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Research Article

Unnecessary serum protein electrophoresis test requests in the follow-up of multiple myeloma patients can be prevented

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Abstract

Objectives: Appropriate testing is a part of good laboratory practices. "Requesting the right test with the right method, at the right time, to the right patient, to produce the right result at the right cost" has been defined as an appropriate test request. This study was intended to measure the impact of an attend to regulate requests for serum protein electrophoresis tests before and after applying rejection rules and clinical management.

Methods: In a meeting in December 2022, hematologists declared to be more careful about proper testing in electrophoresis. In addition, the laboratory was decided to be involved in test request management through test rejection rules. Multiple myeloma patients with measurable M protein spikes in the gamma regions of serum protein electrophoresis tests were chosen due to relatively well-defined follow-up protocols. Number of hospital visits of the patients and electrophoresis test requests were compared with the year before (2022) and the year after (2023) the meeting.

Results: Selected 92 patients visited our hospital 493 times in 2022 and 583 times in 2023 (number of visits). A total of 423 serum protein electrophoresis (SPE) and 416 serum immunofixation electrophoresis (SIFE) tests were requested in 2022 while 427 SPE and 470 SIFE tests were requested in 2023. In 2023, 51 SPE and 36 SIFE test requests were rejected according to the defined test rejection rules.

Conclusion: From 2022 to 2023 total patient visits increased by 18%, while SPE test requests increased by less than 1% and SIFE test requests increased by 13%. The common will by the Hematology Clinic and the Clinical Biochemistry Laboratory to reduce unnecessary electrophoresis test requests achieved their goal as the rise in test requests were under the rise in hospital visits. After a year of experience, we could confidently propose that our test rejection rules can be adopted by laboratories and used for electrophoresis test management.

Keywords: Continuous quality management, electrophoresis, good laboratory practices, medical laboratory, multiple myeloma

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Appropriate testing is a part of good laboratory practices. "Requesting the right test with the right method, at the right time, to the right patient, to produce the right result at the right (reasonable) cost" has been defined as an appropriate test request [1]. Particularly considering serum protein electrophoresis (SPE) and serum protein immunofixation electrophoresis (SIFE), in addition to the high cost of the tests, a major concern is the cost of time and effort of a very specialized technician and laboratory specialist. Gel electrophoresis is one of the last conventional tests in the clinical laboratory. Semi-automated gel electrophoresis requires plenty of handwork of a specialized and experienced technician while reporting the tests requires extra time and effort of a specialized and experienced laboratory specialist [2].

SPE and/or SIFE tests maintain their importance in the diagnosis and follow-up of multiple myeloma (MM) patients. The effort in harmonization of reporting electrophoresis test results is guided by the fact that the test report must provide the clinician with sufficient data to observe the response of the patient under treatment [3]. While the changes in the amount of M

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(myeloma) protein detected in SPE are evaluated as an indicator of the tumor's response to treatment; appearance or disappearance of a monoclonal band defines the clinical condition of the MM patient as relapse or remission. There are international and national guidelines (Multiple Myeloma Diagnosis and Treatment Guidelines) which update at regular intervals [4, 5].

This project of utilization of SPE and SIFE test requests was limited to patients with an M protein spike in the gamma region of SPE due to relatively clear-cut directions for the follow-up electrophoresis test requesting in the guidelines. It started with a meeting attended by laboratory specialists and hematologists. In the meeting, a joint decision was taken so that the hematologists would pay extra care in test requesting while the laboratory specialists would contribute by rejecting the unnecessary tests that escaped the clinician's attention. This retrospective study aimed to measure the effect of the project by comparing electrophoresis test requests one the year before (2022) and one year after (2023) the meeting.

Materials and Methods

Good laboratory practices

In December 2022, we conducted a presentation at The Hematology Clinic with the participation of all hematologists, where we repeated the basics of follow-up of MM patients with SPE and SIFE in line with the national clinical guideline [4]. Any request made outside the agreed national guideline was defined as inappropriateness. While the hematologists owed to be more careful about their test requests, some test rejection rules to be performed by the laboratory were defined:

Rejection rule 1: When SPE and SIFE were requested together and SPE showed a measurable M protein in the same location with the previous SPE, SIFE was rejected as an inappropriate test request, if the patient had a previous positive SIFE.

Rejection rule 2: When SPE and SIFE were requested together and SIFE was negative, SPE was rejected as an inappropriate test request.

All electrophoresis test requests were checked for rejection rules prior to performing the test. Previous electrophoresis test results were checked in detail by the laboratory specialist. The clinicians requesting the tests, which were decided to be rejected, were informed by text messages. The requested tests were rejected only after the approval of the requesting hematologist. Patient samples of the rejected tests were stored at 2–8°C for 48 hours as a caution.

Patients

The study was conducted at a 1270-bed tertiary care, medical school–affiliated medical center. Laboratory information system was searched retrospectively between 01/01/2022 and 31/12/2023. Patients who admitted to the Hematology inpatient or out-patient clinics were filtered. Within the 2 years, patient visits with at least 1 electrophoresis test request and type of electrophoresis tests requests in a visit were recorded (Visit: Visits with at least 1 electrophoresis test request). Test data were included from both in-patient and out-patient clinical encounters where any of the following were ordered: SPE and/or SIFE. Number of patients was high enough to select group patients with more than 1 year follow-up. Patients with a measurable M spike in the gamma region of a positive SPE were selected. Only patients with MM diagnosis were included (Fig. 1). The diagnosis of the patients was identified by the ICD code and confirmed by the hematologist.

This study was performed in accordance with the ethical standards set by the Declaration of Helsinki and was approved by the local ethics committee (2024-165).

Microsoft Excel 2013 was used to calculate results and create graphics.

Results

The results of 470 patients who admitted to The Hematology inpatient and out-patient clinic and with at least one SPE and/or SIFE were evaluated retrospectively. Patients without any positive SPE and/or SIFE, patients with less than 5 visits were excluded. 390 patients were with at least one SPE and/or SIFE positive test result. Of these 390 patients, 256 (65.64%) were male and 134 (34.35%) 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

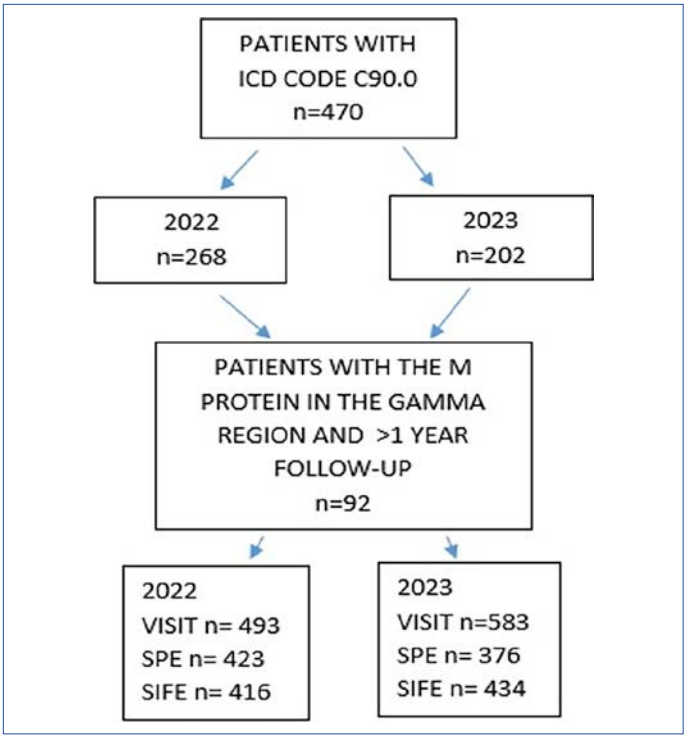

Figure 1. A total of 470 patients admitted to hematology outpatient and inpatient clinics and with the ICD code used to follow-up of monoclonal gammopathy patients in 2022 and 2023. Among the 470 patients, 390 had at least one positive SPE and/or SIFE. 92 of these 390 patients had a measurable M protein in the gamma region of SPE and had more than one year follow-up.

SPE: Serum protein electrophoresis; SIFE: Serum protein immunofixation electrophoresis.

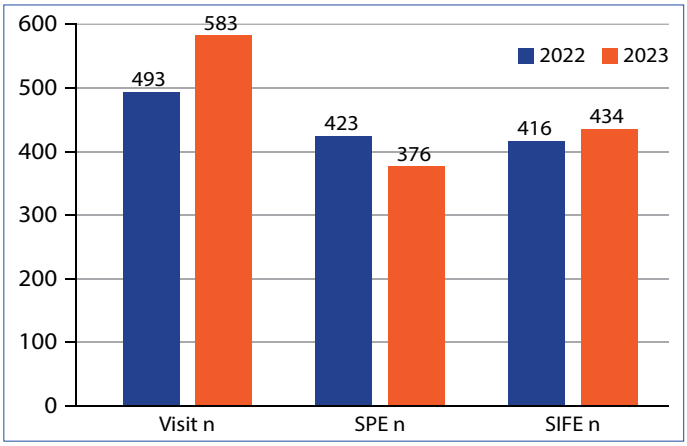

Figure 2. From 2022 to 2023 total patient visits increased by 18%, while SPE test requests increased by less than 1% and SIFE test requests increased by 13% which showed positive effort of the clinicians. The figure shows the number of tests after 51 SPE and 36 SIFE test requests were rejected by the laboratory according to test rejection rules in 2023.
SPE: Serum protein electrophoresis; SIFE: Serum protein immunofixation electrophoresis.

types of paraproteinemia, in order of frequency, we detected IgG-Kappa in 158 patients (40.51%), IgG-Lambda in 81 patients (20.76%), IgA-Kappa in 48 patients (12.30%), IgA-Lambda in 20 patients (5.12%), IgM- Kappa in 15 patients (3.84%), IgM Lambda in 7 patients (1.79%), monoclonal Kappa in 34 patients (8.71%) and monoclonal Lambda in 27 patients (6.92%).

92 of 470 patients were diagnosed and followed with MM diagnosis for more than one year period including 2022 and 2023. Of these 92 patients, 45 were male (48.91%) and 47 were female (51.08%); with a mean age of 65.76 (±8.97) in men and 66.09 (±11.49) in women. When patients were examined in types of paraproteinemia, in order of frequency, we detected IgG-Kappa in 55 patients (59.78%), IgG-Lambda in 25 patients (27.17%), IgA-Kappa in 5 patients (5.43%), IgA-Lambda in 4 patients (4.34%), IgM-Kappa in 1 patient and IgM-Lambda in 2 patients.

These 92 patients visited our hospital 493 times in 2022 and 583 times in 2023 (number of visits). A total of 423 SPE and 416 SIFE tests were requested in 2022 while 427 SPE and 470 SIFE tests were requested in 2023 (Fig. 2). In 2023 51 SPE and 36 SIFE test requests were rejected by the laboratory according to test rejection rules.

Discussion

In MM patients with a measurable M spike in the gamma region of SPE, all characteristics of the M protein are followed in the SPE test [4, 5]. The International Myeloma Working Group has determined the limit of 1 g/dL for SPE and concentrations above this limit mean a measurable M protein [3]. At concentrations below these levels, detection of M protein changes is considered clinically unreliable. Methodically, MM patients with an M protein level above 1 g/dL can be followed by protein electrophoresis until the measured M protein level drops below 1 g/dL during the treatment process. After the M protein level drops below 1 g/dL, the quantitative follow-up of the M protein by SPE will continue qualitatively by SIFE. Patients whose M protein disappears in the SPE test and without a detectable M protein in subsequent SIFE tests will now be followed up with the diagnosis of "Complete Remission" [1, 6, 7]. Unfortunately, MM is still an incurable disease and every patient will inevitably face a relapse in which the disappeared M protein will re-appear in follow-up electrophoresis tests. The Turkish Hematology Association Multiple Myeloma Diagnosis and Treatment Guideline recommends that the tests for the assessment of response to MM treatment be repeated once a month or every two months until a response is achieved, and once a response plateau is achieved, the intervals should be increased and repeated every 3–6 months [4]. In case of possible biochemical progression, the follow-up intervals are reduced to 1–2 months again [4].

MM is a very heterogeneous disease and the follow-up of each patient will include differences in its own way [4]. For example, in about 2% of patients, tumor cells do not synthesize M protein (non-secretory MM). Electrophoresis applications are naturally useless in the follow-up of these patients. In approximately 15% of cases, the M protein consists only of light chain immunoglobulins. This type of M protein may not be detected in the SPE test due to its low molecular weight and rapid clearance from the serum. M protein peaks located in the alpha and beta areas in serum protein electrophoresis may not be measured accurately due to the natural protein loads of these areas. Nevertheless, MM cases outside these groups, which show measurable M protein located in the gamma area in SPE, constitute 66% of all cases (54% in the gamma area, 12% in the gamma-beta border) [6, 7]. In the follow-up of these cases, a standard method agreed between laboratory and clinical branches should consider cost-effectiveness balances as well as proper follow-up of patients. During the treatment process, as long as detectable M protein can be observed in the gamma field, SPE alone will be sufficient to evaluate the patient's response to treatment [4]. If the patient continues to respond well to treatment, M protein will gradually decrease, and when M protein finally falls below the detectable threshold in SPE, follow-up with more sensitive tests, such as serum and urine immunofixation tests, will be appropriate. The sensitivity of serum immunofixation electrophoresis to detect M protein is approximately 10 times higher than that of the SPE test. Therefore, it is a mathematical reality that as long as measurable M protein is present in the SPE test, the SIFE test will be positive, and as long as the SIFE test is negative, the SPE test will not be positive. In national and international guidelines, MM patients with measurable amounts of M protein in the gamma field are followed up quantitatively with the SPE test [1, 6]. At this stage, the SIFE test, which gives qualitative results, has no clinical benefit and is considered an unnecessary test request [7].

Although not intended to be measured at the beginning of the study, a surprising finding of the study was the 'more than expected' decrease in MM patient hospital visits that we observed during the early post-pandemic period. It was evidenced by the 18% increase in patient visits from 2022 to 2023 which we call to be turning to the normal. This finding will contribute to the difficulty of the pandemic conditions in

this patient group, which we know to be extremely adherent and meticulous about treatment protocols. The impacts of COVID-19 pandemic on the therapy delivery in MM were significant. Utilizing access to electronic patient reports from health care organizations, Martinez-Lopez and colleagues were able to highlight the decrease in the survival of newly diagnosed MM patients [8]. Interrogating multi-national datasets, the authors found that MM patients have been more severely impacted by COVID-19 pandemic than non-MM patients.

From 2022 to 2023 total patient visits increased by 18%, while SPE test requests increased by less than 1% and SIFE test requests increased by 13% (Fig. 2). In 2023 51 SPE and 36 SIFE test requests were rejected according to the rejection rules. Both SPE and SIFE test requests were lower than the % visit rise. We were more successful in SPE test requests than SIFE test requests. After all laboratory tests of the patients were studied and verified by the laboratory and the patients were evaluated by the hematologists none of the rejected tests were re-requested confirming the feasibility of the application. A main concern of false rejection did not happen.

Pressure on hospitals to restrain health-care expenditure has resulted in cost-cutting strategies. In this regard, Turkish Ministry of Health released 'Good Laboratory Practices Project' in 2018 [9]. A practical guide for adequate test requesting was part of this project. Practically, attempts to reduce unnecessary laboratory test requests include two major approaches: education of the clinicians and designing the test requests [10–12]. Our experience showed that the educational approach is short-lived, with effects disappearing shortly after cessation of the educational effort. On the other hand, efforts to design the test ordering practice of clinicians promise a longer-lived effect. Designing test ordering practices necessitate close co-operation of the clinicians and the laboratory [13]. In our project, we were lucky to have a national clinical guide to compose a consensus between the clinicians and laboratory specialists. We did not set a target goal in reducing unnecessary electrophoresis test requests when we started the project. We are confident to call our effort 'successful' just because it works. Our rejection rules are evidence based, in line with the national clinical guide on multiple myeloma; so they can safely be used by all hospitals and laboratories for this purpose. Most importantly, we managed to decrease unnecessary test requests.

Conclusion

Considering the proportion of patients in this group who have M protein in the gamma field in the electrophoresis test, standardizing the treatment follow-up of this limited group in accordance with the guidelines will be quite efficient in terms of labor and cost. Laboratories should play an active role in the diagnosis and treatment of monoclonal gammopathies, including multiple myeloma.

Urine protein electrophoresis and urine immunofixation electrophoresis were not included in this project due to different applications of clinicians on these tests like using serum free light chain assays instead.

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