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Clinical features of patients with monoclonal gammopathy

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ABSTRACT

Objectives: In this study, we aimed to demonstrate ordered immunofixation electrophoresis (IFE) testing for distinct indications from different inpatient and outpatient clinics, interrelate the IFE results and patients' clinical and laboratory characteristics, and classify the confirmed cases of monoclonal gammopathy (MG).

Methods: We included 4,474 IFE tests conducted between December 2013 and July 2016 in this study. Out of these, the tests of 472 patients with MG were retrospectively evaluated.

Results: The patients' median age was 64 years (range, 17–90). Seventy-four percent of the IFEs were ordered by Hematology, 13.1% by the General Internal Medicine Department, 5% by other internal medicine departments, and the rest were ordered by different clinics. Moreover, 59.5% of IFEs were ordered as diagnostic workups for multiple myeloma, 13.3% for lymphoma; 2.5% for polyneuropathy, and 0.4% for amyloidosis. Among the patients with definitive diagnosis and MG, 44.5% had plasma cell diseases and 14.6% had lymphoproliferative diseases. The most common non-hematological condition associated with MG was rheumatic disease.

Conclusion: Clinicians should be aware of other indications for ordering IFE in diagnostic workups of rare diseases with different clinical presentations, such as unexplained polyneuropathies or autoimmune diseases, which may be associated with MG.

Keywords: Monoclonal gammopathy, Immunofixation electrophoresis, Plasma cell disorders, Lymphoma, Rheumatologic disorders

The monoclonal gammopathies are a group of disorders characterized by the proliferation of a single clone of plasma cells or lymphoplasmacytic cells; this produces an immunologically homogenous protein, commonly referred to as a paraprotein or monoclonal protein (M-protein), which can be detected via immunofixation of serum, urine, and/or other body fluids. The finding of a monoclonal protein represents one of the most common laboratory abnormalities in adults and one of the most frequent causes of hematology consultation. The presence of an M-protein in the serum or urine indicates, among other disorders, an underlying clonal plasma cell or lymphoproliferative, connective tissue, dermatological, or infectious disorder.[1, 2]

Although there have been several prevalence and incidence studies of monoclonal gammopathy of undetermined significance (MGUS) performed in the literature.[3, 6], there has been no research study indicating the aim of ordering immunofixation electro-

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phoresis (IFE) tests in different medical departments. Therefore, in this study, we aimed to evaluate the ordered IFE testing for different indications from different inpatient and outpatient clinics, interrelate the IFE results and patients' clinical and laboratory characteristics, and classify the confirmed cases of monoclonal gammopathy (MG).

METHODS

Patients and Study Design

We conducted a retrospective study of the all patients in whom immunofixation studies were done at a multidisciplinary hospital, over a nearly 2-year period (December 2013–July 2016). Of the 4,474 patients tested with IFE, 472 were identified with confirmed MG positivity. The available medical files and biological results of all IFE-positive patients were retrospectively reviewed. Age, gender, serum, and urine IFE results, indications for IFE testing, clinical data, and final diagnoses were analyzed in these patients. Subgroups of monoclonal proteins were recorded. Patients were then grouped according to their immunofixation findings, and associations with the above demographic, diagnosis, clinical, and laboratory variables were assessed.

Ethical considerations

The study protocol was approved by the institu-

Table 1. Distribution of medical departments that ordered the immunofixation electrophoresis

DEPARTMENT	Ordered IFEs		M band +	
	n (4474)	%	n (472)	%
MEDICAL DEPARTMENT				
Hematology	2003	44.8	349	74
General Internal Medicine	1076	24	62	13
Physical Therapy and Rehabilitation	472	10.6	13	2.9
Nephrology	*234*		*9*	
Rheumatology	*109*		*6*	
Gastroenterology	*40*		*1*	
Oncology	*35*		*2*	
Endocrinology	*22*		*1*	
Neurology	161	3.6	8	1.7
Cardiology	64	1.4	2	0.4
Pulmonary Medicine	55	1.2	2	0.4
Infectious Diseases	47	1	7	1.5
Dermatology	10		1	0.2
SURGICAL DEPARTMENT				
Neurosurgery	52	1.1	2	0.4
Transplant Centre	37	0.9	4	0.8
Otorhinolaryngology	17		0	
General Surgery	12		1	0.2
Gynecology	11		0	
Thoracic Surgery	7		1	0.2
Orthopedic Surgery	4		0	
Plastic and Reconstructive Surgery	3		0	
Ophthalmology	3		0	
TOTAL	**4474**			

Abbreviations; IFE; immunofixation electrophoresis

tional ethics committee (date/number:17.08.2016/468) and conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. There was no sponsor for the study.

Statistical analysis

All statistical analyses were performed using the SPSS 20.0 program (SPSS, Chicago, Illinois, USA). The chi-square test was used for categorical data. The findings are given as the median, minimum, and maximum for age. Descriptive values for the other data are given as numbers (percent).

RESULTS

In this study, we investigated which clinical department performed the IFE for 4,474 patients (Table 1). Of the patients tested, 472 (10.5%) had positive immunofixation test results. The mean age for the patients who had positive immunofixation test results was 64 (range, 17–94) years, comprising 247 men and 225 women. The preliminary diagnoses of the 472 patients are given in figure 1. The most common preliminary diagnoses were multiple myeloma (59.5%), lymphoma (13.3%), neuropathic diseases (2.5%), and amyloidosis (0.4%), but for 114 (24.3%) patients, there were various other reasons for performing IFE, including pancytopenia, thrombocytopenia, neutropenia, muscle weakness, and unknown.

The reasons for performing IFE and which department performed the testing were evaluated. The reasons for performing IFE in the department of endocrinology were not clear. In the other departments, IFEs were performed infrequently for cancer screening in patients presenting with consistent symptoms and laboratory results, including unexplained fatigue, weight loss, anemia, and elevated sedimentation rates. These patients were then diagnosed with multiple myeloma (MM) or myelodysplastic syndrome.

The definitive diagnoses of 472 patients are given in figure 2. As expected, plasma cell neoplasms were the most frequent disorder; 144 (87.6%) patients were diagnosed with multiple myeloma and 69 with lymphoproliferative disorder. Most of them were non-Hodgkin lymphoma (NHL; 72.5%). Diffuse large B-cell lymphoma cases were the most common subtype of NHL cases. However, lymphoma subtype analysis could not be performed or the data could not be retrieved for about half of the NHL cases. The distribution of diagnoses for the 84 patients in figure 2a labelled ‘other’ are given in table 2. Rheumatoid arthritis and ankylosing spondylitis were the most frequently detected rheumatological disorders. In 11 patients with known chronic kidney disease and MG who had been followed up in other services, sufficient data could not be obtained.

Heavy- and light-chain distributions of plasma cell disorders, lymphoproliferative disorders, rheumatological disorders, chronic kidney diseases, and myelodysplastic syndromes are presented in Tables 3, 4, and 5, respectively. The most commonly observed monoclonal protein subtype was immunoglobulin G (IgG) kappa. Heavy and light chain distributions of rheumatological disorders, chronic kidney disease and

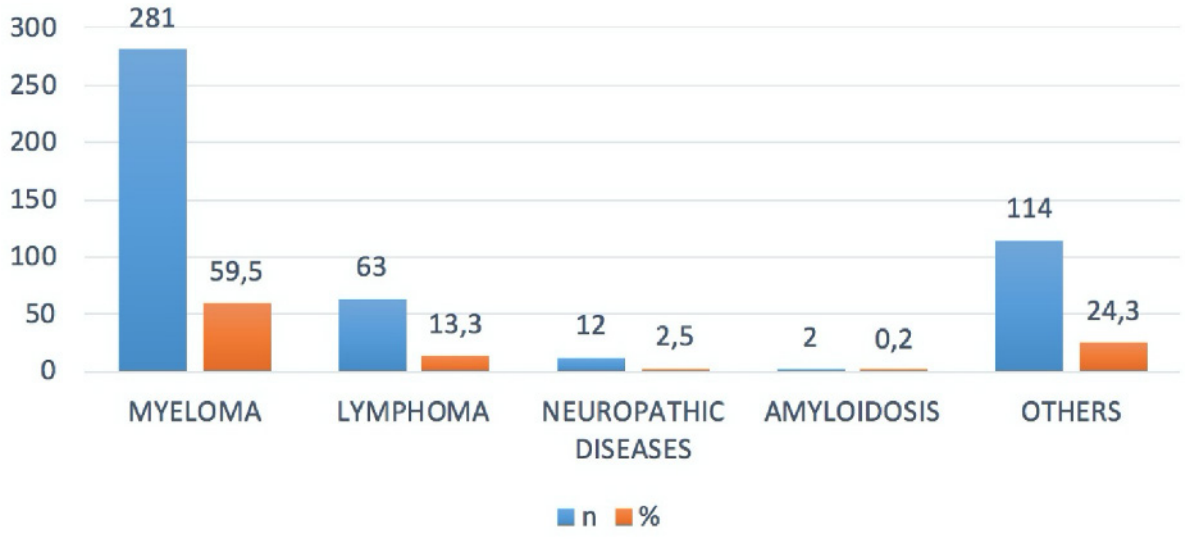

Figure 1. **Distribution of preliminary diagnoses**

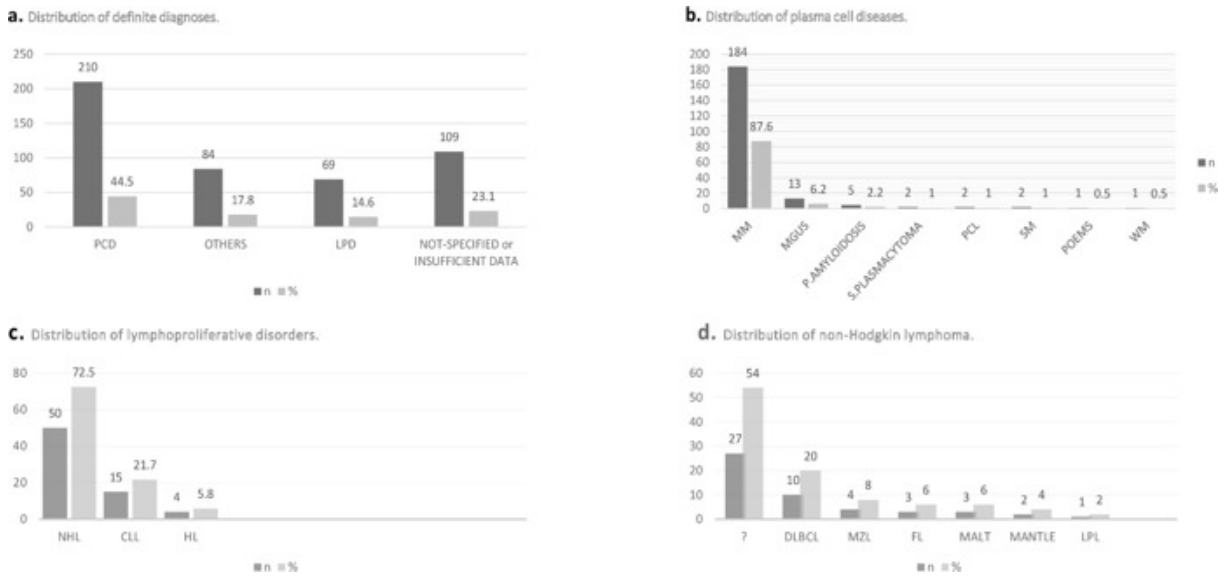

Figure 2. Distribution of diagnoses

myelodysplastic syndrome are given in Table 6.

DISCUSSION

This was a single center study in which IFE results from different medical and surgical departments were screened; 472 patients with monoclonal band positivity were evaluated retrospectively. We aimed to identify the reasons for IFE testing at different clinics, and in this way, evaluate physician awareness. As we know, there is no similar study in the English literature.

In terms of demographic characteristics, the median age and gender characteristics of the patients with monoclonal band positivity were similar to those

Table 2. The distribution of diagnosis for 84 patients in graphic 2 named 'others'

Disorders	n (84)	%
Rheumatic Disorders	30	35.7
Chronic Kidney Disease	11	13.1
Myelodysplastic syndrome	11	13.1
Solid Tumor	8	9.5
Leukemia (ALL/AML)	6	7.2
Myelofibrosis	4	4.7
Organ Transplantation	4	4.7
Renal transplantation	3	3.5
Liver transplantation	4	4.7
MG associated neuropathy	1	1.2
MG associated crystal keratopath	1	1.2
MG associated cryoglobulinemia type 1	1	1.2
HIV infection	2	2.4
Iron Deficiency Anemia	2	2.4
Paroxysmal nocturnal hemoglobinuria	1	1.2
Autoimmune Hemolytic Anemia	1	1.2
Antiphospholipid Antibody Syndrome	1	1.2

Abbreviations; ALL;acute lymphocytic leukemia, AML; acute myeloidleukemia, MG; monoclonal gammopathy, HIV; human immunodeficiency virus

Table 4. Heavy and light chain distribution of plasma cell disorders

Plasma cell disorders	n (210)	%
MM	**184**	**87.6**
IgG (κ / λ)	97 (71/26)	45.4
IgA (κ / λ)	37 (22/15)	17.7
IgM (κ / λ)	5 (3/2)	02.3
Light chain (κ light chain/ λ light chain)	44 (26/18)	21.8
IgD λ	1	0.04
MGUS	**13**	**06.2**
IgG (κ / λ)	9 (5/4)	04.4
IgM (κ / λ)	2 (1/1)	00.9
Light chain (κ light chain/ λ light chain)	2 (1/1)	00.9
Primer Amiloidoz	**5**	**02.2**
IgG (κ / λ)	4 (2/2)	01.8
IgM λ	1	00.4
Solitary plasmacytoma	**2**	**01.0**
IgA κ	1	00.5
IgG κ	1	00.5
Plasma cell leukemia	**2**	**01.0**
κ light chain	1	00.5
IgG λ	1	00.5
Smoldering myeloma	**2**	**01.0**
IgG κ	2	01.0
POEMS	**1**	**00.5**
IgA λ	1	00.5
WM	**1**	**00.5**
IgM κ	1	00.5

Abbreviations; MM; multiple myelom, IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, IgD; immunoglobulin D, MGUS; monoclonal gammopathy of undetermined significance, POEMS; Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes syndrome, WM; Waldenström makroglobulinemisi

of two previous studies.[7, 8] Like in other studies, the most commonly observed monoclonal protein isotypes were IgG kappa and kappa MG in serum and urine, respectively. IFE tests were mostly planned by Hematology and General Internal Medicine clinics. Plasma cell disorders and lymphoproliferative disorders were the most frequent, and MM was the most common among the plasma cell disorders. These results were similar to those reported in the Mayo Clinic study by Kyle *et al*.[9]

In 84 patients in the "other disorder with MG" class, the most common disorders were rheumatological diseases; among these, rheumatoid arthritis and ankylosing spondylitis were the most common. In addition, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, and psoriatic arthritis cases were observed. A meta-analysis performed by McShane *et al*.[10] did not show a significant increase in risk between the development of MGUS in rheumatoid arthritis and ankylosing spondylitis patients, but in this study, the number of cases was insufficient and a heterogeneous group was evaluated. In another prospective study of patients with Sjogren's syndrome, MG was detected more prevalently in the patients, and hematological malignancy was later reported in these patients.[11]

One patient presenting with angioedema had IgM lambda MG and C1 inhibitor deficiency in the serum; this patient was diagnosed with splenic mar-

Table 5. Heavy and light chain distribution of lymphoproliferative disorders

Lymphoproliferative disorders Type of M component	n (69)	%
Non-Hodgkin Lymphoma	**49**	**71.0**
IgG (κ / λ)	14 (10/4)	
IgA (κ / λ)	2 (1/1)	
IgM (κ / λ)	16 (10/6)	
Biclonal	5	
κ light chain	9	
λ light chain	2	
Triclonal	1	
CLL	**15**	**27.1**
IgG (κ / λ)	8 (6/2)	
IgA (κ / λ)	2 (1/1)	
IgM (κ / λ)	3 (2/1)	
Biclonal	1	
κ light chain	1	
Hodgkin Lymphoma	**4**	**05.8**
IgG (κ / λ)	2(1/1)	
IgM κ	1	
λ light chain	1	
LPL	**1**	**01.4**
IgM κ	1	

Abbreviations; IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, CLL; chronic lymphocytic leukemia, LPL; Lenfoplazmasitik Lenfoma

ginal zone lymphoma. In a study evaluating acquired C1 inhibitor deficiency and MG prevalence at the time of diagnosis of 19 patients with C1 inhibitor deficiency-related angioedema, MG was detected in 12 patients. Eleven of these 12 patients had the same heavy- and light-chain isotype as the C1 inhibitor antibody, and 3 of these patients developed lymphoproliferative disease within 6 years. A possible underlying mechanism for this is the clonal increase of B-cells producing C1 inhibitor antibody; thus, it should be kept in mind that lymphoid malignancies may develop in patients presenting with angioedema and MG.[12] In another study involving 32 patients with acquired C1 inhibitor deficiency, 9 were diagnosed with NHL.[13]

One patient presented with generalized livedo reticularis as the first manifestation of type 1 cryoglobulinemia. There are many skin manifestations associated with MGs. Today, these are classified as MG of cutaneous significance.[14] Type I cryoglobulinemia (CG) is usually asymptomatic. When it is symptomatic, it most commonly causes signs related to hyperviscosity and blood vessel occlusion due to the precipitation of immunoglobulins in response to cold. The Raynaud phenomenon, livedo reticularis, and digital ischemia may occur and are often found on acral areas. Type I CG is usually associated with multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, or MG of unknown significance.

One patient presented with blurred vision as the first manifestation of MG-related crystal keratopathy. IgG kappa and kappa MGs were observed in the patient's serum and urine, respectively. Crystalline keratopathy is a rare result of MG and estimated to occur in up to 1% of cases with MG. Pathological changes leading to visual dysfunction may be observed or corneal deposits may be the only manifestation of MG in patients who are otherwise systemically asymptomatic. In symptomatic patients with paraproteinemic crystalline keratopathy, treatment of the underlying disorder is the mainstay of management. Thus, it is

Table 6. Heavy and light chain distribution of rheumatological disorders, chronic kidney disease and myelodysplastic syndrome.

Rheumatic Diseases		
Type of M component	**n (30)**	**%**
Rheumatoid arthritis	**12**	**14.3**
IgG κ	8	9.5
IgA (κ / λ)	2 (1/1)	2.4
κ light chain	1	1.2
Biclonal	1	1.2
Ankylosing spondylitis	**5**	**6.0**
IgG (κ / λ)	3 (2/1)	3.6
κ light chain	1	1.2
IgM λ	1	1.2
SLE	**4**	**4.7**
IgG (κ / λ)	3(2/1)	3.5
κ light chain	1	1.2
Sjogren's syndrome	**3**	**3.6**
IgG κ	3	3.6
Psoriatic arthritis	2	2.4
IgG κ	2	2.4
Chronic Kidney Disease		
Type of M component	**n (11)**	**%**
IgG (κ / λ)	10 (9/1)	11.9
Biclonal	1	1.2
Myelodysplastic Syndrome		
Type of M component	**n (11)**	%
IgG κ	8	9.5
IgA λ	1	1.2
κ light chain	1	1.2
Biclonal	1	1.2

Abbreviations; IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, SLE; Systemic Lupus Erythematosus.

important to keep in mind that MG may be present in patients via awareness of ocular damage, as well as that ocular lesions may heal with treatment of the underlying disease. In addition, patients with known MG should be aware of the possibility of developing associated ocular disease.[15]

One patient with IgM kappa MG in the urine was remarkable in our study. He had been diagnosed with type 2 diabetes and Waldenstrom's macroglobulinemia years before. We described the presence of IgM in the urine with the patient's nephrotic-level proteinuria due to uncontrolled diabetes mellitus. There was another patient presenting with Evans syndrome and the IgG kappa, IgM kappa, M heavy chain triclonal band in his serum; he was diagnosed with splenic marginal zone lymphoma.

In practice, a significant number of patients who present with back pain and have been diagnosed with multiple myeloma are referred to an orthopedist or neurosurgeon before an Internal medicine or Hematology admission. For this reason, it is expected that more IFEs will be studied in Orthopedic and Neurosurgical departments with a multiple myeloma prevalence. Similarly, while many plasma cell diseases

present with skin lesions, far fewer IFE tests were performed by Dermatology in our study than we expected.

Due to the difficulty in accessing patient data and the fact that some of the data obtained were inadequate, which was the limitation of our study, only the patients who were found to be positive for MG were evaluated. MG of undetermined significance is an asymptomatic, premalignant, clonal plasma cell disorder, and there is a life-long risk of progression to MM or lymphoma at a constant rate of 1% per year. No treatment is required for patients with MGUS. The current approach is monitoring these patients. However, for each case, the clinician should question whether the symptoms are associated with MG and exclude "MG-related" conditions before a diagnosis of MGUS is established. This awareness will further clarify the patient's follow up in terms of both primary disease progression and neoplasia development. More research is needed on MG in specific autoimmune diseases, not only in plasma cell disorders and lymphoproliferative diseases. Increasing the awareness of physicians in other medical and surgical branches concerning this issue will enable more patients to be diagnosed correctly and receive treatment at the appropriate time.

Authors' Contribution

Study Conception: YM, UI, HS, TU, OS, SO, LU,; Study Design: YM, UI, HS, TU, OS, SO, LU,; Supervision: OS, SO, LU,; Materials: YM, UI, HS, TU, OS, SO, LU,; Data Collection and/or Processing: YM, UI, HS, TU,; Statistical Analysis and/or Data Interpretation: YM, UI, HS, OS, SO,; Literature Review: YM, UI, HS, TU, OS,; Manuscript Preparation: YM, UI, HS, TU, OS, SO, LU and Critical Review: UI, TU, OS, LU.

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