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Original Article

Evaluation of serum protein electrophoresis in suspected cases of multiple myeloma

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ABSTRACT

Background: Plasma cell neoplasm is a spectrum of diseases ranging from monoclonal gammopathy of unknown significance to plasma cell leukaemia. These plasma cells secrete immunoglobulin, which can be isotyped by immunoelectrophoresis or immunofixation. This study aimed to detect M protein in suspected cases of multiple myeloma and to identify the isotype of the M protein identified.

Materials and Methods: Serum samples received in the Department of Pathology, Maharajgunj Medical Campus, Kathmandu, Nepal, from May 2022 to April 2024 were included in the study. Protein electrophoresis and isotyping were performed by automated capillary electrophoresis, Sebia Capillarys 2 Flex Piercing System. SPSS Vs 16 was used for statistical analysis.

Results: Among the 1839 serum samples received, M-protein was seen in 94 cases (5.1%). Protein electrophoresis showed M spike in the gamma region in 62 cases (65.9%). In 33 cases (35.1%), where bone marrow diagnosis was available, multiple myeloma was seen in 23 cases (69.6%), lymphoplasmacytic lymphoma in eight cases (24.2%), and marginal zone lymphoma in two cases (6.2%). Forty-seven cases (50%) had immunotyping, which showed IgG kappa in 19 cases (40.4%), followed by IgA lambda. Elevated IgG kappa was associated with multiple myeloma, 83.3%, and Ig M kappa with lymphoplasmacytic lymphoma, 71.4%, p 0.001.

Conclusions: IgG kappa is the most common immunoglobulin identified in multiple myeloma. In plasma cell neoplasm, the M spike is primarily IgG kappa located in the gamma region. However, when Ig M is observed in the beta region, other possibilities must also be considered.

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INTRODUCTION

Multiple myeloma is a neoplasm of plasma cells where abnormal growth of plasma cells outnumbers other normal hematopoietic cells in the bone marrow. These plasma cell clones secrete huge quantities of abnormal immunoglobulin that can result in end-organ dysfunction.[1]

It accounts for 10% of all the haematological malignancies.[2] Plasma cell neoplasm is a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukaemia. The symptoms that are suspicious for a plasma cell disorder include back pain, weakness,

fatigue, osteolytic lesions, renal failure, spontaneous fractures, and recurrent infections.

The abnormal immunoglobulin, M-protein, can be detected in serum and urine by electrophoresis. Serum protein electrophoresis (SPEP) is a laboratory technique wherein serum is applied to a support medium and then subjected to an electric current. The serum proteins then separate into six fractions, namely – albumin, α1, α2, β1, β2, and the γ globulin.[3] The elevated immunoglobulin can be isotyped by immunoelectrophoresis (IEP) or immunofixation (IFE).

In serum protein electrophoresis, most attention is on the gamma region, which is composed predominantly of immunoglobulins. There is a decrease in gamma-globulin fraction in hypogammaglobulinemia and agammaglobulinemia, whereas it is increased in diseases like chronic lymphocytic lymphoma, Waldenström's macroglobulinemia, connective tissue disorders, granulomatous inflammation, liver diseases, multiple myeloma, and amyloidosis.[4]

This study aimed to detect M protein in suspected cases of multiple myeloma and to identify the isotype of the M protein identified.

MATERIALS AND METHODS

Serum samples of suspected cases of multiple myeloma received in the Department of Pathology, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Kathmandu, Nepal, from May 2022 to April 2024 were included in the study. Protein electrophoresis was performed by an automated capillary electrophoresis system, Sebia Capillarys 2 Flex Piercing System. Isotyping of the raised M protein was done by IEP using the same analyzer. Bone marrow aspiration, biopsy, and immunohistochemistry of the cases that had "M spike", if available, were analysed. SPSS version 16 was used for statistical analysis.

RESULTS

In the two-year study period, 1839 serum samples of suspected cases of multiple myeloma were received for protein analysis in the department. M protein was seen in 94 cases (5.1%). The age of these patients ranged from 28 to 93 years, with a mean age at 62.7years. The most common age group was 61-70 years, 35 cases (37.3%). The maximum age range was 91-100 years, one case (1.1%). The youngest age group was 21-30, comprising two cases (2.2%). The male: female ratio was 1.5:1.

In the serum protein electrophoresis, the M spike was seen in the gamma region in 62 cases (65.9%), followed by the beta 2 region with 32 cases (34.1%) (fig. 1). The concentration of M protein ranged from 8.2 to 102.7 gm/L with a median value of 23.7 gm/L.

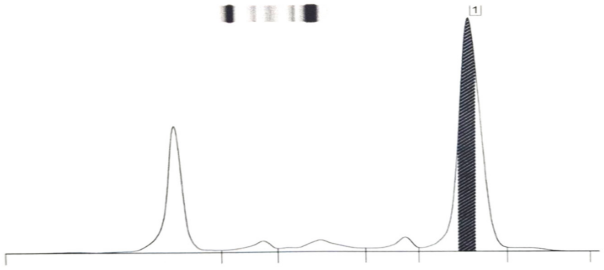

Figure 1: *"M" spike seen in beta 2 region in serum protein capillary electrophoresis*

In 33 cases (35.1%), bone marrow aspiration, biopsy, and immunohistochemistry were available. Multiple myeloma was diagnosed in 23/33 cases (69.6%), lymphoplasmacytic lymphoma in eight cases (24.2%), and marginal zone lymphoma in two cases (6.2%). In cases of multiple myeloma, M spike was predominantly seen in the gamma region, 17 cases (74%). In lymphoplasmacytic lymphoma, the peak was commonly seen in the beta 2 region, 5 cases (62.5%). A significant statistical correlation could be established between the region of M spike and the diagnosis of multiple myeloma with p-value 0.002 (Chi-square test). Hence, the spike in the gamma region was more likely in multiple myeloma.

Table 1: Age and sex distribution of patient with "M" spike

Age	Sex		Total (%)
	Male (%)	Female(%)	
21-30	0 (0)	2 (5.4)	2 (2.1)
31-40	1 (1.8)	1 (2.7)	2 (2.1)
41-50	5 (8.8)	6 (16.2)	11 (11.7)
51-60	12 (21)	7 (19)	19 (20.2)
61-70	22 (38.5)	13 (35.1)	35 (37.3)
71-80	14 (24.6)	8 (21.6)	22 (23.4)
81-90	2 (3.5)	0 (0)	2 (2.1)
91-100	1 (1.8)	0 (0)	1 (1.1)
Total	57 (100)	37 (100)	94 (100)

Out of the 94 cases, 47 cases (50%) had serum immunotyping done for subtyping the immunoglobulin. From the total of these 47 cases, the most common type of immunoglobulin identified was IgG kappa [19/47 cases (40.4%)], followed by Ig A lambda [nine cases (19.2%)]. Other immunoglobulins noted were IgG lambda in seven cases (14.9%), IgM kappa in 8 cases (17%), IgM lambda and IgA kappa in one case each (2.15). Free light chain lambda was detected in two cases (4.35%).

Table 2: Bone marrow diagnosis and region of "M" spike in protein electrophoresis

Region	Bone marrow			Total (%)
	LPL (%)	MM (%)	MZL (%)	
Beta 2	5 (62.5)	6 (26)	0 (0)	11 (33.3)
Gamma	3 (37.5)	17 (74)	2 (100)	22 (66.4)
Total	8 (100)	23 (100)	2 (100)	33 (100)

LPL lymphoplasmacytic lymphoma, MM multiple myeloma, MZL marginal zone lymphoma

Both the bone marrow diagnosis and immunotyping could be correlated in 25 cases. Among the subtypes of immunoglobulins, elevated IgG kappa was associated with multiple myeloma [ten cases (83.3%)], and IgM kappa with lymphoplasmacytic lymphoma, five cases (71.4%). A significant statistical correlation between immunoglobulin subtype and diagnosis of multiple myeloma could be established, p-value 0.001(Chi-square test). Hence, IgG kappa was more likely to be seen in multiple myeloma.

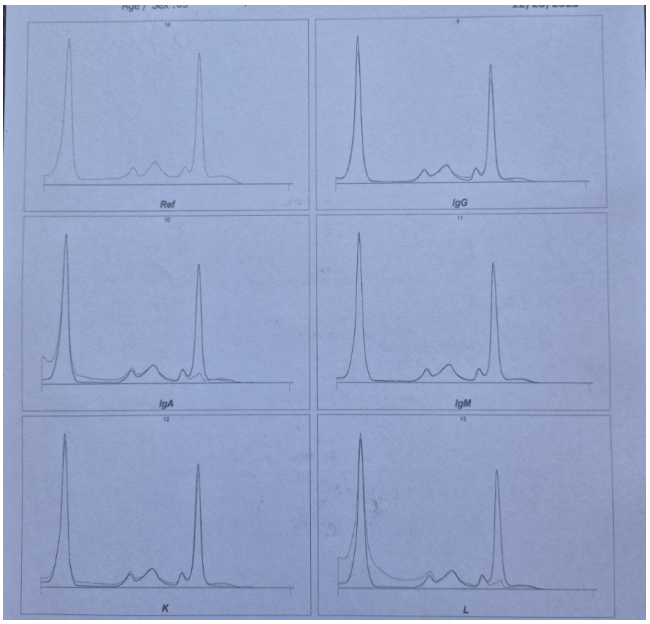

Figure 2: *Immunoelectrophoresis pattern showing Ig A lambda in beta 2 region*

Table 3: Isotype of immunoglobulin along with their regional location

Region	Ig G κ (%)	Ig G λ (%)	Ig M κ (%)	Ig M λ (%)	Ig A κ (%)	Ig A λ (%)	Free light chain λ (%)	Total (%)
Beta	5 (26.3)	1(14.3)	6 (75)	0 (0)	1(100)	6(66.7)	0(0)	19(40.4)
Gamma	14(73.7)	6(85.7)	2(25)	1(100)	0(0)	3(33.3)	2(100)	27(59.6)
Total	19 (100)	7(100)	8(100)	1(100)	1(100)	9(100)	2(100)	47(100)

Ig immunoglobulin, K kappa, λ lambda

Table 4: Bone marrow diagnosis and isotyping of M protein

Diagnosis	Ig G κ (%)	Ig G λ(%)	Ig M κ (%)	Ig M λ (%)	Ig A λ (%)	Total (%)
LPL	2 (16.6)	0 (0)	5(71.4)	1(100)	0 (0)	8 (32)
MM	10 (83.4)	1 (100)	0(0)	0 (0)	4 (100)	15 (60)
MZL	0 (0)	0 (0)	2(28.6)	0 (0)	0 (0)	2(1.3)
Total	12 (100)	1 (100)	7(100)	1 (100)	4 (100)	25 (8)

LPL lymphoplasmacytic lymphoma, MM multiple myeloma, MZL marginal zone lymphoma

DISCUSSION

The detection of monoclonal gammopathy can be a casual finding in a routine workup of a patient. This can point the clinician towards the diagnosis, or the search for M spike, often suggested by the clinical presentation. The monoclonal gammopathies is seen in malignancies like plasma cell dyscrasias, Non-Hodgkin lymphoma e.g. chronic lymphocytic leukaemia, mantle cell lymphoma, marginal zone lymphoma, some cases of diffuse large B-cell lymphoma and benign idiopathic forms of unknown significance e.g. aging, carcinoma, post cardiac surgery, viral and parasitic infections, and associated with certain drug therapy (penicillin, diphenylhydantoin, sulfonamides etc.).[5-6]

In our study, 5.1% (94 cases) of the suspected cases had monoclonal gammopathy. Various other studies reported a range of positivity, 4.8%[6], 5.8%[7] and 24.4%.[5] We found a male-to-female ratio of 1.5:1, whereas it was 1.2:1 in a study by Chopra et al.[5] A slight male predominance was seen in a similar study conducted by Nayak et al.[8]

Though the disease is common in males, only limited data on reproductive and hormonal factors that can explain this difference are available. Use of menopausal hormone therapy (MHT) has been associated with an increased risk of carcinomas of other organs but no significant association has been detected between MHT and multiple myeloma.[9-10] Similarly, no significant association with age at first birth, parity, number of abortions,[11-12] previous diagnosis of endometriosis,[13] or the time since last birth has been found.[14]

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A peak (35 cases, 37.3%) was seen in the age group 61-70 years in both sexes in our study. Whereas, a study found that the disease was more common in 61-70 years age group in females, as compared to 51- 60 years in males.[15] Males presented a decade earlier in their study. We found a mean age of presentation at 62.7years. Nayak et al. reported a mean age of 61 years.[8]

We found that the gamma region was the most common site for M spike followed by Beta 2 region. Similar findings were seen in studies conducted by Chopra et al[5] and Tripathy et al[15]. The median value of the monoclonal protein in serum protein electrophoresis was 23.7 gm/L. Fonsea et al reported a median value of 13.5 gm/L in their study of 72 patients with monoclonal gammopathy.[16]

Out of the 33 cases where bone marrow studies were available, 23 (69.6%) of the cases fulfilled the criteria for diagnosis of multiple myeloma.[17] Eight were diagnosed as lymphoplasmacytic lymphoma and two as marginal zone lymphoma on bone marrow studies.

In multiple myeloma, IgG kappa was the most common immunoglobulin followed by IgA lambda. Other studies found that IgG lambda was more common (50%) as compared to IgG kappa myeloma (40%).[15] IgM kappa and IgA lambda myeloma were found in only 5% each in their study.[15] Ig G kappa predominance was reported in a study by Fonsea et al.[16]

When monoclonal protein is detected in serum protein electrophoresis, the heavy – and light-chain isotypes are further subtyped by IEP or IFE. While interpreting an IEP, if there is a subtraction in the light chain curve without the corresponding abnormality in the IgG, IgA or IgM region, then the possibility of IgD or IgE paraprotein should be investigated. IgD or IgE myeloma was not detected in our study, as in other studies.[8] IFE is more sensitive than IEP and therefore is particularly helpful in the detection of a small residual M component after therapy treatment.[15]

Two cases of free light chain–lambda myeloma were detected in our study in a 74-year-old and a 76-year-old male. Light-chain myeloma is a subtype of myeloma that accounts for 8 - 20 % of all myelomas. This frequency is probably underestimated because of the difficulty in the diagnosis of this biological subtype.[18-19] Light-chain myelomas are likely to be missed in protein electrophoresis as the amount of M proteins in these patients is low and M-protein peaks are not obviously seen in electrophoresis.[8] Reports of light chain myeloma has been seen in literature.[20-21]

In our study all cases of LPL had predominantly IgM monoclonal gammopathy. By definition, it is always associated with IgM paraproteinemia.[22] In contrast to this, cases of LPL associated with IgG monoclonal gammopathy have been reported.[23] Two cases (2/8 cases, 25%) of LPL in our study were associated with IgG gammopathy. Bone marrow infiltration by lymphoplasmacytic cells along with M spike is required for the diagnosis of Waldenstrom macroglobulinemia.

Patients with other types of Non-Hodgkin lymphoma can also exhibit IgM gammopathy, 20.2% of chronic lymphocytic leukemia, and 7.1% of marginal zone lymphoma, as reported in a study.[24] In our study, 8% (2 out of 8 cases) of IgM spike was associated with marginal zone lymphoma.

CONCLUSIONS

Serum protein electrophoresis is a simple laboratory test that can be utilized for the detection and quantification of monoclonal gammopathy. It is recommended as an initial test for suspected cases of multiple myeloma. In plasma cell neoplasm, the M spike is primarily IgG kappa located in the gamma region. However, when IgM is observed in the beta region, other possibilities must be considered.

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