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RESEARCH ARTICLE

PLASMA CELL ENTITIES: A DIAGNOSTIC CHALLENGE

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ABSTRACT

The prevalence of multiple myeloma is increasing and is the most common hematological malignancy in old age. Despite increasing knowledge at times the criteria for multiple myeloma are not fulfilled. This study was carried out to show the significance of diagnostic modalities in diagnosis of multiple myeloma based on hematological, biochemical, serum and urine electrophoresis, radiological imaging techniques, and bone marrow plasmacytosis since the clinical features of multiple myeloma are variable. It is important to make early diagnosis as diagnostic delays can cause morbidity and mortality. We report 29 cases of plasma cell dyscrasias out of which 25 cases were multiple myeloma, 3 MGUS & 1 of dysgammaglobulinaemia.

INTRODUCTION

Multiple myeloma is a hematological cancer characterized by proliferation of malignant plasma cells in the bone marrow, which produces an abnormal monoclonal paraprotein and evidence of end organ damage with increasing frequency in old age group (Dipti Talaulikar 2013). Multiple myeloma affects the bones, immune system and RBC count. The aggressiveness of multiple myeloma depends upon the extent of derangement of various biological parameters. In spite of recent therapeutic advances, which have doubled the median survival time, myeloma continues to be a mostly incurable disease with a high morbidity. (Michael Kuchl *et al.*, 2012) Multiple Myeloma presents with multiple sub clones at diagnosis, which have been shown to appear and disappear with treatment over the course of the disease and account for the ultimate failure to eradicate the disease. (Sundar Jagannath, *et al.*, 2013) The current treatment options for plasma cell dyscrasias include watchful waiting, treatment with immune modulating medications and stem cell transplant.

Objectives of the study

The objective of the present study is to highlight the role of diagnostic modalities for plasma cell dyscrasias with review of literature.

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MATERIALS AND METHODS

Study design

A retrospective study designed to establish the significance of diagnostic modalities in patients with plasma cell dyscrasias.

Study population and sampling size

Of the 367 bone marrow study 45 cases showed plasmacytosis both on bone marrow aspiration and biopsy. The study was carried out over a period of two years in the Department of Pathology, BMCRI, Bengaluru from January, 2012 to December, 2013.

Methods of sample collection

The study was performed on 45 patients of suspected cases of plasmacytoma in the Department of Pathology, BMCRl, Bengaluru. The data collected includes age, sex, presenting history, hematological, biochemical, radiological findings, urine and serum electrophoresis. Both bone marrow aspiration and biopsy was done on all 45 patients. The air dried smears stained with leishman stain and bone marrow biopsy sections stained with hematoxylin and eosin. The findings were observed using light microscopy.

RESULTS

A total of 45 cases of suspected plasmacytoma were evaluated. Out of which 25 cases were multiple myeloma, 16 reactive

plasmacytosis, 3 MGUS and 1 case of dysgamma globulinaemia. The age ranged from 25 and 75 years with a majority of the cases seen in the fourth and fifth decade of life. The majority of the patients were males (62) % while (38%) were females and male to female ratio was 3 : 2. The major presenting symptoms were fatigue (80%) bone pain (30%), fever (45%), weight loss (60%). The most common radiological features were lytic bone lesion and bone marrow examination revealed plasmacytosis. There was also increase in the M spike on serum electrophoresis in all 25 cases of multiple myeloma.

DISCUSSION

Normally plasma cells produce antibodies and play a key role in immune function. Multiple myeloma cells differ from healthy plasma cells because they retain the potential for a low rate of proliferation. Multiple myeloma usually is associated with end-organ damage that can include bone lesions, anemia, immunodeficiency and decreased renal function. (Malpas *et al.*, 2004) A complete blood count, ESR, serum creatinine calcium, serum & urine electrophoresis, radiography and vitamin D levels can assist in differential diagnosis. (Konrad *et al.*, 2008) The findings of hematological and biochemical parameters are shown in (Table 1).

Table 1. Incidence of presenting symptoms in patients with multiple myeloma

Parameters		Incidence
Anemia	Normocytic normochromic anemia	6
	Dimorphic anemia with thrombocytopenia	2
	Pancytopenia	1
	Normocytic normochromic anemia with thrombocytopenia	2
	Microcytic Hypochromic Anemia With Relative Neutrophilia And Thrombocytopenia	1
Symptoms	Fatigue	80%
	Bone pain	30%
	Pathological fractures	30%
	Fever	45%
Renal failure	Acute renal failure	8
	Cast nephropathy	2
	Chronic renal failure	7
	Uti with uremia	1
Asymptomatic		8

Multiple myeloma anemia is typically normocytic normochromic in 60% of patients at diagnosis. It is due primarily to the decreased production of red blood cells by marrow infiltration with plasma cells and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin, which can worsen the degree of anemia. (Sundar Jagannath *et al.*, 2013) We have reported 8 cases of normocytic normochromic anemia, 2 cases of dimorphic anemia, and one case of pancytopenia. Secretion of paraproteins in cases of multiple myeloma increases the viscosity of blood, thereby increasing the sedimentation rates which are typically > 50 mm/hr although patients with Bence Jones myeloma often have values of less than 20mm/hr. (San Miguel *et al.*, 2006) In the present study we observed average ESR of 89mm/hr. However one patient had a value of < 18 mm/hr in our study. At diagnosis 70% of patients have lytic bone lesions, which are due to accelerated bone resorption. These changes are due to pathological imbalance between osteoblast and osteoclast activity in the bone marrow microenvironment induced by the presence of myeloma cells. (Sundar Jagannath *et al.*, 2013) In the present study lytic bone lesions were seen in 15 cases out of 25 cases of Multiple myeloma. The 10 cases which did not have lytic bone lesions is reasoned to think, probably there may be a defective plasma cells production with a lack of cytokines to stimulate osteoclastic activity in patients with multiple myeloma.

Upto 20% of patients have hypercalcemia secondary to progressive bone destruction. Hypercalcemia should be suspected in patients who have nausea, fatigue, confusion, polyuria or constipation. It may also suggest high tumor burden (Sundar Jagannath *et al.*, 2013). In the current study hypercalcemia was seen in 15 cases with fatigue being the common presenting symptom. Urine dipstick test are insenstitive for Bence-Jones protein. Urine protein electrophoresis and immunofixation are recommended in all patients with plasma cell dyscrasias. (Kyle 1994) In the current study 10 cases showed presence of Bence-Jones protein on urine examination. However 15 cases were negative for Bence-Jones protein. Urine examination in most of the cases may be negative due to lack of specificity. Bone marrow aspiration and biopsy are the gold standard option to detect quantitative and qualitative abnormalities of bone marrow plasma cells. Bone marrow aspirate analysis should be performed in patients with abnormal serum or urine proteins and requires multiple aspirates because findings may be focal. As a result plasma cell count may be normal when an aspirate misses the focal aggregates of plasma cells that are better visualized radiographically or on direct biopsy where the degree of plasmacytosis will commensurably be high.[(2)] In our study we found mature plasma cells, plasmablasts and atypical plasma cells (Fig 1,2,3,4). Diagnostic abnormalities associated with multiple myeloma are shown in (Table 2).

Table 2. Haematological parameters in patients with plasmacytosis

Underlying pathology	Incidence	Bone Marrow findings	Serum findings	Inference
Reactive plasmacytosis	16	Mature plasma cells <20% of nucleated cells	No m-spike, b.urea and s.creatinine within normal limits	No end organ damage
Mgus	3	Mature plasma cells 7-28% of nucleated cells	M-spike present, raised b.urea and s.creatinine levels	No myeloma related organ and tissue impairment
Symptomatic cases	25	Mature plasma cells, plasma blasts, atypical plasma cells, binucleate and trinucleate plasma cells	M-spike present, raised b.urea and s.creatinine levels	At least one myeloma related organ and tissue impairment
Dysgammaglobulinemia	1	12% mature plasma cells	No m-spike, b.urea and s.creatinine within normal limits	No end organ damage

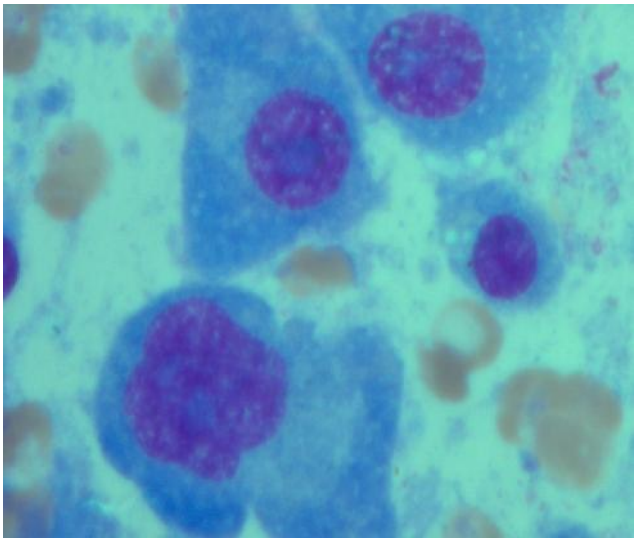

Fig 1. Photomicrography of bone marrow aspiration smears showing plasmablasts with nucleoli and irregular nuclear margins. Cytoplasm is deep blue with distinct perinuclear halo x 1000 (Leishman stain)

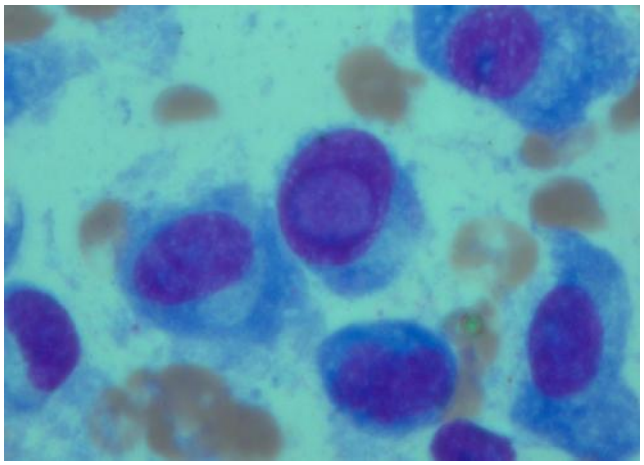

Fig 2. Photomicrography of bone marrow aspiration smears showing plasma cells having intranuclear inclusion .Cytoplasm is deep blue with distinct perinuclear halo x 1000 (Leishman stain)

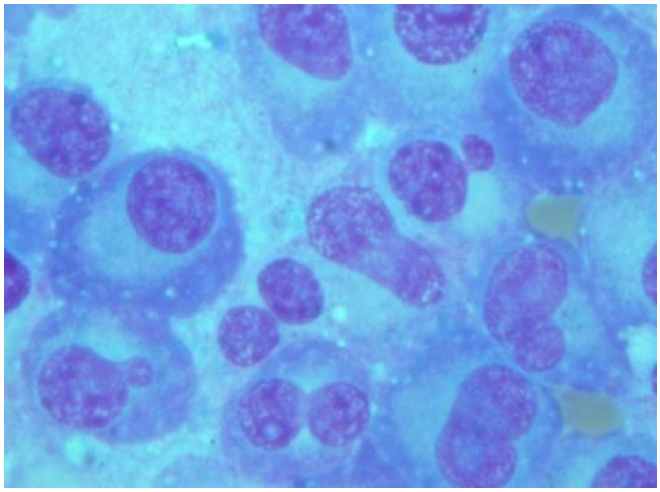

Fig 3. Photomicrography of bone marrow aspiration smears showing plasma cells exhibiting nuclear budding, binucleation. Cytoplasm is deep blue with distinct perinuclear halo x 1000 (Leishman stain)

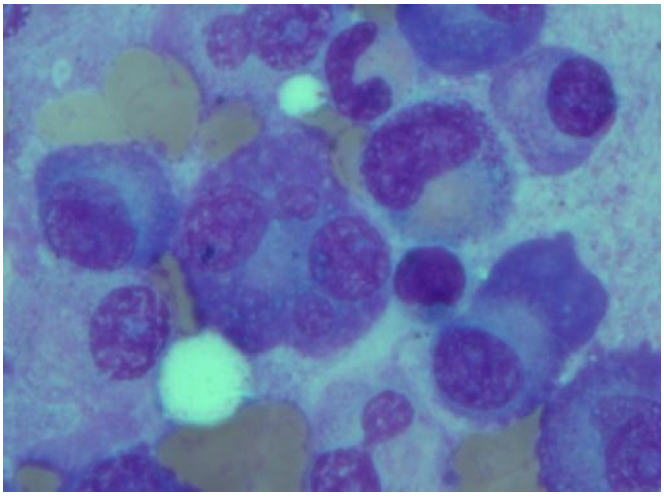

Fig 4. Photomicrography of bone marrow aspiration smears showing multinucleate and binucleate plasma cells .Cytoplasm is deep blue with distinct perinuclear halo x 1000 (Leishman stain)

MGUS is distinguished clinically from multiple myeloma by having no detectable end- organ damage, a serum Ig of <3 gm/dl and bone marrow plasma cells <10% of mononuclear cells. (Kyle *et al.*, 2010) MGUS by having a serum mIg > 3 gm/dl or bone marrow plasma cells >10% has an average rate of progression to symptomatic multiple myeloma of 10% per year. (Zingone *et al.*, 2011) In the current study we reported 3 cases of MGUS with no end-organ damage, a serum Ig of < 3 gm/dl and bone marrow plasma cells < 10% in two cases and one case with bone marrow plasma cells >28 %. Not all cases with increased paraprotiens produced by plasma cells can be diagnosed as multiple myeloma. The diagnosis of multiple myeloma also requires >1 major abnormalities such as anemia, lytic bone lesions, renal impairment or hypercalcemia. Renal impairment in multiple myeloma is often due to excess production of proteins and increased serum calcium levels. Kidney function is abnormal at diagnosis in about half of individuals with multiple myeloma. In the present study, we reported 17 cases of multiple myeloma with renal impairment. (Table 3).

Table 3. Diagnostic Parameters In Patients With Multiple Myeloma

Parameters	Number Of Cases With The Abnormality
Blood urea	16
Serum creatinine	16
Serum m protein electrophoresis	25
Bence jones proteins	10

The most common cause of renal disease is cast nephropathy (myeloma kidney) which accounts for about 70% of dialysis – dependent renal failure in patients with multiple myeloma. (Irish *et al.*, 1997) We reported 2 cases of cast nephropathy on renal biopsy who were dialysis dependent with increase in free light chains on protein electrophoresis. The indicators that shorten survival includes increased C reactive protein, DNA hypoploidy, high plasma cell count, labeling indices and plasmablastic histology. (Sundar Jagannath *et al.*, 2013) In this study all 25 cases had high plasma cell count and 17 cases had plasmablastic histology. The limitations of this current study

relate to financial constraints as patients referred to us were economically poor and unaffordable for further investigations. Few of the patients were referred to cancer centre for further management. Hence the follow-up of the patients was not possible and the prognosis of the disease was not determined.

Conclusion

Inspite of improved outcomes in multiple myeloma, the disease is seldom cured, although treatment can relieve symptoms, induce remission and prolong life. Since the clinical manifestations of plasma cell dyscrasias are variable, screening of older age group for plasma cell dyscrasias is one of the important recommendation in health care. Hence it mandates to have a protocol for diagnosis of the disease with an investigative screening modality. It also mandates for an early diagnosis and treatment to reduce the morbidity. It is the need of the hour for research in the field of detection of biomarkers.

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