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Newly Diagnosed Monoclonal Gammopathies in 2024 in a Single Center: A Retrospective Study from a Perspective of Initial Testing in Diagnosis

2024 Yılında Yeni Tanı Alan Monoklonal Gamopatiler: Tanısal Testler Perspektifinden Retrospektif Bir Çalışma

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ABSTRACT

Background: There is no consensus on the initial testing in diagnosing monoclonal gammopathies (MG). This retrospective analysis reports on newly diagnosed MG patients at the University of Health Sciences Türkiye, Antalya Training and Research Hospital and assesses the necessity of serum immunofixation electrophoresis (SIFE) as an initial diagnostic test.

Materials and Methods: All serum protein electrophoresis (SPE) tests performed and reported between 1 January 2024 and 31 December 2024 were retrospectively reviewed from the institute's archival database. Patients with any electrophoresis test results and patients without any previous electrophoresis test results were included in the study.

Results: Our laboratory diagnosed 115 new patients with MG in 2024. Of these 115 patients, 67 (58%) were male and 48 (42%) were female, with mean ages of 65.98 ± 10.78 years in men and 66.22 ± 10.37 years in women. Sixty-three of 115 patients were positive on both the SPE and the serum free lightchain ratio (rFLC). Of 115 patients, 31 were positive only for SPE and negative for rFLC, whereas 5 were positive only for rFLC and negative for SPE. Six of 115 patients were negative for both SPE and rFLC, but were diagnosed by a positive SIFE.

Conclusion: After a retrospective review of 115 newly diagnosed MG patients in 2024, we concluded that 6 of these patients might have been missed (undiagnosed) if a combination of SPE + rFLC tests had been used as the initial diagnostic tests. None of these six cases showed a measurable M protein on SPE, nor did they receive medication for MG.

Keywords: Serum-free light chain ratio, multiple myeloma, general practice, diagnostic work-up, reflective test

ÖZ

Amaç: Monoklonal gamopatilerin (MG) tanısında ilk test yöntemi konusunda bir fikir birliği yoktur. Bu retrospektif analiz, Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi'nde yeni tanı almış MG hastalarını sunmakta ve ilk tanı testi olarak serum immünfiksasyon elektroforezinin (SIFE) gerekliliğine odaklanmaktadır.

Gereç ve Yöntemler: 1 Ocak 2024 ile 31 Aralık 2024 tarihleri arasında gerçekleştirilen ve raporlanan tüm serum protein elektroforez (SPE) testleri arşiv veri tabanından retrospektif olarak incelenmiştir. Herhangi bir elektroforez testi sonucu olan ve daha önce elektroforez testi sonucu olmayan hastalar çalışmaya dahil edilmiştir.

Bulgular: Laboratuvarım sonuçları ile 2024 yılında 115 yeni MG hastası tanı almıştır. Bu 115 hastanın 67'si (%58) erkek, 48'i (%42) kadın olup, erkeklerde ortalama yaş 65,98 (± 10,78), kadınlarda ise 66,22 (± 10,37) idi. Yüz on beş hastanın 63'ü hem SPE hem de serum serbest hafif zincir oranı (rFLC) açısından pozitifti. Yüz on beş hastanın 31'i sadece SPE pozitif, rFLC negatifken, 115 hastanın 5'i sadece rFLC pozitif, SPE negatifti. Yüz on beş hastanın 6'sı hem SPE hem de rFLC negatifti ve bu hastalara pozitif SIFE ile tanı konuldu.

Sonuç: 2024 yılında yeni tanı almış 115 MG hastası retrospektif olarak incelendiğinde, ilk tanı testleri olarak SPE + rFLC testlerinin kombinasyonu kullanılırsa, bu hastalardan 6'sının muhtemelen gözden kaçabileceği (tanı konulamayacağı) sonucuna vardık. Bu 6 vakanın hiçbiri SPE'de ölçülebilir bir M proteini göstermedi veya MG için herhangi bir tedavi almadı.

Anahtar Kelimeler: Serum serbest hafif zincir oranı, multiple myelom, genel uygulamalar, tanısal testler, reflektif test

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Introduction

According to the latest Global Cancer Observatory statistics, there were an estimated 190,000 cases of multiple myeloma (MM) in 2022, ranking 21st in disease incidence and 17th in mortality globally (1). Lifetime risk of developing MM is 0.24% in men and 0.17% in women, indicating a higher risk in men (2). With the introduction of proteasome inhibitors and immunomodulatory drugs, the 5-year overall survival of MM patients has increased significantly. However, MM remains incurable (3).

MM is a member of the large family of monoclonal gammopathies (MG). Serum protein electrophoresis (SPE), by gel or capillary methods, has been the most widely used laboratory test for diagnosing MG (4). Serum immunofixation electrophoresis (SIFE) and immunosubtraction have been used to identify and characterize the detected monoclonal neoplastic immunoglobulin protein (M protein). After a quarter of a century, serum free light chain (FLC) assays are now recognized as essential in all diagnostic protocols for MG. Mass spectrometry and quantitative measurements of heavy- and light-chain isotypes are emerging diagnostic tests for MG. Laboratories may choose to use one, all, or a combination of these diagnostic test panels (5). In May 2022, Keren et al. (6) published their paper on laboratory detection and initial diagnosis of MG. The paper presented evidence-based recommendations from an expert panel established by the College of American Pathologists (CAP). Besides recommendations on specimen requirements and appropriate tests for the initial laboratory detection of M proteins, they concluded their work with a flowchart outlining diagnostic testing for MG.

There have been attempts to ensure appropriate initial test requests for the diagnosis of MG in line with good laboratory practice (5–8). Appropriate testing is part of good laboratory practice, and "requesting the right test with the right method, at the right time, for the right patient, to produce the right result at the right (reasonable) cost" has been a major goal of modern laboratories (9). This study aimed to provide feedback and information to support future efforts to regulate test protocols used in the diagnosis of MG, with a particular focus on the SIFE test.

Materials and Methods

All SPE test results between 1 January 2024 and 31 December 2024 were retrospectively retrieved from the laboratory information system and reviewed. Age, sex, and electrophoresis test results for each patient were recorded. It was recorded whether the electrophoresis tests were used alone or in various combinations. SPE showing a depressed gamma region was subjected to reflective SIFE and FLC tests. M protein measurements were performed using the perpendicular-drop method. M protein concentrations >1 g/dL were considered measurable. SPE and SIFE results were reported as "monoclonal band not detected" (negative) or "monoclonal band detected" (positive). The immunophenotype of the positive monoclonal band was included in the report. FLC tests were reported as Kappa and Lambda FLC quantities in the patient's serum, and as the ratio of Kappa to Lambda test results FLC ratio (rFLC). Values outside the normal range (0.31–1.56) were considered positive. Only patients with first-time electrophoresis test results were included; patients with any prior electrophoresis test results were excluded.

SPE were performed using the serum protein 6-band format on agarose gel (Helena Diagnostics, UK) platform with SAS plus and SAS-2 24 SB kit. SIFE was performed on the same platform using the Helena Biosciences SAS-1 IFE-4 kit to confirm the presence of M protein and to characterize isotypes, employing monospecific antisera against immunoglobulin G (IgG), IgM, and IgA heavy chains and κ and λ light chains. Serum FLC were measured in batch mode using N Latex FLC Kappa and Lambda assays (Siemens Healthcare Diagnostics, Marburg, Germany) on a Siemens BNII nephelometer, according to the manufacturer's instructions.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee (decision number: 4/15, dated: 27.02.2025).

Statistical Analysis

Windows Excel 2013 (Microsoft, USA) was used to perform calculations and generate statistical data.

Results

The study was conducted at a 1,270-bed tertiary-care medical center affiliated with a medical school. Our laboratory diagnosed 115 new MG patients in 2024. Of these 115 patients, 67 (58%) were male and 48 (42%) were female, with a mean age of 65.98 (± 10.78) in men and 66.22 (± 10.37) in women. When patients were examined in types of paraproteinemia, in order of frequency, we detected IgG-Kappa in 44 patients (38.2%), IgG-Lambda in 32 patients (27.8%), IgA-Kappa in 8 patients (7%), IgA-Lambda in 8 patients (7%), IgM-Kappa in 6 patients (5.2%), IgM Lambda in 2 patients (1.7%), light chain Kappa in 5 (4.3%), light chain Lambda in 6 (5.2%) patients, heavy chain IgA in 2 patients (1.7%), biclonal IgG Kappa + IgG Lambda and IgG Kappa + IgA Kappa in 2 patients (1.7%). In 103 of these patients, a combination of SPE, SIFE, and

rFLC tests was requested as initial testing. 7 patients, diagnosed with the combination of SPE + SIFE test while 3 patients were diagnosed only with SIFE and 2 patients were diagnosed with only SPE test.

The positive and negative initial electrophoresis tests were as follows (Figure 1):

Of 109 patients with a positive SPE and/or rFLC, 63 were positive for both SPE and rFLC. 31 of 109 patients were positive for SPE but negative for rFLC, whereas 5 of 109 patients were positive for rFLC but negative for SPE. Heavy-chain components were observed in SIFE in these five cases.

Of 115 patients, 6 were negative for both SPE and rFLC. They were diagnosed based on a positive SIFE.

Ten of 116 patients were positive for monoclonal FLC only and negative for IgG, IgM, and IgA antisera. IgD or IgE positivity could not be excluded. rFLC values were significantly abnormal (either elevated or reduced, depending on the affected light chain) in all cases. SIFE were negative, and SPE were depressed or apparently normal, without a visible M protein.

Discussion

In the vast majority of our patients (95.5%), a combination of SPE, SIFE, and rFLC was requested by clinicians as initial diagnostic tests. The combination was in line with the recommendations of International Myeloma Foundation's International Myeloma Working Group (IMWG) for diagnostic testing for MG (6). After retrospectively reviewing the 115 newly diagnosed MG patients in 2024, we concluded that 6 of these patients could have been missed (undiagnosed) if any combination of initial diagnostic tests that did not include SIFE had been used. None of the six cases showed a measurable M protein on SPE, and their rFLC values were within the normal range. In two of the six cases that showed a monoclonal IgA band in the beta region, the SPE tests were nearly normal. In the other four cases with a monoclonal band in the gamma region (2 IgG Lambda, 1 IgG Kappa , and 1 IgA Lambda), slight irregularities in the SPE tests were detectable only with a high index of suspicion. All six cases were re-evaluated by an expert hematologist; all were diagnosed with MG of undetermined significance (MGUS) and did not receive any treatment for MGUS (Table 1).

One of the main reasons for including sFLC tests as essential first-line tests is the detection of FLC MM (6,10). In 2024, we diagnosed 10 patients with FLC MM. Although IgE- or IgD-heavy-chain components were not detected serologically, these cases were classified and treated as FLC MM. In 7 of 10 FLC MM cases, the gamma region on SPE was depressed and reported as positive. Particularly, considering FLC MM single SPE without rFLC or SIFE tests

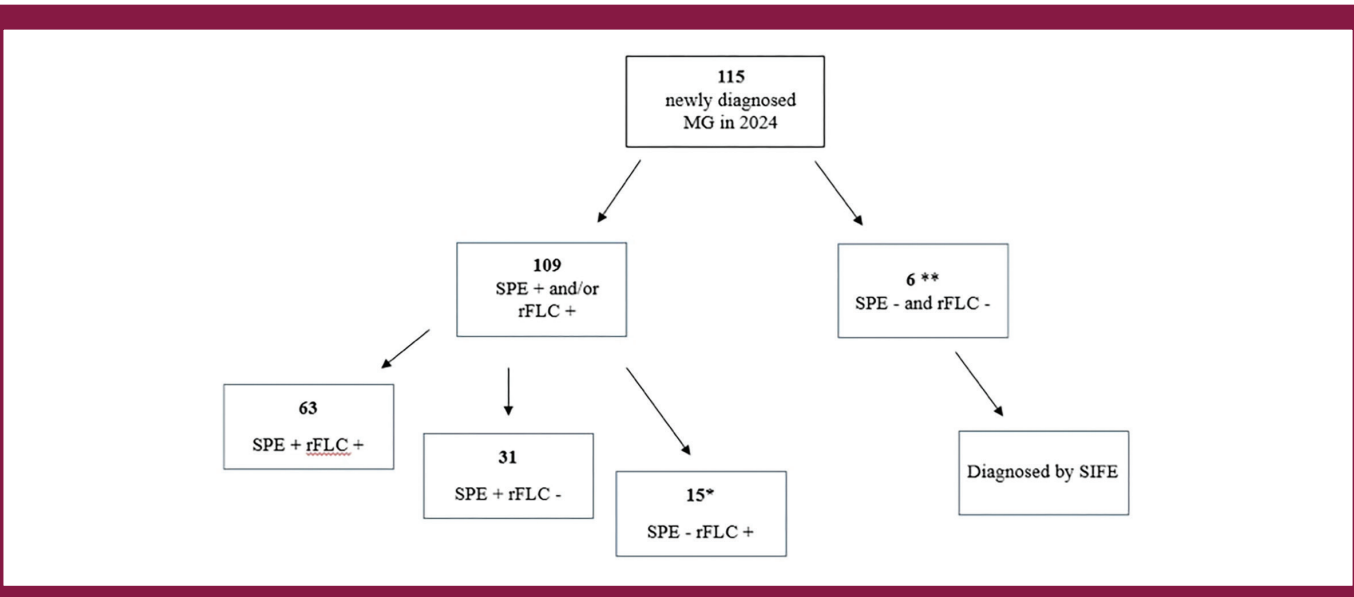

Figure 1. Our laboratory diagnosed 115 new MG patients in 2024. One hundred nine patients were positive for SPE and/or rFLC, which meant that the SPE and rFLC combination was sufficient as an initial diagnostic test. Sixty-three of 109 patients were positive for both SPE and rFLC; 31 of 109 patients were positive for SPE and negative for rFLC; and 15 of 115 patients were positive only for rFLC and negative for SPE. In the last group of 15 patients, 10 were positive for monoclonal FLCs only, without a heavy-chain component, after SIFE (*). Six of the 115 patients were negative for both SPE and rFLC (**). They were diagnosed based on a positive SIFE performed as the initial test. These six cases could be missed when a combination of SPE and rFLC is used as the initial test. MG, monoclonal gammopathy; rFLC, ratio of free light chains; SIFE, serum immunofixation electrophoresis; SPE, serum protein electrophoresis.

Table 1. In retrospective analysis of 115 newly diagnosed MG patients, in 6 patients SIFE was the diagnostic test and these cases could have been missed by initial SPE + rFLC tests (without SIFE). Three of the patients underwent bone marrow biopsy and diagnosed as MGUS. Patients 1 was without a follow-up, no further investigations were performed on patient 3 because of old age and patient 4 was followed-up by electrophoresis and treated like MGUS.

Patient	rFLC	SPE	SIFE	Details	Diagnosis
1	0.95	A distorsion at the center of a normodense gamma region.	Vague IgG Kappa	No follow-up.	Treated like MGUS*
2	0.85	Invisible in the beta region.	Clear IgA Lambda	Undergone bone marrow biopsy.	MGUS
3	0.34	A distorsion at the anodal end of normodense gamma region.	Vague IgA Kappa	92 years old, no further investigation.	Treated like MGUS*
4	0.38	Invisible in the beta region.	Clear IgA Lambda	Followed by electrophoresis.	Treated like MGUS*
5	0.79	A distorsion at the cathodal end of normodense gamma region.	Vague IgG Lambda	Undergone bone marrow biopsy.	MGUS
6	0.36	A distorsion at the cathodal end of normodense gamma region.	Vague IgG Lambda	Undergone bone marrow biopsy.	MGUS

MGUS, monoclonal gammopathy of undetermined significance; rFLC, serum free light chain ratio; SIFE, serum immunofixation electrophoresis; SPE, serum protein electrophoresis; treated like MGUS*, final diagnosis was not confirmed by bone marrow biopsy; Ig, immunoglobulin.

may be challenging for inexperienced laboratory specialists when diagnosing MG. In 3 of the 10 FLC MM patients, SPE did not show any aberrant signs of positivity. In all cases of FLC, MM rFLC were extremely alarming. We can confidently conclude that the performance of the rFLC test was highly satisfactory for detecting FLC MM in these patients.

Many cost-effective applications advise clinicians to use stepwise testing when diagnosing MG. In 2017, Genzen et al. (5) reported results from a survey of 774 laboratories in 38 countries that quantified patterns of electrophoresis test use for detecting M protein. The findings indicated substantial variation in practice compared with current IMWG guidelines. They reported SPE, used as a first-line screening test followed by other confirmatory tests, as the most common application. To support a stepwise approach, the laboratory must maintain reflex or reflective testing capabilities to avoid repeated sampling. In our study, reflective SIFE was performed in two cases with positive SPE to avoid repeat sampling. Although performed in only two patients, our study showed that stepwise testing was successful with reflective testing of SIFE.

Appropriate testing is a part of good laboratory practices. "Requesting the right test with the right method, at the right time, for the right patient, to produce the right result at the right (reasonable) cost" has been defined as an appropriate test request. Particularly for SPE and SIFE, a major concern, in addition to the high cost of the tests, is the time and effort required of a highly specialized technician or laboratory specialist (9,11). Gel electrophoresis remains one of the last conventional tests used in the clinical laboratory. Semi-automated gel electrophoresis requires substantial manual work by a specialized, experienced technician, while reporting the tests requires additional time and effort from a specialized, experienced laboratory specialist. In the absence of an evidence-based guideline from a systematic review, laboratories have developed disparate practices for M protein detection and quantitative measurement, complicating harmonization of results (6–8,12).

In May 2022, Keren et al. (6) published their paper on laboratory detection and initial diagnosis of MG. The paper presented evidence-based recommendations from an expert panel established by the CAP. The expert panel included a broad representation of experts in the diagnosis and treatment of MG and in the laboratory procedures used for their initial detection. They called their work a contemporary guideline and a first step toward harmonizing the initial detection of MG. They finalized their work with a flowchart for stepwise diagnostic testing to detect MG, in which SPE and rFLC were the first-line tests, followed by confirmatory SIFE if needed. Compared with the recommendations by Keren et al. (6), the IMWG recommendations include SIFE testing as an initial diagnostic test in addition to SPE and rFLC. Willrich and Katzmann (13) demonstrated that the combined use of SPE and rFLC identified 94.3% of M proteins in 1877 patients (100% for MM and 88.7% for MGUS). This retrospective study demonstrated that the combined use of SPE and rFLC could miss some cases of MG that would be diagnosed by adding SIFE to the first-line diagnostic test panel. Our six had no measurable M protein on SPE, did not receive any medication for MG, and were confirmed or accepted as MGUS. Although considering SIFE as a first-line test in the screening and diagnosis of MG is a matter

of debate, we believe our findings will be valuable. The guideline by Keren et al. (6) was declared to be reviewed every four years after its publication. The expert panel is expected to discuss potential changes and recommend revision of the guideline if necessary.

Our findings should be considered and discussed from a cost-effectiveness perspective. Pressure on hospitals to restrain health-care expenditure has resulted in cost-cutting strategies. In this regard, the Turkish Ministry of Health launched the "Good Laboratory Practices Project" in 2018. A practical guide for requesting appropriate tests was included in this project. In practice, attempts to reduce unnecessary laboratory test requests include two major approaches: educating clinicians and designing test requests. Our experience showed that the educational approach was short-lived, with effects disappearing soon after the educational effort ceased. On the other hand, efforts to design clinicians' test-ordering practices are likely to result in longer-lasting effects. Designing test ordering practices necessitates close co-operation between the clinicians and the laboratory (9).

Study Limitations

The main limitation of our study was its retrospective nature. The cases were actually not missed, but our judgment was that they could have been missed. We did not consider urine IFE because its use across departments was limited. Our findings were based on gel electrophoresis, and results from capillary electrophoresis could differ from our conclusions.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee (decision number: 4/15, dated: 27.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.K., Concept: Ö.A., V.K., Design: Ö.A., Data Collection or Processing: M.D., Ö.A., Analysis or Interpretation: Ö.A., V.K., Literature Search: M.D., Ö.A., Writing: V.K.

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REFERENCES

1. Global Cancer Observatory. Cancer Today. Lyon, France: International Agency for Research on Cancer. [Crossref]
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. [Crossref]
3. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review 1975–2016. Bethesda, MD: National Cancer Institute; 2019. [Crossref]
4. Aydin O, Erturk I. Serum protein electrophoresis in diagnosing monoclonal gammopathies. Turk Clin Biochem J. 2022;20:106–114. [Crossref]
5. Genzen JR, Murray DL, Abel G, Meng QH, Baltaro RJ, Rhoads DD, et al. Screening and diagnosis of monoclonal gammopathies: an international survey of laboratory practice. Arch Pathol Lab Med. 2018;142:507–515. [Crossref]
6. Keren DF, Bocsi G, Billman BL, Etzell J, Faix JD, Kumar S, et al. Laboratory detection and initial diagnosis of monoclonal gammopathies. Arch Pathol Lab Med. 2022;146:575–590. [Crossref]
7. Aydin O, Erturk I. Stepwise testing in the diagnosis of monoclonal gammopathies. LLM Derg. 2023;7:40–42. [Crossref]
8. Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009;23:215–224. [Crossref]
9. Aydin O, Karakus V, Dincer M, Aykal G, Ellidag HY. Unnecessary serum protein electrophoresis test requests in the follow-up of multiple myeloma patients can be prevented. Int J Med Biochem. 2025;8:125–129. [Crossref]
10. Singh G. Serum and urine protein electrophoresis and serum-free light chain assays in the diagnosis and monitoring of monoclonal gammopathies. J Appl Lab Med. 2020;5:1358–1371. [Crossref]
11. Aydin O, Erturk I. Electrophoresis testing in the follow-up of multiple myeloma patients with a measurable M protein in gamma region: good laboratory practice for the laboratory specialist. LLM Derg. 2023;7:82–85. [Crossref]
12. Aydin O, Ellidag HY, Eren E, Yilmaz N. The laboratory should actively be involved in the therapeutic drug monitoring (TDM) process. In J Phar Pract. 2016;9:9–13. [Crossref]
13. Willrich MA, Katzmann JA. Laboratory testing requirements for diagnosis and follow-up of multiple myeloma and related plasma cell dyscrasias. Clin Chem Lab Med. 2016;54:907–919. [Crossref]