmablasts and the diagnosis multiple myeloma- non secretory type. Free light chain report was available when the bone marrow biopsy report was already confirming the multiple myeloma diagnosis.

Treatment

Patient was treated with chemotherapy.

DISCUSSION

Multiple myeloma is a disorder of the bone marrow which accounts for 10-15% of all blood cancers and 1% to 2% of all malignancies (SES, 2009). Among the varied presentation, 10-40% is asymptomatic and 50-70% will have bony pain due to lytic lesions and pathological fractures (SES, 2009). A high index of suspicion should be kept in mind to avoid diagnostic delay.

These tumors are characterized by proliferation of malignant plasma cells in the bone marrow and most often associated with production of monoclonal immunoglobulins (M-component) secreted in blood and urine. The protein is detected by serum electrophoresis. In about 1 to 5 % of the cases, these may not be demonstrated and these cases are termed as non-secretory multiple myeloma (Ana, 2011).

Non secretory multiple myelomas were first described in 1958 by Serre (Ana, 2011). Since then numerous case reports have appeared describing variations in microscopic appearances of the tumor. It has been postulated that there may be reduced protein synthesis or increase in breakdown of abnormal

immunoglobulin chains intracellular or extracellular. Immunoglobulin is synthesized but not secreted possibly due to reduced permeability of intracellular transport of the light chains. It may mean that there may be intermittent excretion of immunoglobulin evading detection. With increased sensitivity of detection of M-protein and the development of new techniques for detection of small amounts of free light chains in the serum and urine, the diagnosis of true NSMM is decreasing (Ana, 2011)

Some researchers have further classified the non-secretory myeloma based on the finding of intracytoplasmic immunoglobulin. They separated them in two types, non-producer (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 the blood.

The above patient was classic case of non-secretory myeloma and meets the criteria laid down by international myeloma working group. It was also a diagnostic dilemma as other disorders like secondaries, hyperparathyroidism can present with similar picture. Patient with NSMM seem to have less incidence of renal insufficiency presumably because light chains are not being secreted in the urine. Once diagnosed, treatment remains the same as for multiple myeloma. The response to treatment and prognosis remains the same. Arguments have been placed in earlier reports about patients with NSMM having better survival rates because of their early presentation and absence of renal insufficiency. However, there is bound to be some delay in the diagnosis as they do not demonstrate the paraprotein in blood and urine which may shorten their survival. Hence high index of suspicion should be kept in mind.

Conclusion

In conclusion, absence of paraprotein in the blood and urine does not exclude multiple myeloma. Comprehensive image studies and histopathological confirmation at different sites are necessary for diagnosing patients suspected of having plasmacytoma.

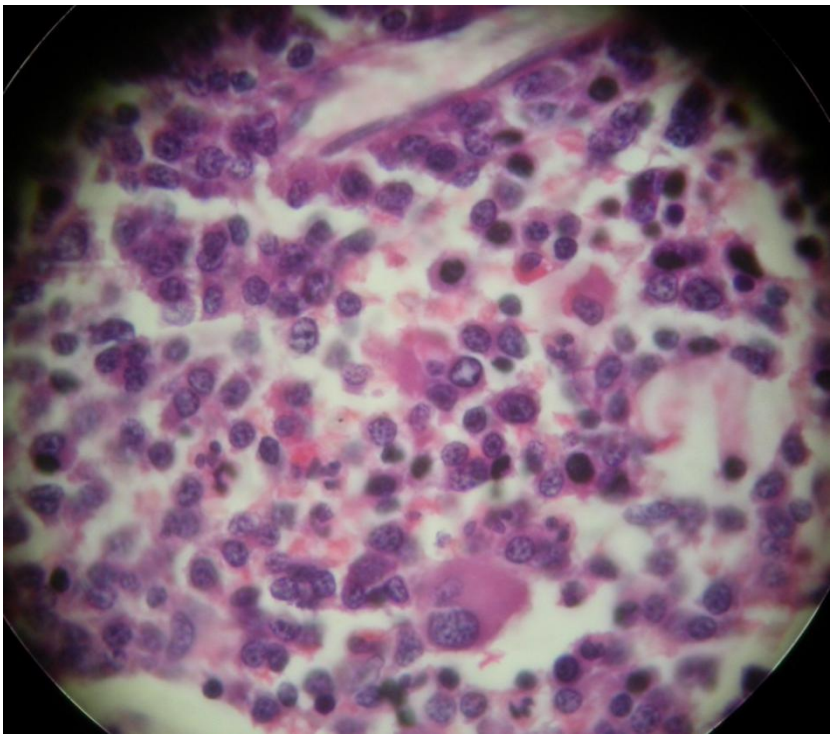

Figure 1: Bone Marrow Trephine Biopsy: Hypercellular marrow showing proliferation of plasmablastic cells with all three series of cells – erythoid, myeloid and megakaryocyticcells which are relatively suppressed.

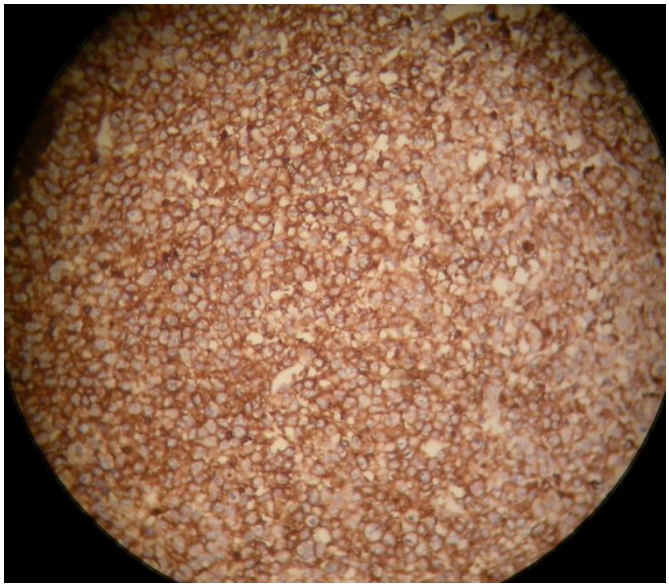

Figure 2: Immunohistochemistry for CD 138 shows positivity in plasmablastic cells.

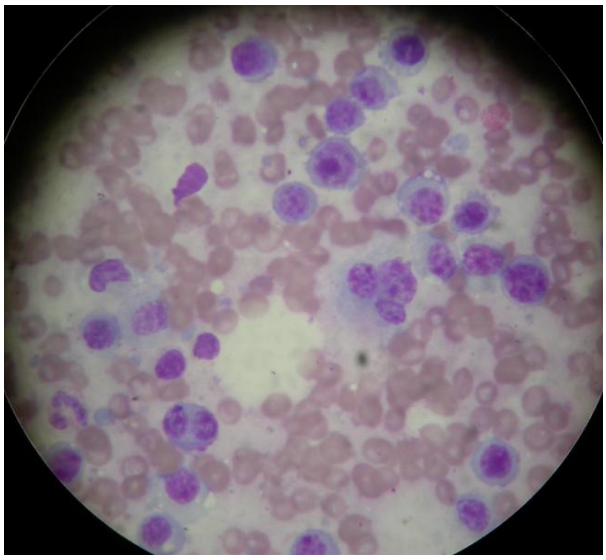

Figure 3: Bone marrow aspirate: Majority of cells appear as atypical plasmablastic cells with bi and multinucleate cells.

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