Research Paper

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Smoldering Multiple Myeloma

Medical Science

Keywords : Plasma Cell Dyscrasias, Serum Protein Electrophoresis, Immunofixation, Bone Marrow Aspiration And Trephine Biopsy.

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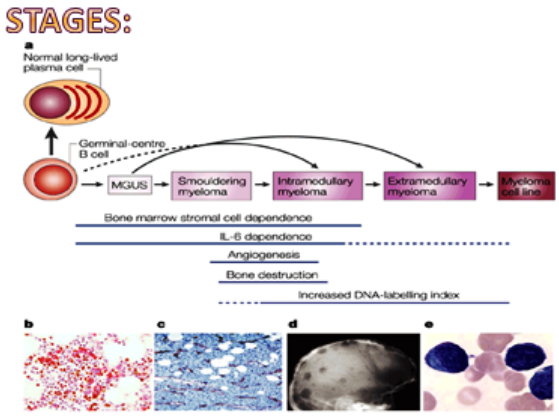
ABSTRACT

68 year old female patient presented with complaint of persistent weakness and pedal oedema.Her hemoglobin level was fluctuating between 8-10gm% which was not improved even after blood transfusion , iron and folic acid supplements.We ruled out all possible causes of pedal oedema.Total Protein ,Albumin , Globulin and A/G ratio was done. Globulin was 6.3gm%(increased).A/G ratio was reversed.ESR was markedly elevated.Protein electrophoresis was done which showed M-Band.Bone marrow showed 22% of plasma cells.Trephine biopsy was done which showed interstitial infiltrate of about 20% of plasma cells.S.creatinine ,S.calcium were normal.X-ray skull,pelvis and hip joint were normal.Diagnosis of Smoldering multiple myeloma was put. Patient was put on Dexamethasone and pamidronate.She was followed after 3 months with protein electrophoresis and other biochemical reports.

INTRODUCTION:

Plasma cell dyscrasias is a neoplastic proliferation of plasma cells with production of immunoglobulin .It is subclassified in 2 groups:1)Malignant proliferation: MM,Waldenstrom- macroglobulinemia,Plasmacytoma,Heavy- chain disease.2)Relatively benign proliferation:Monoclonal gammopathy of undetermined significance,Primary systemic amyloidosis.(12)Benign disorders are important since there is increased risk of their transformation to multiple myeloma.Stages of development of multiple myeloma is as follow.(12)



Median age of presentation is 65years.Men :Women ratio is 3:2(7).Most common presenting feature is anemia related to direct infiltration and replacement of bone marrow.HB concentration is directly related to % of myeloma cells in S phase.Erythropoietin deficiency secondary to renal insufficiency may also contribute to it.Bone lesion may lead to persistent bone pain. Commonly involved bone is vertebra,ribs,skull,pelvis and proximal humerus. Pathologic fractures occur in multiple myeloma due to proliferation of plasma cells in the bone and secondarily to activation of osteoclasts. Proliferation is dependent on interleukin 6 (IL-6). Osteoclasts are activated by osteoclast activating factors (OAF) which is made by myeloma cells. These OAFS are mediated by various other cytokines including IL-1, lymphotoxin and tumor necrosis factor (TNF).(3)The lesions produced are lytic as opposed to blastic lesions. This destruction of bone can lead to hypercalcemia and should be suspected if a patient presents with bone pain, nausea, fatigue, constipation, polyuria or confusion(9).Free light chain proteinuria is a risk factor for renal insufficiency.Decreased level of polyclonal immunoglobulin is risk factor for infection which leads to fever.M-protein lead to bleeding from gums,respiratorytract,GIT.Amyloidosis lead to macroglosia,neuropathy and GIT problems(12).The importance of assessing for complications is the foundation of treatment. Common laboratory findings:Peripheral blood smear show normocytic normochromic aneamia,rouleux formation of RBCS with basophilic background due to high globulin level.Few plasma cells or plasmacytoid cells are also present.ESR is markedly elevated.(3,5,12)Bone marrow is hypercellular or normocellular. Myeloid and Erythroid cells are normal with normoblastic maturation.Megakaryocytes are normal.Hallmark of disease is increase in plasma cells cells vary from 30-90%.(12)Bone marrow biopsy show either infiltrative,focal or nodular,packed or paratrabecular pattern.Thinning of bony tabeculae with increased osteoclastic resorption of bone.Abnormal plasma cells are positive for CD38,CD138 and negative for CD19.Normal plasma- cells are CD19 positive.CD56 is strongly positive.Monoclonality can be demonstrated by using anti-kappa and anti-lambda chain marker.In short CD38,CD138 and CD45 is used to identify plasma cells and CD19,CD56 is used to differentiate between normal and malignant plasma cells.(6,12)Primary screening test for detection of M-protein is Serum protein electrophoresis.(3,5)A localised dense band with sharp margin in γ to α2 region indicates M-Band.Position of band indicates type of immunoglobulin .IGG is located in γ region and IGA is located in α2 region.Normal serum protein electrophoresis is as follow.(5)

Urine and Serum protein electrophoresis should be done in all cases of plasma cell dyscrasias.Immunofixation is required

for identification of nature of M-protein.Myeloma cells secrete monoclonal immunoglobulin.IGG is 60%,IGA is 20%.Quantification of monoclonal immunoglobulin is important for assessing the disease severity and response to treatment.It is done by Single radio- immuno diffusion.(4)Free light chain assay measures the amount of free kappa to lambda chain ratio(normal 0.26 to 1.65) ,Ratio <0.26 indicates Monoclonal lambda chain myeloma.If ratio is >1.65 indicates Kappa chain myeloma. Bence jones proteins are free light chain detected in urine by heat method or by Urine electrophoresis.(9)24 hour urinary protein should also be measured.Biochemical investigations are increased S. creatinine ,S.alkaline phosphatase normal or increased ,S.calcium is increased.S.β2microglobulin >6µg is associated with high tumour mass.Prognostic factors are S.β2-microglobulin,CRP,Plasma cell morphology, S.LDH, Marrow-involvement, Plasma cell labeling index,S.creatinine,Deletion 13q,11q, hypodiploidy,S.IL-6 level and Angiogenesis on bone marrow biopsy.(4,12)Predictor of progresssion to multiple myeloma are high plasma cell labeling index,IGA subtype,Urine M-protein >50 mg%. Treatment of multiple myeloma is divided into symptomatic relief and systemic chemotherapy. Treatment for bone pain consists of steroids (such as dexamethasone), hydration, bisphosphonates and radiation.

CASE REPORT:

68 year old female patient, known diabetic and hypertensive presented in out patient department with complaint of persistent weakness.HB was done which was fluctuating between 8-10gm% which was not improved even after blood tranfusion , iron and folic acid supplements.Patient was also complaining of Pedal oedema. Investigations were carried out to rule out all possible causes of pedal oedema.HB was 10gm%.Routine urinalysis was done which was normal.S. creatinine was 1mg%. Ultrasound was done which showed normal kidney size and echopattern.Thyroid function test results were normal.EKG and Echocardiogram was normal.However peripheral smear showed rouleux formation(FIGURE-1).ESR was markedly elevated.Then S.Protein was done.Total protein was 10.1gm% (N:6.6 to 8.3 gm%),S. Albumin was 3.8gm%(N:3.5-5.5gm%),S. Globulin was 6.3gm%(N:2-3.5gm%).A/G ratio was 0.6(N:0.9-2).Serum protein -electrophoresis and immunofixation was done which showed following results(FIGURE-2,3).Free kappa chain was 25.67mg%(N:3.30-19.40mg%),Free lambda chain was 226.28mg%(N:5.71-26.30mg%),Free kappa chain/Free lambda chain ratio was 0.11(N:0.26-1.65). Bone marrow aspiration was done which showed Plasmacytosis with 22% of plasma cells.Some atypical and immature plasma cells were also seen. (FIGURE4,5) Trephine biopsy was also done which showed interstitial infiltrate of about 20% of plasma cells.Bony trabecula was normal which was consistent with plasma cell myeloma. Urine for Bence jones protein was normal .X-ray skull ,X-ray pelvis with both hip joint was done to look for lytic lesion which showed normal results.Patient had been operated for carpal tunnel syndrome 2 years back.After all work up final diagnosis was put ,Smoldering multiple myeloma.Patient was reffered to oncologist for treatment .She was put on Dexamethasone and pamidronate.she was followed after 3 month with serum protein electrophoresis which showed following results.(FIGURE-6).S.Calcium was done which was 10.9mg%(8.6-10.3mg%),S. Creatinine was 1.07.IGG was 16.267(7-16gm%).Hb was 10.5gm%.

DISCUSSION:

In Smoldering multiple myeloma, Bone marrow plasma cells are 10-30%,No lytic lesion ,No myeloma related symptoms like renal failure ,No Hypercalcemia or tissue impairment.(6,12) Serum globulin was increased which is responsible for tendency towards rouleux formation and raised ESR.(6)Amyloidosis present in about 10-15% of patients of multiple myeloma which can cause carpal tunnel syndrome .Follow up Protein electrophoresis showed decreased band intensity as compare to previous report.The mechanism for steroids in multiple myeloma is not different from that in other cancers. Steroids cause inhibition of cytokines, mediators of the inflammatory response. Interestingly, alexanin et al. has shown that high dose dexamethasone is the most active single agent for treatment of myeloma and in inducing remission.(2)Pamidronate is a bisphosphonate for which the mechanism of action is to inhibit osteoclastic activity and reduce bone resorption. Berenson et al have shown the efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. In a study involving 392 patients, all of who were receiving chemotherapy; 196 of who received pamidronate and the remaining receiving a placebo. Those in the pamidronate group had significantly lower skeletal events 24% vs. 41%. Those that received pamidronate also had less bone pain and improved performance status and quality of life.(4) Another form of treatment is thalidomide. Thalidomide works as an anti-angiogenic drug therapy by inhibiting fibroblast growth factor and hence inhibiting vascularity. In myeloma it does this particularly in the bone marrow . This theoretically inhibits the physical progression of myeloma cells. Thalidomide is also believed to reduce TNF-α by accelerating the degradation of TNF-┌ encoding protein.(7)Singhal et al showed that using thalidomide in progressively increasing doses in refractory myeloma patients, led to a serum or urine paraprotein level decrease of 32 percent overall. These reductions were apparent within two months in nearly 80% of patients. Subsequent bone marrow showed decreased plasma cells along with increased hemoglobin levels.(11) In relapsing cases, VAD has been shown to be the treatment of choice; leading to remission in nearly 40% of patients.(1)In patients who had a response, survival was prolonged by one year. Interferon-α has been tested to assess maintenance of remission in multiple myeloma. In vitro it inhibits growth of plasma cells and in studies has induced remission in nearly 20% of patients. Studies however have been unclear and inconclusive regarding its role in remission. Stem cell transplantation is the most promising modality for long term disease free survival following chemotherapy. One study has shown greater than 4 years of remission in 7 of 90 patients treated with allogenic bone marrow transplant following chemotherapy. However this therapy option is limited to myeloma patients who have an HLA compatible relative and who are under 50 years old, as the rate of mortality with BMT can approach 40%.Finally patients with smoldering multiple myeloma requires follow up every 3 to 6 months and skeletal survey should be done once in a year.

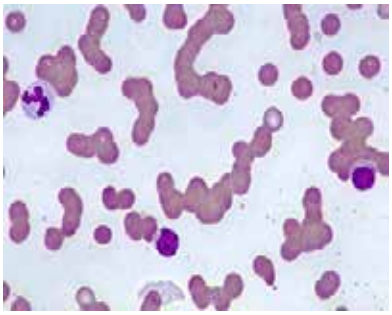


FIGURE- I ROULEUX FORMATION

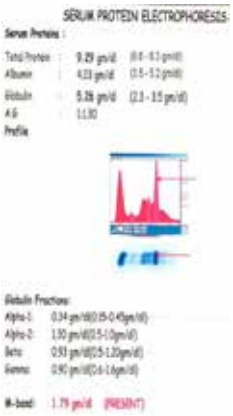


FIGURE-2
SERUM PROTEIN ELECTROPHORESIS

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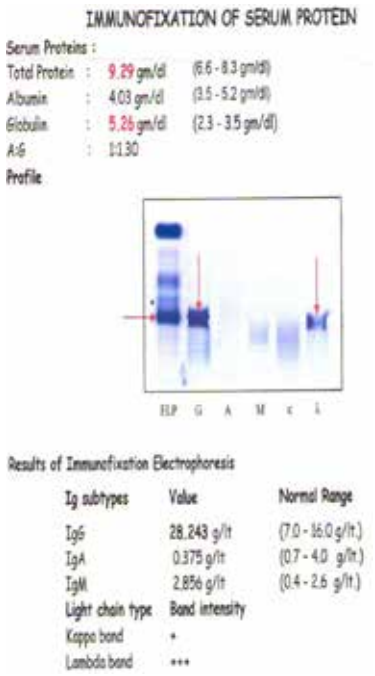

IMMUNOFIXATION OF SERUM PROTEIN

Serum Proteins :

Total Protein	:	9.29 gm/dl	(6.6 - 8.3 gm/dl)
Albumin	:	4.03 gm/dl	(3.5 - 5.2 gm/dl)
Globulin	:	5.26 gm/dl	(2.3 - 3.5 gm/dl)
A:G	:	1:1.30	

Profile

Results of Immunofixation Electrophoresis

Ig subtypes	Value	Normal Range
IgG	28.243 g/lt	(7.0 - 16.0 g/lt.)
IgA	0.375 g/lt	(0.7 - 4.0 g/lt.)
IgM	2.856 g/lt	(0.4 - 2.6 g/lt.)
Light chain type	Band intensity	
Kappa band	+	
Lambda band	+++	

FIGURE -3
SERUM PROTEIN IMMUNOFIXATION

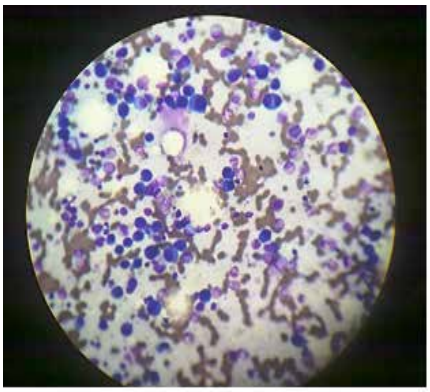


FIGURE-4
BONE MARROW ASPIRATION(40X)

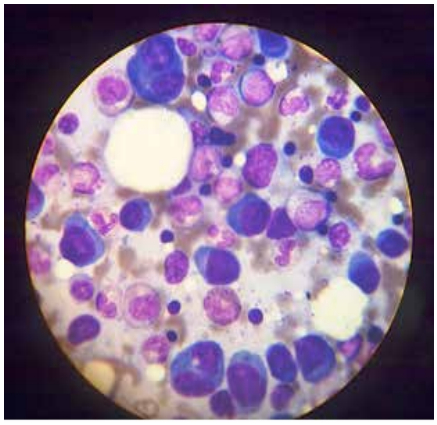
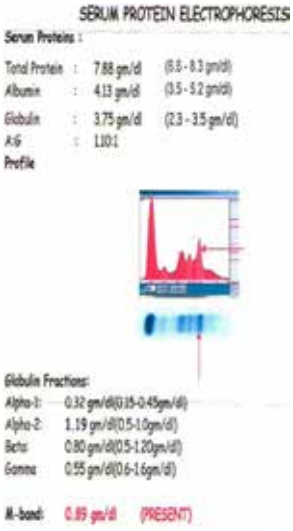


FIGURE-5
BONE MARROW ASPIRATION(100X)


SERUM PROTEIN ELECTROPHORESIS

Serum Proteins :

Total Protein	:	7.88 gm/dl	(6.6 - 8.3 gm/dl)
Albumin	:	4.13 gm/dl	(3.5 - 5.2 gm/dl)
Globulin	:	3.75 gm/dl	(2.3 - 3.5 gm/dl)
A:G	:	1.10:1	

Profile

Globulin Fractions:

Alpha-1:	0.32 gm/dl	(0.15-0.45gm/dl)
Alpha-2:	1.19 gm/dl	(0.5-1.0gm/dl)
Beta:	0.80 gm/dl	(0.5-1.20gm/dl)
Gamma:	0.55 gm/dl	(0.6-1.6gm/dl)

M-band: 0.89 gm/dl (PRESENT)

FIGURE-6
FOLLOW UP SERUM PROTEIN- ELECTROPHORESIS

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