



MULTIPLE MYELOMA

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ABSTRACT

BACKGROUND: Multiple myeloma is a malignant disease characterised by proliferation of clonal plasma cells in the bone marrow and typically accompanied by the secretion of monoclonal immunoglobulins that are detectable in the serum or urine. It is the second most commonly diagnosed hematologic malignancy with an annual incidence and prevalence in the United States of approximately 15,000 and approximately 45,000, respectively. The incidence is higher with increasing age (median age at diagnosis 67 yr). Multiple Myeloma accounts for approximately 1% of all malignancies and 10% of hematological malignancies, representing the second most frequently occurring hematological malignancy in the United States.[1] **Aims & Objectives:** 1) To study hematological findings and biochemical parameters in plasma cell Myeloma. 2) To determine optimal diagnostic markers. 3) Evaluation by international staging system. **Materials & Methods:** A total of 2458 hemograms over a period of 2 years were studied. 24 cases showed rouleaux formation & increased ESR. These cases were further evaluated with clinical history, hematological investigations, biochemical analysis and radiological findings. **Results:** 24 cases were analyzed, which showed raised ESR and severe anemia in all the cases. Haematological investigations including bone marrow examination, urine examination confirmed the diagnosis and all the patients were graded according to recent staging system. **Conclusion:** Current research goals are to further increase our knowledge, to identify additional targeted therapies, and to reduce adverse effects and improve response rate. This review focuses on recent clinical advancement in myeloma strategies with additional discussion dedicated to emerging drugs that may prove beneficial to patients with this disease.

KEYWORDS: Plasma cell neoplasm, multiple Myeloma post germinal center B cell.

INTRODUCTION

Myeloma is a disease of neoplastic B lymphocytes that invariably mature into plasma cells that synthesize abnormal amounts of immunoglobulin fragments.^[2] Myeloma belongs to a spectrum of disorders referred to as plasma cell dyscrasias. These disorders include clinically benign conditions such as essential monoclonal gammopathy and biologically intriguing disorders, such as Castleman's disease, heavy chain disease, macroglobulinemia, solitary plasmacytoma with a high potential for cancer when arising in soft tissue and the most common malignant entity plasma cell Myeloma, a disseminated B cell malignancy, that is not curable with conventional dose chemotherapy. Most plasma cell dyscrasias result from expansion of a single clone of cells with resultant, monoclonal protein secretion. Oligoclonal & polyclonal protein abnormalities accompanying some disease conditions such as Castleman disease (or) AILP. Environmental exposure to

radiation (or) chemicals has been associated with an increased incidence of plasma cell Myeloma.^[3]

The disease can cause clinical symptoms via tumor mass effect (cord compression), cytokine production (anemia) bone destruction (pain) and immunosuppression (infection). Clinical manifestations of Myeloma vary as a result of the heterogeneous biology, spanning the entire spectrum from indolent disease to highly aggressive Myeloma with intra medullary features.

Studies of atomic bomb survivors showed an increased incidence of plasma cell Myeloma 15-20 yrs after radiation exposure.^[4] On the other hand, result of epidemiologic studies attempting to establish association between Myeloma and certain infections (or) autoimmune diseases are inconclusive.

RESULT

A total of 24 Cases were studied in detail and following findings were identified.

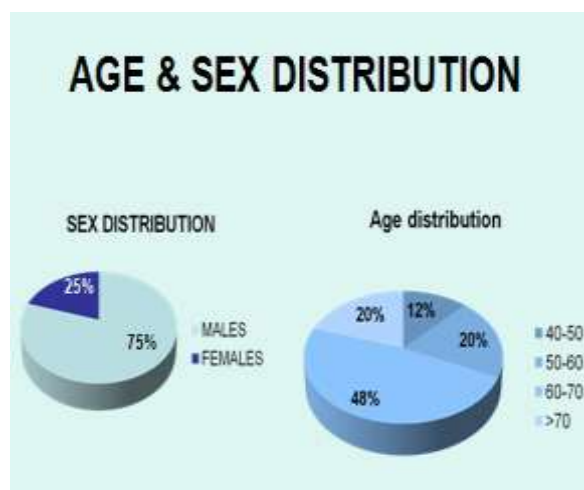
The age of the patient ranged between 46 yr- 80 yr. Most of the patients in our study i.e. 12 cases were between 41-50 yrs of age.

Table 1: AGE RANGE

AGE	No. of case
40-50	12
51-60	3
61-70	4
71-80	5

Of total 24 cases, 18 were of males and the remaining were females in our study.

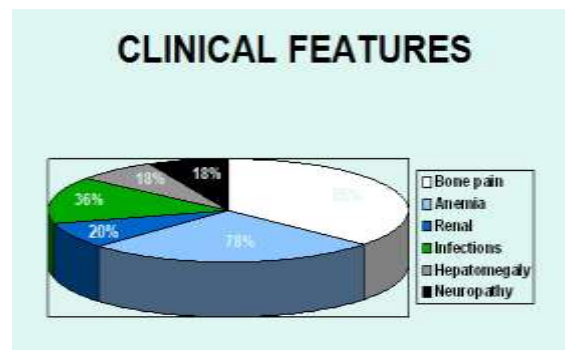
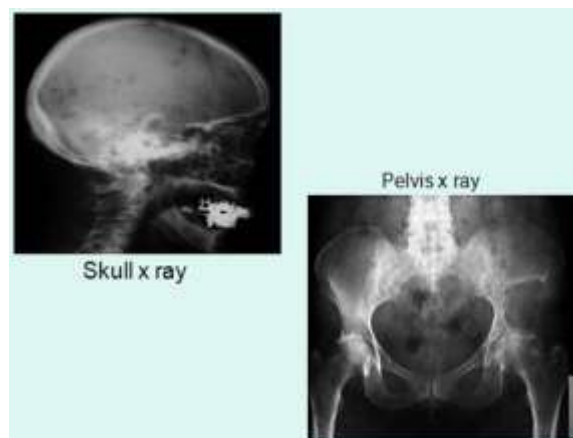
M:F ratio is 3:1.

**Chart 1: Age and sex distribution.**

The presenting features in our study are bone pain, weakness, cord compression, infections and renal manifestations.

Table: 2 Clinical manifestations

SIGNS & SYMPTOMS	No .OF CASES
Bone pain	19
Anemia	18
Cord compression	5
Infections	9
hepatomegaly	5
Renal manifestations	6

**Chart: 2 clinical manifestations**

Laboratory investigations done in all 24 cases which showed the following results.

LABORATORY INVESTIGATIONS

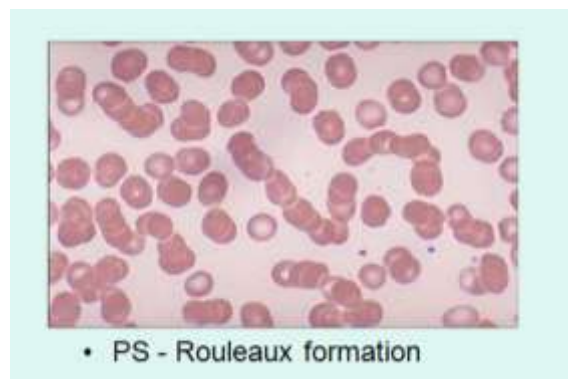
S.No	PARAMETER	PERCENTAGE (%)
1	Hb <10 gm/dl	66
2	Raised ESR	99
3	S.Ca (>11 mg/dl)	40
4	S.Creati (>2 mg/dl)	20
5	Albumin	>3.5 =31 <3.5 =63
6	M Band	97
7	Free K & λ	80
8	B2 Microglobulin	<3.5mg/l=31 3.5 to 5.5mg/l=63 >5.5 mg/l=6
9	BMA (10-30%)	100

Most of our patients in our study group were having raised ESR, anemia, increased beta 2 microglobulin levels, increased levels of free kappa and lambda light chains and all the cases showed presence of increased number of plasma cells in the bone marrow.^{[5][6][7]}

Following table showing the staging and grading of multiple myeloma cases based on International Staging System.

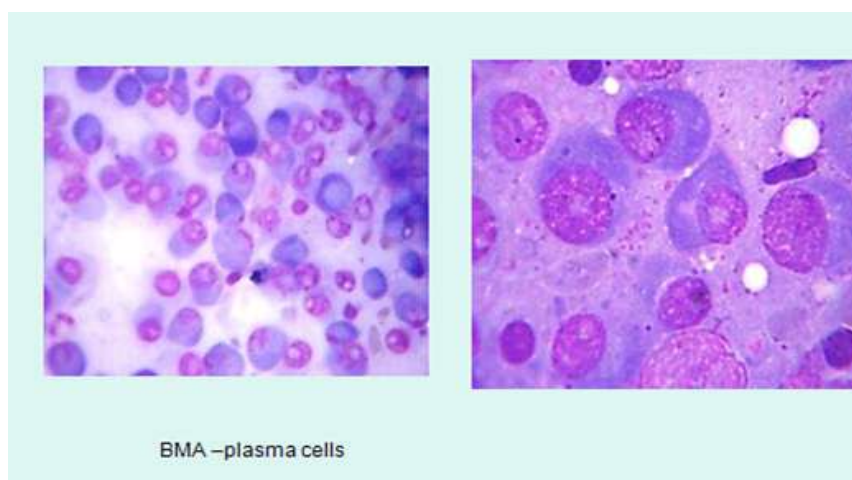
ISS Staging	
• Stage I	
– Serum albumin >3.5gm%	
– β 2 microglobulin <3.5 mg%	
• Stage II	
– Not meeting criteria of I & III	
– Serum albumin <3.5gm%	
– β 2 microglobulin 3.5-5.5 mg%	
• Stage III	
– β 2 microglobulin >5.5 mg%	

Our study group predominantly comprises cases belong to stage 2 according to ISS staging system.(10).



DISCUSSION

Multiple myeloma is a malignant disease characterized by plasmacytosis, paraprotein production, bone lesions, hypercalcemia, susceptibility to infections, and renal impairment. The underlying pathophysiologic phenomena of the clinical features include suppression of humoral- and cell-mediated immunity, elevation of IL-6, abnormalities of the bone marrow microenvironment, and increased osteoclastic activity. Overwhelming predictors of prognosis include albumin, β 2-microglobulin, and chromosomal karyotype. With modern, intensive therapy including autologous hematopoietic stem cell transplantation, the median survival is approximately 5 yr. The disease is incurable and eventually relapses; requiring salvage therapy. The development of newer agents such as thalidomide, bortezomib, and lenalidomide—drugs that interfere with several of the complex pathophysiologic steps—has improved the outlook of relapsed disease significantly. Current studies are directed at exploring the use of these novel agents earlier in the course of therapy, development of newer targeted therapies, and the use of gene expression profiling to individualize therapy.



Criteria for Δ of MM

Major criteria

Plasmacytoma on tissue biopsy
 Marrow plasmacytosis with >30% plasma cells
 Monoclonal globulins spike on serum electrophoresis
 >3.5g/dl for IgG (or) >2g/dl for IgA.

Minor criteria

Marrow plasmacytosis - 10-30%
 Monoclonal globulins spike percent but less than the levels depend above
 Lytic bone lesions.

Current research focuses as inflammatory alterations of the marrow microenvironment, which may contribute to the progression from essential monoclonal gammopathy to Myeloma.^[8]

Most cases of symptomatic Myeloma evolve from the precursor condition monoclonal gammopathy.^[8,9] Which is a stable neoplasm until it undergoes unpredictably, clonal evolution to Myeloma. De novo Myeloma, without a preceding stage of monoclonal gammopathy has been postulated for a small proportion of patients who develop the disease at a very young age (<30 yrs). The presence of somatic hypermutation in the Ig variable region genes of plasma cells of subjects with monoclonal gammopathy and Myeloma study in a B cell that has undergone differentiation in the germinal center. A major breakthrough in Myeloma genetics was the successful application of gene expression profiling of highly purified CD₁₃₈ plasma cells.

Myeloma is a malignancy of late stage B cells that mature principally into neoplastic plasma cells that produce a complete and or partial monoclonal immunoglobulin Proteins.^[11] Myeloma cells can induce alterations in the marrow microenvironment, which in turn provides survival factors that contribute to the resistance of Myeloma cells to many anti cancer drugs.^[13]

Plasma cell disorders encompass a spectrum including monoclonal gammopathy of unknown significance (MGUS), smoldering or indolent myeloma, and symptomatic myeloma, in order of increasing tumor burden.^[12] The differences between these are both quantitative and qualitative; MGUS and smoldering and indolent myeloma are very slowly proliferative and relatively stable diseases in contrast to active myeloma.

Although the disease is largely incurable, the past decade has seen dramatic progress in therapy and understanding of its pathophysiology. Since 1998, three new agents with significant anti-myeloma activity (thalidomide, bortezomib, and lenalidomide) have been identified.^[14] In contrast, the preceding three decades had been characterized by reliance on two active classes of agents: Alkylating agents (melphalan and cyclophosphamide) and corticosteroids. The median survival from diagnosis of patients with symptomatic disease that requires therapy is approximately 5 yr—an increase from 3 yr or so a decade ago, likely a result of widespread application of high-dosage chemotherapy with hematopoietic stem cell transplantation (HSCT) and new drugs.^[15]

The second player in MM pathogenesis consists of the interaction between the malignant clone and stromal cells through direct contact, soluble molecules, or exosomes, thus promoting tumor progression and drug resistance. The bone marrow (BM) microenvironment also includes T, natural killer, and dendritic cells, which play a critical role in immune surveillance; the importance of immune

monitoring will likely increase with the revival of immunotherapy and the possibility of therapeutic intervention through the blockade of immune checkpoints. In this series, both players (tumor cell genetics and tumor microenvironment) are reviewed in detail by Bianchi and Munshi.

Comparative studies

- 1) Robert A, Kyle et al (2008)
Diagnostic criteria : 10% plasma cells in marrow
❖ Monoclonal protein in serum/urine
❖ Evidence of elevated levels of immunoglobulins.
❖ In our study-criteria -10 to 30% of plasma cells
- 2) Michael Mulligen et al (2005).
Inclusion of at least skull, humerus, ribs, pelvis, femoral are important for diagnosis.
In our study-only axial skeletal involvement was noticed
- 3) Sharat et al(2011): Whole body MRI along with PECCT has positive predictive value of 100% for diagnosis of MM.
- 4) S. Vincent Raj kumar et al (2011).
❖ Plasma cell labelling index is a new marker for high risk disease.
- 5) G. Firman et al-Diagnostic critiering (2011).
❖ Presence of 'M' component in serum & urine
❖ Clonal plasma cells in BM
❖ Serum calcium >11.5mg/dl.
❖ s.creatine >2mg/dl
Same criteria has been used in our study.

CONCLUSION

Bone marrow aspiration cannot be taken as single diagnostic marker.

Ancilliary diagnostic tools,

- ❖ Serum protein electrophoresis, radiological & hematological evaluation.
- ❖ Beta₂ microglobulin is the single, most efficient progrowth & diagnostic marker.
- ❖ International staging system is useful predictive of survival.

This review focuses on recent clinical advancement in myeloma strategies with additional discussion dedicated to emerging drugs that may prove beneficial to patients with this disease.

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