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VARIED PRESENTATION OF PLASMACYTOSIS SEEN IN BONE MARROW AT A TERTIARY CARE SET-UP

Tiwari Neema[1], Sharma Richa[2], Goyal Shefali[1], Mittal Salony[4], Gupta Vatsala[1].

1. *Assistant Professor, Department of Pathology, School of Medical Sciences and Research, Sharda University, Greater Noida.*
2. *Senior Resident, Department of Pathology, School of Medical Sciences and Research, Sharda University, Greater Noida.*
3. *Professor, Department of Pathology, School of Medical Sciences and Research, Sharda University, Greater Noida.*
4. *Associate Professor, Department of Pathology, School of Medical Sciences and Research, Sharda University, Greater Noida.*

Corresponding Author:

Dr Vatsala Gupta, Assistant Professor, Department of Pathology, School of Medical Sciences and Research, Sharda University, Greater Noida.

Contact no:9709276112

Email: vatsala.gupta@sharda.ac.in

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ABSTRACT:

Bone marrow plasmacytosis can have many causes ranging from non neoplastic to neoplastic conditions. The clinical presentations and the percentage of plasma cells may vary from one disease to the other. In the given case series, we have compiled the similar cases received at our tertiary care center and found interesting clinical presentations. Through this case series, we emphasise upon the utility of bone marrow aspiration in patients of Pyrexia of unknown origin to refractory anemias and/or lymphadenopathy.

KEYWORDS: Plasma Cell, Bone marrow Plasmacytosis, multiple myeloma

INTRODUCTION

Bone marrow plasmacytosis occurs in association with variety of conditions both Neoplastic(eg. Plasma cell dyscrasia, Lymphoplasmacytic lymphomas off-late Castleman's disease) to non-neoplastic conditions like infections, immune disorders, various type of anemias like aplastic anemia,IgG4 disorders etc. The percentage of plasma cells varies from, ~10- 20% of all nucleated cells in reactive conditions to 50% in neoplastic diseases. WHO has even set criteria's for diseases like Multiple myeloma and Lymphocytic lymphomas.[1] It is important to differentiate reactive plasmacytosis in non-neoplastic conditions from the malignant ones.

Plasma cell dyscrasias (PCDs) are a spectrum of disease involving defect in plasma cells leading to expansion of population of monoclonal bone-marrow plasma cells that produce monoclonal immunoglobulins.[2] There is a wide variety of plasma cell dyscrasias ranging from benign symptomatology to malignant presentation.

Monoclonal gammopathy of undetermined significance (MGUS) is at the benign end of the disease process, where the plasma-cell clone usually does not expand. Smouldering MM comes in the middle where there are fixed WHO criteria's as per which the lesion is progressing to a full-blown multiple myeloma. At the other end of the spectrum leading to malignant manifestation is Multiple myeloma (MM) .In MM there is evidence of neoplastic proliferation of a clone of plasma cells in the bone marrow with resulting end-organ damage, including skeletal destruction (lytic bone lesions), hypercalcemia, anemia, and renal insufficiency.[2]

The clinical presentation and symptoms of plasma cell lesions differ. These cases can be defined as Secretory Myelomas and Non-Secretory myelomas based on the type of immunoglobulin produced. In secretory myelomas these cases can further be classified into Heavy chain secretors and light chain secretors. It is also important to note that the type of immunoglobulin secretion is intact or just a particular part is being secreted.[3]

The disease entity of heavy chain diseases comprises of a rare disorder known as Waldenstrom's macroglobulinemia (WM). It is a variant of lymphoplasmacytic lymphoma (LPL), characterized by high levels of monoclonal immunoglobulin M (IgM) protein in the blood. The major clinical features of LPL/WM comprise of anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and rarely hyperviscosity syndrome. 10% clonal lymphoplasmacytic in bone marrow confirms the diagnosis of WM. Advanced investigations involving molecular and cytogenetic workup include L265P mutation in MYD88 is detectable in more than 90% of cases. The consequences of IgM in the circulation manifest as symptoms of hyperviscosity, mainly neurological, which includes blurring of vision, headache, and rarely stroke and coma.[4]

The authors compiled all the cases received in the past 3 years in our set up which was reported with plasmacytosis in bone marrow workup to highlight various causes of plasmacytosis benign as well as malignant diagnosed at our set up.

CASES UNDER STUDY

Clinical features	**Age**	**Percentage of plasma cells**	**Diagnosis**	**Supportive investigations**	**Final diagnosis and Treatment**
Pyrexia of un-known origin and anemia	60/Male	12%	Reactive marrow with plasmacytosis	LFT-Mildly deranged bilirubin levels KFT-Normal	Broad spectrum antibiotic treatment for ??Infection
Pancytopenia	38/Male	15%	Hypoplastic (28% cellularity)marrow	LFT-Mildly deranged	Treatment for Aplastic

			with lymphocytosis and plasmacytosis		anemia
Fever and anemia	25/Female	10%	Micronormoblastic erythroid response with reactive plasmacytosis	NA	Treatment for Iron deficiency anemia and broad spectrum antibiotic for infection
Difficulty in sitting/bone pain	60/Male	55%	Plasma cell dyscrasia Waldenstrom's macroglobulinemia	-Sample in EDTA for CBC show RBC agglutination which was relieved mildly on incubation -Serum electrophoresis shows M spike -Bence Jones negative -CRAB criteria- not met completely	Multiple myeloma
Bone pain and renal failure	52/Male	26%	Plasma cell dyscrasia	-M spike on HPLC seen -CRAB criteria fulfilled	Multiple myeloma
Lymphadenopathy and weakness	32/Male	8% and 92% atypical lymphoid cells replacing the marrow diffusely	Waldenstrom's macroglobulinemia /NHL(small cell type)/Lymphoplasmacytic lymphoma	-No M spikes -Bence Jones negative -Sample agglutinated in EDTA vial	NHL
Pancytopenia	44/Male	10%	Aplastic anemia	LFT mildly deranged	Aplastic anemia
Bony pains and pathological fracture shaft	56/Male	52%	Plasma cell dyscrasia	M spike present CRAB criteria	Multiple myeloma

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Fever and splenomegaly	23/Female	13%	Reactive marrow	NA	Infection
Fever and weight loss for 4 months	60/Female	25%	Metastatic adenocarcinoma	Protein electrophoresis -Normal(No M band) IHC on the biopsy showed normal results(CD19, CD20, CD38, CD138) - CRAB lesions- Negative - CK7, CK20, MUC1, MUC2, MUC5A, CDX2-Positive in IHC	Bone marrow biopsy showed metastatic adenocarcinoma and patient was manages accordingly
Bone pain	67/male	55%	Multiple myeloma	M spike on electrophoresis CRAB criteria fulfilled	Multiple myeloma and managed accordingly

DISCUSSION

The spectrum of disorders comprising of plasmacytosis ranges from non-neoplastic conditions like infections, autoimmune disorders,IgG4 disorders to Neoplastic lesions like plasma cell dyscrasias include multiple myeloma (MM), solitary bone plasmacytoma and extramedullary plasmacytoma. Reactive plasmacytosis is polyclonal characterized by a diffuse distribution of mature plasma cells in the bone marrow. In reactive conditions, the percentage range was 5%- 24%.[5]

The age range in our study ranged from 24 years to 60 years. Out of 11 cases 8 cases were males and 3 were females. All of the neoplastic plasma cell lesions including metastatic adenocarcinoma with plasmacytosis belonged to the age group of 50-60 years. This matches most of literature data showing plasma cell dyscrasias and solid malignancies are common in older age groups while reactive changes can occur in any age.

In non-neoplastic conditions plasma cells were chiefly mature however, in plasma cell dyscrasias range of mature and immature plasma cells was found. Non-specific

morphological features suggesting a reactive nature of plasma cells, are mature forms of plasma cells and sometimes perivascular location of plasma cells . Some types of infection and abnormal immune reactions also lead to marked proliferation of plasma cells [6]. Cytokines like IL-6 or IL-10 are known to stimulate plasma cell generation, may also contribute to this process [7]. Reactive conditions such as chronic infection, autoimmune diseases, hypersensitivity states, megaloblastic anemia, hemolytic anemia, diabetes mellitus, cirrhosis, drug related agranulocytosis, angio-immunoblastic lymphadenopathy and multicentric Castleman's disease are associated with bone marrow plasmacytosis .[8]

Neoplastic aetiologies having plasmacytosis commonly are Plasma cell dyscrasia, Lymphomas, sometimes AMLs and vary rarely reactive plasmacytosis can occur in metastatic solid tumor diseases. Detection of bone marrow metastatic deposits is important to determine the stage of the malignancy, prognosis, mode of treatment, chemotherapeutic response, and follow-up in case of relapse [9]. Common symptoms for marrow metastasis are anaemia or pancytopenia which does not improve on treating with hematinics. Just like the metastatic adenocarcinoma showing reactive plasmacytosis some authors have noted eosinophilia, reactive plasmacytosis, osseous metaplasia, desmoplasia, granulomas, necroinflammation and infections in the bone marrow as a response to metastatic deposits [10]. Sometimes megakaryocytes, crushed artefacts, stromal cells may be misinterpreted as metastatic deposits. [11]

However, in cases of plasma cell dyscrasias the range varied from 20- 40%. Neoplastic cells usually produce great amounts of monoclonal light or heavy chains of immunoglobulin that can be detected in serum or urine. Neoplastic processes are diagnosed based on morphological findings, protein electrophoresis and bone marrow immunohistological examination. In Neoplastic plasma cell disorders like multiple myeloma, the marrow can be cellular to hypocellular and the plasma cells are mainly abnormal, shifted to the left, focal in distribution, associated with reticulum cells, and usually more than 20% however there are set WHO criteria's for each neoplastic plasma cell lesion for percentage ,radiology findings ,CRAB criteria etc. [12]

Lymphoplasmacytic lymphoma (LPL) is defined in the WHO Classification of Tumours of Hematopoetic and Lymphoid Tissues, fourth edition as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen, which does not fulfil the criteria for any of the other small B-cell lymphoid neoplasms that can also have plasmacytic differentiation. WM is defined as LPL involving bone marrow associated with an IgM monoclonal paraprotein of any concentration, and is found in the majority of patients with LPL.[13] The great majority (>90%) of LPLs have MYDBB L265P mutation, which can make the diagnosis either more or less likely; however, this abnormality is neither specific nor required.[13]As per WHO 2016 criteria, WM has been kept under the heading of mature B-cell neoplasm with subcategory of LPL. Plasma cell neoplasms also include WM partly. The overall incidence of WM is approximately five cases per one million persons per year. The incidence has remained steady over time as suggested by Wang et al., who reported an incidence of 0.38 per100,000 persons per year. It accounts for about 1–2% of hematologic malignancies. The incidence is highest among white people and is rare in other population groups.[14] LPL occurs in adults, with a median age in the seventh decade of life, and shows a slight male predominance.[15] It is diagnosed by infiltration

of lymphoplasmacytoid cells in BM in the presence of IgM protein in the blood. WM is rarely reported in Indian clinical settings

In a study conducted they saw that less than 10% plasmacytosis has been chiefly found in various types of anemia, 10- 30% plasma cells were found infections and hypoplastic marrows. This was similar to the cases we saw with reactive plasmacytosis ranging between 8-12%. In one study, maximum cases (84.2%) with plasmacytosis had a benign etiology. In our study 54.5% were malignant(plasma cell dyscrasias, lymphomas or metastasis) and 45.4% were benign. [16,17,18]

Bone marrow plasmacytosis can present as diagnostic dilemma and be challenging to differentiate reactive from neoplastic condition as there is an overlap both in counts and morphology.

CONCLUSION

Plasma cell lesions are a group of non-neoplastic and neoplastic diseases. Each case with plasmacytosis especially in grey area requires complete clinical evaluation to arrive at a final diagnosis for patient management.

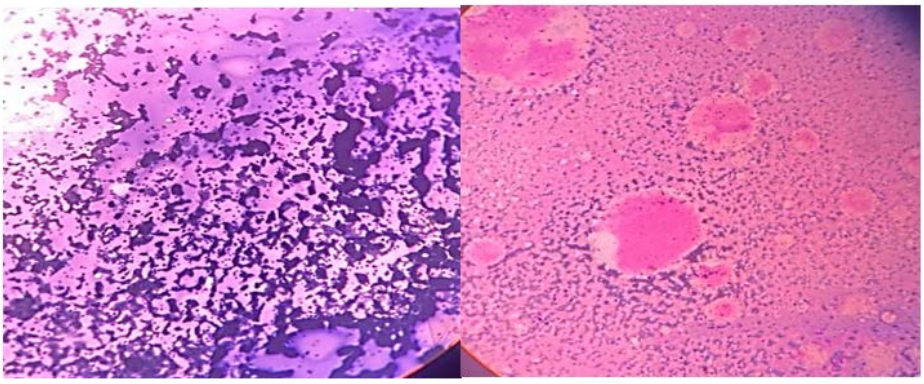

Fig 1.Background of aspirate and peripheral smears showing bluish/pinkish hue on giemsa and lesihman respectively with RBC agglutination in cases of LPL.

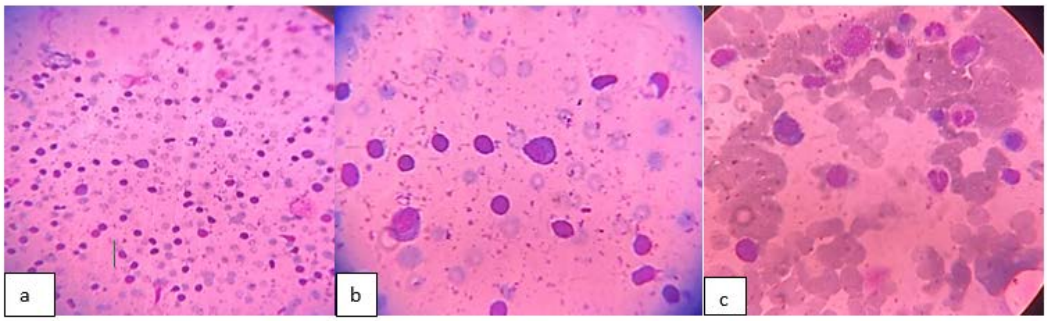

Fig 2.Multiple images from bone marrow aspirates show plasma cells. a/b: Atypical lymphoid cells, with plasma cells in LPL. c:Plasma cell in suspected Plasma cell dyscrasia.

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