

Review Article

Plasma Cell Disorders

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Abstract

Plasma cell disorders are monoclonal neoplasm due to underlying clonal plasma cell or B cell. This is a group of disorders that comprise of multiple myeloma, Waldenstrom's macroglobulinemia, amyloidosis and heavy chain disease together called monoclonal gammopathy. Immunoglobulins or its fragments secreted by these neoplastic plasma cells cause clinical manifestations. Protein electrophoresis identifies the presence of these monoclonal proteins whereas immunofixation identifies the fragments like heavy or light chain and clonality, flow cytometry identifies the cell type. Treatment modalities with drugs and stem cells are focused to prolong survival by reducing tumour load and its effects.

Key Words: Plasma Cell Disorders, Multiple Myeloma, Amyloidosis, Monoclonal Gammopathy

Introduction

Plasma cell disorder is a group of disorders characterised by uncontrolled proliferation of a single clone of immunoglobulin secreting terminally differentiated B cells or so called plasma cells. Also the immunoglobulins or its fragments produced are identical or homogeneous, they produce discrete spike called Monoclonal (M) protein or paraprotein during electrophoresis. Pathophysiological effects of paraproteins are as follows: Raised serum globulin level, hypoalbuminemia, hyponatremia, dilutional anemia, raised ESR, rouleaux in blood flow, hyperviscosity, interference with platelet function and coagulation pathway, peripheral neuropathy, proteinuria, renal failure, amyloidosis and cryoglobulinemia.

Conditions included under plasma cell disorder are multiple myeloma, Waldenstrom's Macroglobulinaemia, amyloidosis, heavy chain diseases and monoclonal gammopathy of undermined significance

(Table 1) and Plasmacytoma (medullary / extramedullary), Plasma cell leukemia, Immunoglobulin light chain amyloidosis, Osteosclerotic multiple myeloma, B-cell lymphocytic neoplasms, other neoplastic conditions like Chronic Lymphocytic Leukemia, Chronic Myeloid Leukemia, Carcinoma breast, colon and non-neoplastic conditions like cirrhosis, sarcoidosis, autoimmune disorders, skin diseases like lichen myxedematosus, necrobiotic xanthogranuloma.

As far as the pathogenesis is concerned there is an interaction between plasma cells and their microenvironment –bone marrow stroma cells through adhesion molecules belonging to Beta-1 integrin family and vascular cell adhesion molecules respectively. This micro environment provides a sanctuary for plasma cells by promoting proliferation and blocking apoptosis leading to disease progression and drug resistance. Reduction of this interaction stops the cell growth and its replication which is of benefit to patients².

Clinical Approach

Appropriate diagnosis can be obtained by taking a detailed history and by doing physical examination. Multiple myeloma patients present with features of renal failure, hypercalcaemia (lethargy, weakness, depression and confusion), hyperviscosity (headache, fatigue, shortness of breath, visual disturbance, ataxia and somnolence), bone pain or fractures, lytic lesions (Fig 1,2), skin infiltration, polyneuropathy. Presence of dyspnea, hepatomegaly, edema, macro-glossia and entrapment neuropathy invoke the possibility of amyloidosis³⁻⁵.

In **Waldenstrom's Macroglobulinemia** there may be features of hyperviscosity causing recurrent epistaxis and bleeding from mouth and gum, lymphadenopathy, hepatosplenomegaly and anemia.

CLASSIFICATION OF MONOCLONAL PROTEINS

Laboratory finding		
Clinical implication	Non-IgM monoclonal proteins	IgM monoclonal proteins
Premalignant or undetermined	IgG, IgA, light chain, and other MGUS	IgM MGUS other lymphoproliferations
Intermediate	SMM(Smoldering multiple myeloma)	Smoldering macroglobulinemia
Malignant	Active MM Plasma cell leukemia	Waldenstrom macroglobulinemia or other lymphoproliferative disorders

Table 1 - Classification of monoclonal proteins'

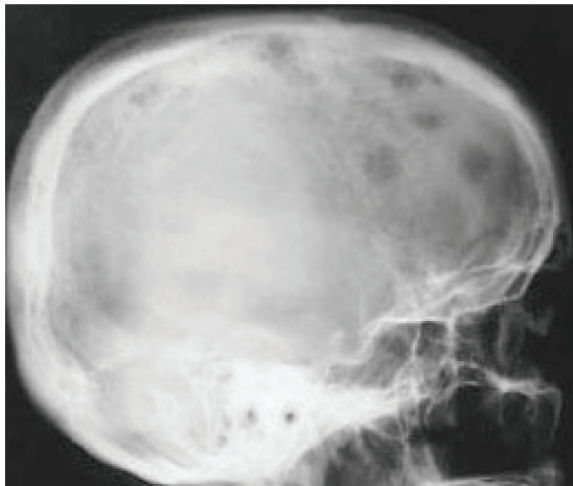


Fig 1 : Lytic lesions - skull

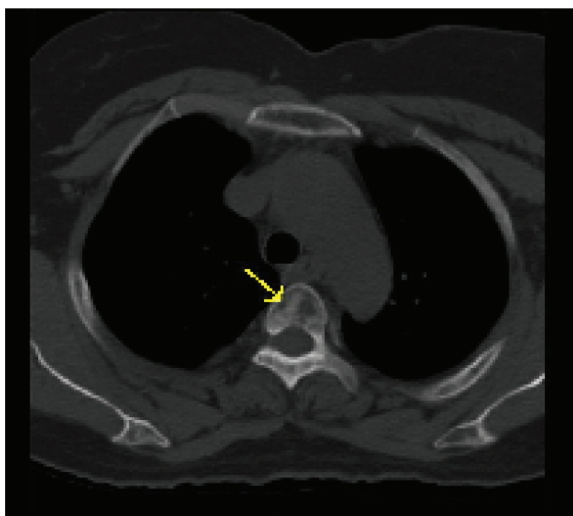


Fig 2 : Lytic lesions in Vertebra

POEMS syndrome includes Polyneuropathy, Organomegaly, Endocrinopathy (hypogonadism, hypothyroidism, diabetes mellitus, adrenal dysfunction), M-protein and skin changes (hyperpigmentation, acrocyanosis, hypertrichosis, multiple haemangiomas).

Gamma heavy chain disease manifests as lymphadenopathy, hepatosplenomegaly, anemia, weakness and a peculiar symptom of palatal edema causing respiratory compromise due to involvement of Waldeyer's nodes. Patients with **Alpha** heavy chain disease manifest with weight loss, chronic diarrhea, malabsorption due to mesenteric adenopathy. Patients with **Mu** heavy chain disease present with hepatosplenomegaly, lytic bone disease, cast nephropathy due to light chain proteinuria.

Investigations

Complete blood count and differential peripheral blood film - Anemia is due to plasma volume expansion with paraproteinemia, infiltration of bone marrow and cytotoxic drugs. Leucopenia is due to cytotoxic drugs. Because of Rouleaux formation blood grouping may be difficult.

Chemistry including calcium, creatinine - Increased calcium and creatinine may be seen in Multiple myeloma due to renal insufficiency. **Serum protein Electrophoresis and Immunofixation** : Used to identify type of monoclonal protein either light or heavy chain⁶, **Nephelometric quantification of immunoglobulin** : Used to measure serum immunoglobulin, **24 hrs Urine collection for electrophoresis and immunofixation** To quantify urinary light chains.

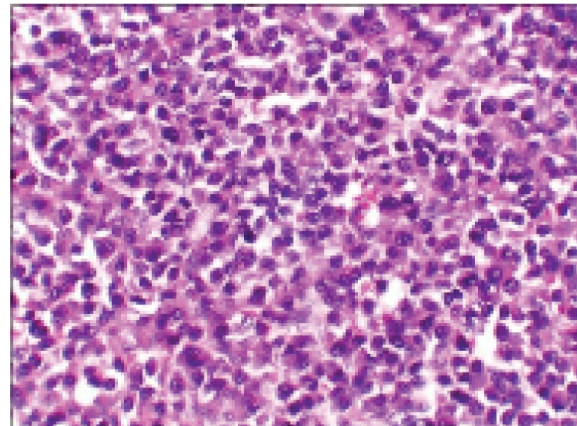


Fig 3 : Sheets of plasma cells

Bone marrow aspirate / Biopsy to assess for plasma cell morphology (Fig 3), proliferation rate, immunophenotyping⁷ (to identify aberrant phenotyping markers), cytogenetic analysis⁸ (provides evidence of clonality, confirms specific diagnosis, prognostic information, indicates whether neoplasm is therapy induced or not).

FISH (Fluorescence In situ Hybridization): Uses labelled oligonucleotide probe that binds to specific DNA sequences. Performed in the plasma cells from the bone marrow aspirates to identify chromosomal abnormality. Locus specific probes detect oncogenes and tumour suppressor genes. Centromeric probes detect monosomy and trisomy as well as to study two genes involved in specific translocation or other rearrangements.

Radiological skeletal bone survey : Chest and bone radiographs to identify lytic lesions. CT is used to detect bone defects. **MRI** reveals extent of bone marrow infiltration, cord or root compression in patients with pain syndrome. **PET** to assess disease activity.

BETA - 2 Microglobulin, CRP (C-reactive protein), LDH (lactate dehydrogenase) : Serum levels of Beta 2 microglobulin (the light chain of HLA class 1 glycoproteins) correlates with tumor mass. **Measurement of free Monoclonal light chain, Multiparameter Flow Cytometry**. It is performed in the peripheral blood to confirm the presence of clonal circulating plasma cells⁹.

PCR / RT PCR : Used in detection of rearrangements of immunoglobulin heavy and light chain loci and TCR loci. It provides evidence of clonal disorder, if a monoclonal rather than an oligoclonal or polyclonal pattern is detected. The advantage here is only small amount of DNA is required, no need for dividing cells.

Differential Diagnosis

Monoclonal Gammopathy Of Unknown significance: Most of the patients with this disorder remain asymptomatic and there is no evidence of end organ damage. MGUS have <3g/dl monoclonal proteins and <10% bone marrow plasma cells. Progression to myeloma is 1 % per year¹⁰. **Smoldering multiple myeloma (SMM):** Usually asymptomatic or presents with mild anemia. Diagnostic criteria of >10% clonal bone marrow plasma cells and M protein >3 gm/dl and <4.5 gm/dl is seen in SMM. Around 10 to 20 % patients with SMM progress to myeloma in a year¹¹. Stringent follow up and bone marrow evaluation is mandatory. **Multiple myeloma:** Features are hypercalcaemia, renal insufficiency, anemia, bone disease (CRAB criteria) and underlying clonal plasma cell disorder. Bone diseases manifest in the form of lytic lesions, severe osteoporosis, compressive features, bacterial infections, extra medullary plasmacytoma or associated amyloidosis¹². **Amyloidosis:** Presentations depend upon the organ involved. Patients with restrictive cardiomyopathy presents with dyspnoea, chest pain and renal disease patients may have proteinuria and hypoalbuminemia. Liver disease patients will have hepatomegaly with elevated alkaline phosphatase. In nervous system involvement patient presents with peripheral neuropathy and postural hypotension. Constipation and diarrhea are the clinical manifestation in patients with gastrointestinal involvement.

Special forms of plasma cell disorders

Plasma cell leukemia: Characterised by >20 % peripheral blood plasmacytosis. It presents in two

forms, one as de novo leukemic phase and other form is leukemic phase occurring with myeloma. **Solitary Plasmacytoma of bone:** It occurs usually on the vertebral column, <10% plasma cell infiltration in bone marrow sampling. No evidence of end organ damage. The most common symptom at diagnosis is pain.

Extramedullary plasmacytoma: It arises outside the bone marrow and involves upper respiratory tract or gastrointestinal tract. Treatment of choice is local radiotherapy. **Non-secretory Multiple Myeloma:** This form is difficult to diagnose, clonality is usually assessed by immunophenotyping. **IgM Multiple myeloma:** Definitive diagnosis is arrived by immunophenotype of infiltrating cells and detection of osteolytic lesions. It is a differential diagnosis for Waldenström macroglobulinemia. **Osteosclerotic myeloma (POEMS syndrome):** Presents with M protein, Polyneuropathy and osteosclerotic lesion. Other features not in the acronym are pleural effusion, thrombocytosis, ascites and edema.

Treatment

Multiple Myeloma

Therapeutic measures are focused on preventing early mortality and to prolong survival by rapid cytoreduction and intervening end organ complications.

Therapy is influenced by patient's age and comorbidities. Treatment includes 3 to 6 cycles of induction therapy followed by autologous stem cell transplantation and if needed consolidation/maintenance therapy.

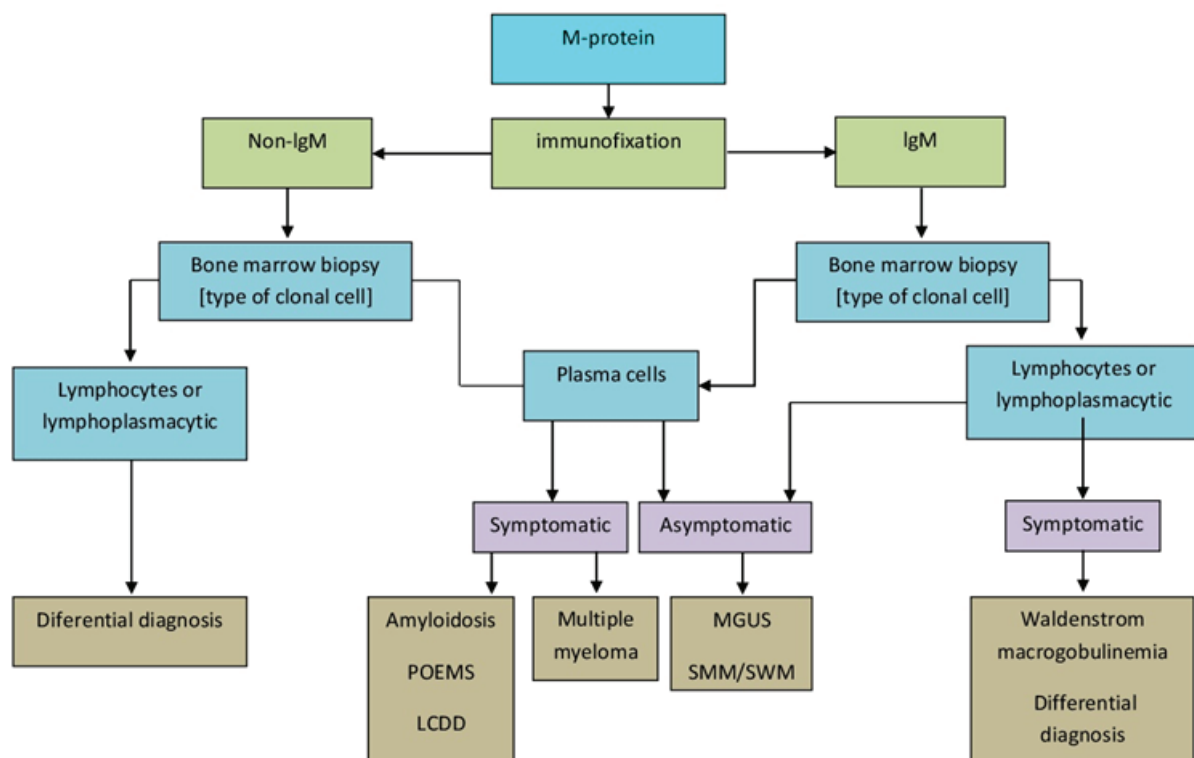


Fig 4 : Diagnostic Algorithm

LCDD - Light chain deposition disease, SMM - Smoldering multiple myeloma

Gold standard regimen for young and newly diagnosed patients is VAD combination (Lenalidomide, bortezomib, dexamethasone).

Most studies favour treatment with Lenalidomide and dexamethasone due to safety profile in patients more than 70 years who are unfit for transplant.

Stem cell based therapy along with drug combination during induction phase showed only modest benefit but not curative compared to drug alone therapy.

Randomized studies in consolidation phase show prolonged progression free and high overall response rates with high dose melphalan therapy with stem cell support compared to standard dose therapy. Tandem transplant i.e two successive high dose melphalan therapy with hematopoietic stem cell support may be valuable in patients with high risk cytogenetics.

Maintenance phase is aimed at prolonging the duration of response after transplantation and remission. Nontransplant patients treated with Lenalidomide, Melphalan, Prednisolone in induction phase and receives Lenalidomide for maintenance are at the risk of second primary malignancy as benefit outweighs the risk. Patients with high risk cytogenetics after transplant are benefited with Lenalidomide and Bortezomib combination therapy^{13,15}.

Relapse cases may respond to 1) Lenalidomide and or Bortezomib combined with dexamethasone or 2) Combination of Bortezomib and doxorubicin.

In refractory cases, thalidomide or high dose Melphalan and stem cell therapy can be used if not initiated earlier.

Second generation proteasome inhibitor Carfilzomib and immunomodulator agent Pomalidomide may be used in refractory and relapsed cases.

Supportive measures address issues like anemia which is treated with erythropoietin and haematinics. Hypercalcemia is treated with bisphosphonates, Plasmapheresis is used for hyperviscosity syndrome, Calcium and vitamin D is given for bone strengthening. Patients presenting with pain and collapsed vertebra are treated with surgical interventions like kyphoplasty and vertebroplasty.

Waldenstrom's Macroglobulinemia

Treatment is initiated in symptomatic patients with worsening anemia, hyperviscosity symptoms. Significant efficacy is achieved with Bortezomib and Bendamustine. Fludarabine and cladribine are also highly effective single agents. Frail elderly patients are treated with single agent Rituximab (anti-CD20) or oral Fludarabine.

Poem's Syndrome

Neuropathic symptoms resolve after local radiotherapy for plasmacytoma. High dose therapy and stem cell transplantation may be useful for selective patients.

Heavy Chain Disease

Gamma heavy chain disease - Symptomatic patients can be treated with either combination chemotherapeutic agents or with rituximab. **Alpha** heavy chain disease is treated with antibiotics and combination chemotherapy. **Mu** heavy chain disease is treated similar to Chronic lymphocytic leukemia.

Conclusion

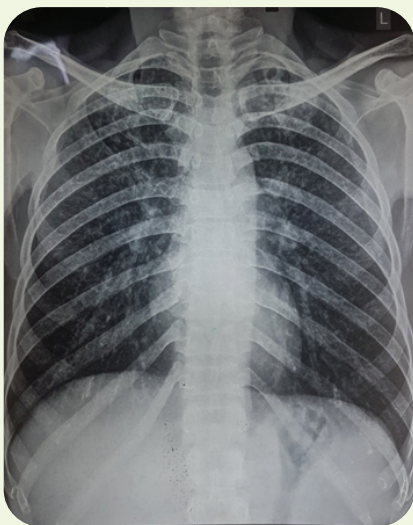
Plasma cell dyscrasias are a heterogeneous group of disorders either present as asymptomatic condition with high potential for transforming to malignancy or as more aggressive form at presentation itself. Clinical presentation may be due to the clone itself or the properties of the secreted Immunoglobulin. Because of this various mode of presentation a systematic approach which includes earliest diagnosis of clinically significant condition is needed to avoid unnecessary testing and treatment. Therapy is largely directed (if indicated) at reducing the underlying clone.

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Image Challenge - 1



Clue: 18 year old boy living in a hostel, presented with low grade fever, weight loss for 45 days.

- Answer in page : 92