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Original Research Paper

Pathology

DIAGNOSTIC AND PROGNOSTIC EVALUATION OF MULTIPLE MYELOMA

Guari Shanker Lal	Assistant Professor, Department of Pathology, Anugrah Narain Magadh Medical College, Gaya , Bihar
Subhash Chandra Jha	Assistant Professor , Department of Pathology, Government Medical College, Bettiah, Bihar
Bibhuti Bhusan Prasad*	Assistant Professor, Department of Pathology, Anugrah Narain Magadh Medical College, Gaya , Bihar *Corresponding Author

ABSTRACT

BACKGROUND: Multiple myeloma (MM) is an incurable clonal B-cell malignancy due to malignant proliferation of plasma cells, with an annual incidence of 1% of all malignancies. AIM: To study the diagnostic, epidemiological features and prognostic features MATERIALS AND METHODS: We conducted a retrospective study at our institute to identify patients diagnosed as MM from 2017 to 2018. We studied diagnostic, psognostic and clinical profile.

RESULTS: Median age at diagnosis was 63 years (range: 45–90 years). IgG myeloma was the most common type seen in 62% of patients. In our study anemia was most common presentation. All cases had plasma cells more than 10% in bone marrow

CONCLUSION: Multiple myeloma is common malignancy of Bihar, India in older population. Older patients presenting with refractory anemia must be evaluatyed for plasma cell dyscrasias , especially protein lectrophoresis and bone marrow study could clinch diagnosis in almost 100% cases.

KEYWORDS : Multiple myeloma, plasma cell dyscrasia,paraprotein, CRAB criteria

INTRODUCTION:

Multiple myeloma is a malignant neoplasm of plasma cells of bone marrow .It is B- cell lymphoproliferative diseases under the World Health Organization (WHO) classification. Multiple myeloma is characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow, leading to production of nonfunctional intact immunoglobulins or immunoglobulin chains. In the WHO classification, multiple myeloma is differentiated from the other plasma cell diseases **(1).**

Multiple myeloma accounts for around 1% of all cancers worldwide and 10–15% of all hematological neoplasms. Multiple myeloma is a malignant disease of plasma cells with a worldwide incidence of 6–7 cases per 100 000 persons per year . There are approximately 19,000 new cases/year in United States of America (USA) and an Indian incidence of 6,000 new cases/year. The male/female ratio is 1.4:1 and mean 5-year survival rate of 33% .As per western literature, median age at onset is 71 years for men and 74 years for women **(2).** The risk of multiple myeloma is much higher in older age groups; onset before the age of 45 is rare (around 2% of cases). The relative 5-year survival rate was about 45% . The etiology of the disease remains poorly understood.

Usually multiple myeloma develops from monoclonal gammopathy of uncertain significance, which is diagnosed, usually incidentally, in 3–5% of persons over the age of 50 years. The average risk of progression to multiple myeloma is around 1% per annum (3, 4). Another transitional phase on the way to symptomatic multiple myeloma is smoldering (asymptomatic) myeloma, which, in common with monoclonal gammopathy of uncertain significance, is characterized by the absence of organ damage (CRAB criteria) (Table 1). In the first 5 years after diagnosis the risk of progression is around 10% per year **(5).** Types of paraprotein :Serum heavy chain immunoglobulins (77%):Immunoglobulin G kappa or lambda multiple myeloma – Immunoglobulin A kappa or lambda multiple myeloma Urinary light chain immunoglobulins or Bence-Jones proteins (20%): – Kappa light chain multiple myeloma – Lambda light chain multiple myeloma No serum or urinary M-protein (3%): Nonsecretory multiple myeloma.

Table. 1.Classification of Monoclonal gammopathy

	MGUS	SMOLDERING myeloma	Symptomatic myeloma
Plasma cell	<10%	>10%	>10%
M protein in marrow	<30gm/dl	>30gm/dl	Detectable in urine& serum
End organ damage	NO	NO	Present

The indication for initiation of treatment for multiple myeloma is essentially determined according to the CRAB criteria. In a recommendation published in 2014, the International Myeloma Working Group (IMWG) revised the criteria and extended them to symptomatic multiple myeloma. The existing criteria were supplemented by newly defined biomarkers that identify asymptomatic patients with an elevated risk of progression. These patients might be treated with the aim to avoid early end-organ damage**(6) .**

Definition of symptomatic multiple myeloma according to the revised IMWG criteria: clonal plasma cells in bone marrow >10% or biopsy –confirmed bone marrow plasmacytoma or an extramedullary manifestation and one of the following myeloma defining events:

CRAB CRITERIA:

hypercalcaemia : Hypercalcemia (> 10.5 mg/dL or > 0.5 mg above normal limits , renal insufficiency :GFR<40ml/min or serum creatnine >177Umol/L ,anemia >2.0g/dl under lower limit of range or < 10g/dl, bone lesions > 1 lesion detected by radiography , computed tomography or positron emission tomography. In new criteria , biomarkers are important, clonal plasma cells in bone marrow >60%,ratio of involved/uninvolved free light chains (FLC)>100 and >1 focal lesion >5mm on magnetic resonance imaging(MRI). Minimal criteria for the diagnosis of multiple myeloma include the presence of at least 10% abnormal plasma cells in the bone marrow or histologic proof of a plasmacytoma, the usual clinical features of multiple myeloma, and at least one of the following abnormalities: monoclonal serum protein (usually greater than 3 g/dL), monoclonal protein in the urine, or osteolytic lesions **(7,8).**

Serum albumin and ß2-microglobulin were identified as independent prognostic markers and form three subgroups. Stage ISS III is associated with the worst survival(9).

Table. 2. International Staging System (ISS)

Stage	Laboratory parameters	Median survival(months)
1	Serum albumin> 35g/L,B2–microglobulin<3.5mg/L	62
2	Neither 1 or 3	44
3	B2-microglobulin >5.5mg/L	29

Cytogenetic changes are found in around one third of patients with multiple myeloma by conventional chromosome analysis and in over 90% when the FISH method is used. The genetic changes associated with a poor prognosis on FISH analysis include the immunoglobulin heavy-chain translocations t (4;14), t (14;16), and t (14;20), the 17p deletion, the 1p deletion, and amplifications of 1q. On conventional chromosome analysis the 13q deletion is also associated with an unfavorable prognosis**(10,11).**

Clinical features and diagnosis:

The symptoms reported by patients with multiple myeloma on presentation are often non-specific and may already have been present for an extended period. Anemia of unknown origin is found in 73% of patients, bone pain in 58%, and fatigue in 32%. Around 25% of them report unexplained weight loss, and renal function is often impaired **(11,12)).** In addition to history taking and physical examination, the diagnostic work-up for multiple myeloma comprises CBC, bone marrow , protein electrophoresis/immunoelectrophoresis,clinical chemistry, cytogenetic analysis of bone marrow, and radiological investigation to detect bone changes.

Immunoelectrophoresis or immunofixation is necessary for the identification of a monoclonal protein. During 1990 at the Mayo Clinic, 787 patients were found to have a monoclonal gammopathy. IgG accounted for 61% of the cases, followed by IgM (18%), IgA (11%), Bence Jones proteinuria (6%), biclonal gammopathy (3.5%), and IgD (0.5%). Monoclonal gammopathy of undetermined significance accounted for approximately two thirds of patients. This denotes the presence of a monoclonal protein in persons without evidence of multiple myeloma, macroglobulinemia, amyloidosis, or other related diseases. During long-term follow-up of patients with monoclonal gammopathy of undetermined significance, we found that one fourth developed multiple myeloma or related disorders. The interval from recognition of the monoclonal gammopathy to the diagnosis of multiple myeloma ranged from 2 to 29 years (median, 10 years)**(13,14).**

MATERIALS AND METHODS:

In this retrospective study, clinical , hematological, relevant biochemical , bone marrow and serum protein/ imm unofixation data of 18 cases of multiple myeloma were collected in years 2010 to 2018, from teaching tertiary hospital of Bihar . Prevalence of various type of monoclonal gammopathy were determined on basis of Immun oelectrophoresis results. CRAB criteria was ascertained on basis of renal function ,hempglobin , bone change and serum calcium findings.

RESULT:

Minimum age was 45 year , maximum age was 90 year and mean age was 63 year. Male female ratio was 2:1 Paraproteins immunoglobin types were IgG 60.5%, IgM 27.9%, IgA 16% . One was nonsecreting type and One case presented with pancytopenia and other one case presented with bicytopenia (anemia and thrombocytopenia)(Table, 3,4) . Rest 16 cases presented with severe anemia .Three cases presented with hypocalcaemia , three had normal serum calcium and rest had raised calcium level as per CRAB criteria. Two patients had bone fracture , one had spinal cord compression with bladder and bowel involvement. All cases except one had prominent M-band(Fig.1)

Table 3. HEMATOLOGICAL PROFILE OF MULTIPLE MYELOMA

CASE NO	GENDER	AGE	HGB	PLT	TLC	PBS ROULEAUX	BM PLASMA CELLS%	BMBX	ESR
1	M	64	5.5	173	3.6	+	32		90
2	F	50	6.2	292	7.6	+	62		152
3	F	58	5.7	180	5.5	+	60	done	90
4	M	50	6.5	155	7.0	-	35		80
5	M	70	6.0	190	5.8	-	80		125
6	F	55	7.5	200	7.0	+	45		100
7	M	70	5.8	80	8.5	+	70		110
8	M	68	9.0	155	5.9	-	45		90
9	F	55	6.5	170	5.8	+	70		100
10	M	50	8.0	180	7.5	+	49		130
11	F	90	4.8	250	11.5	+	75		150
12	M	45	7.5	190	10.5	+	55	done	99
13	M	55	6.8	100	15.9	+	88		120
14	M	68	6.0	215	9.0	+	45		90
15	F	70	5.6	70	3.5	+	78	Done	100
16	M	73	7.5	250	10.00	+	78		110
17	M	58	7.0	190	7.0	+	45		90
18	M	75	5.5	180	7.9	+	35		80

Table 4. BIOCHEMICAL PROFILE OF MULTIPLE MYELOMA

CASE NO.	GENDER	AGE IN YEARS	CREAT	TP	ALB	GLO	Y-GLOBULIN	M BAND	UA	CA	TYPE
1	M	64	0.87	9.51	2.31	7.20	4.96	4.22	7.24	11	IgG
2	F	50	0.90	10.80	2.50	7.30	5.30	4.10	8.00	15	IgG
3	F	58	1.3	11.10	2.05	6.50	5.00	4.50	12.10	8.7	IgA
4	M	50	4.0	5.90	3.50	2.40	2.0	1.50	7.0	7.9	IgG
5	M	52	3.0	7.0	2.5	4.5	3.5	2.00	8	7.0	IgG
6	F	55	5.0	10.00	3.00	7.00	5.60	4.50	9.4	11.5	IgG
7	M	70	1.9	5.5	2.5	3.0	2.5	NO	10.0	12.0	NON
8	M	68	2.5	5.8	2.0	3.8	3.0	2.0	9.0	11.00	IgG
9	F	69	1.8	4.0	3.0	1.0	0.8	TINY	4.5	9.0	IgA

10	M	50	2.8	7.0	2.0	5.0	4.5	3.5	10	12	IgM
11	F	90	3.8	11.5	2.3	9.2	7.5	4.0	12	13.5	IgG
12	M	45	1.2	9.0	3.5	5.5	4.0	3.5	5.8	12.0	IgG
13	M	55	4.8	6.8	2.0	4.8	3.8	3.0	9.7	11.5	IgM
14	F	68	1.9	5.5	1.9	3.6	3.0	2.0	7.8	10.00	IgG
15	F	70	1.5	10.3	3.0	7.5	5.8	5.4	8.0	9.9	IgG
16	M	73	5.8	12.0	2.5	9.5	7.0	5.9	11.5	13.8	IgM
17	M	55	5.9	11.0	3.0	8.0	7.5	5.8	12.0	11.5	IgG
18	M	80	4.5	10.8	6.0	3.2	3.0	2.0	7.9	7.8	IgA

CREAT: creatnine TP: total protein, ALB: albumin, GLO: globulin UA: uric acid CA: calcium

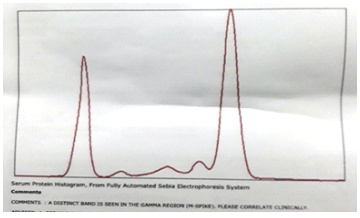

Fig. 1.Serum Protein Electrophoresis

DISCUSSION:

Serum protein electrophoresis and bone marrow are necessary for the identification of a monoclonal protein. Further typing is possible with immunoelectrophoresis.Mayo clinic data revealed IgG 61% of the total cases, followed by IgM (18%), IgA (11%), Bence Jones proteinemia (6%), biclonal gammopathy (3.5%), and IgD (0.5%) **(1).** Our data revealed 62% IgG type multiple myeloma. Monoclonal gammopathy of undetermined significance accounted for approximately two thirds of patients. Minimal criteria for the diagnosis of multiple myeloma include the presence of at least 10% monoclonal neoplastic plasma cells in the bone marrow biopsy or histologic proof of a plasmacytoma, the usual clinical features of multiple myeloma, and at least one of the following abnormalities: monoclonal serum protein (usually greater than 3 g/dL), monoclonal protein in the urine, or osteolytic lesions**(7,8).** In our study bone marrow aspiration findings revealed more than 30% plasma cells alongwith monoclonal gammopathy.Atleast further evaluation is not needed for diagnosis.The most dependable means is serial measurement of the monoclonal protein in the serum and urine and periodic re-evaluation of pertinent clinical and laboratory features to determine whether multiple myeloma, systemic amyloidosis, macroglobulinemia, or other lymphoplasma cell proliferative disease has developed in MGUS**(2,9).** Our study shows that the median age at diagnosis was 63 years which was comparable to the Western population. In addition, the number of patients diagnosed as ISS III was higher in our study as compared to the Western data where the maximum number of patients were in ISS II, perhaps late presentation of patients to tp clinic ,especially in rural areas.

CONCLUSION:

Multiple myeloma is major malignancy of old age, affecting both genders. It is malignant systemic hematological disease occurs due to monoclonal proliferations of plasma cells in bone marrow or presenting as plasmacytoma . It is characterized by the presence of monoclonal immunoproteins in the serum and/or urine.

The diagnostic evaluation of multiple myeloma comprises thorough history-taking and physical examination, various laboratory tests including analysis of a 24-hour urine sample, a bone marrow aspiration, bone marrow biopsy, and skeletal radiography.

The indication for treatment is based on the demonstration of organ damage ,as assessed using the CRAB criteria) and recently defined biomarkers.

The diagnostic work-up comprises mandatory analysis of blood and urine samples, bone marrow evaluation, protein electrophoresis/immunofixation and imaging procedures. In particular, the median survival of patients with multiple myeloma has been markedly prolonged through the use of targeted drugs such as proteasome inhibitors and immune modulators. So early diagnosis is very important.

REFERENCES:

1. Swerdlow SH, Campo E, Harris NL, et al. Lyon, France: IARC Press;; 2008. WHO classification of tumours of haematopoietic and lymphoid tissues.
2. 3. Landgren O, Kyle RA, Pfeifer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113:5412–5417.[PMC free article] [PubMed]
3. 4. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354:1362–1369. [PubMed]
4. 5. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood. 2015;125:3069–3075.[PMC free article] [PubMed]
5. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:538–548. [PubMed]
6. 7. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. Cancer. 1975;36:842–854. [PubMed]
7. 8. Greipp PR, San Miguel JF, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412–3420. [PubMed
8. 10. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78:21–33. [PubMed]
9. 11. Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011;117:4701–4705.[PubMed]
10. 12. Pulte D, Jansen L, Castro FA, et al. Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. J Hematol Oncol. 2016;22 [PubMed]
11. Jacob LA, Suresh Babu M C, Lakshmaiah K C, Babu K G, Lokanatha D, Rajeev L K, Lokesh K N, Rudresha A H, Agarwal A, Garg S. Multiple myeloma: Experience of an institute in limited resource setting. Indian J Cancer 2017;54:340-2
12. Rajkumar SV, Kyle RA, Buadi FK. Advances in the diagnosis, classification, risk stratification and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence. Mayo Clin Proc. 2010;85(10):945-8
13. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011;117(18):4701–4705. doi: 10.1182/blood-2010-10-299529. [PubMed] [CrossRef] [Google Scholar
14. Rajkumar SV. Myeloma today: disease definitions and treatment advances. Am J Hematol. 2016;91(1):90–100. doi: 10.1002/ajh.24236. [PMC free article] [PubMed] [CrossRef] [Google Scholar]