Prevalence of M-proteins in Serum of Hospitalized Patients

Physicians' Response to Finding M-proteins in Serum Protein Electrophoresis*

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ABSTRACT

M-proteins (tall, narrow spikes) are the major finding in serum protein electrophoresis (SPE), and their presence could signify lymphoproliferative diseases. The physicians' response to this finding in 73,630 patients in whom a SPE was performed as part of a routine screening at hospital admission was studied. Serum and urine immunoelectrophoresis (IEP) were requested on the report of SPE in all patients who showed M-proteins on SPE. In 59 percent of these patients, neither serum nor urine IEP were ordered, and it was assumed that the results of SPE were ignored by physicians. The frequency of M-proteins (1.1 percent) in the hospitalized patients was higher than that reported for normal individuals. It is suggested that SPE should not be performed as a screening test in hospitals.

Introduction

The role of the laboratory in patient care has often been discussed, and with the introduction of prospective reimbursement, the need for particular laboratory tests has been reevaluated. Of particular importance in this respect are the screening tests at admission to the hospital, i.e., the so-called admission profiles, which are still common in many hospitals. The clinical value, if any, of these screening tests was often questioned.14 The component tests of an admission profile are different in various hospitals; for example, some profiles include a thyroxine test, others a triglyceride assay, etc. A few hospitals,10,17 including this institution, performed serum protein electrophoresis (SPE) in all newly admitted patients.

It has been reported that physicians often ignore abnormal results from an admission profile or even from tests specifically ordered despite the fact that these abnormal results require prompt action.4,13,29 In this institution, SPE was part of the admission profile for many years. To determine whether or not this...
test, when performed routinely in all patients, has clinical value, the impact of an obvious abnormal finding in SPE, namely, the presence of electropherogram tall spikes owing to M-proteins, was examined retrospectively. This finding can be associated with malignant diseases, and, in the mind of many a physician, this could be a finding of grave significance for a patient. Indeed, multiple myeloma and lymphoma, diseases often associated with M-proteins seen in SPE, can be clinically unsuspected at the time when serum protein abnormalities are found. Also reported here are the frequency of M-proteins in our hospitalized patients and the comparisons of these findings with those reported by others in different geographic areas.

Material and Methods

From 1976 to 1981, all patients admitted to this hospital were supposed to have an SPE performed. However, from comparing the number of electrophoreses performed each year with the number of hospital admissions, it appeared that only about 65 percent of the admitted patients had an SPE performed. The reasons for this discrepancy are unknown. It was noted that patients admitted through the Emergency Department most often did not have an SPE performed at admission to the hospital.

Serum protein electrophoresis was performed on agarose gel in sodium barbital buffer, pH 8.6.* The plates, stained with Amido Black, were visually inspected and were also scanned with a densitometer (Model 720).* The densitometric scans were pasted on an 8" × 11" standard size sheet and inserted in the patient charts. Major electrophoretic abnormalities (e.g., decrease of gamma globulins, hypoalbuminemia, etc.) were recorded in the report in large capital letters by means of rubber stamps. When an M-protein (tall, narrow spike) was observed on the graph, the report stated the electrophoretic location of this protein (β or γ) and, furthermore, a request for additional serum and urine specimens for performing immunoelectrophoresis (IEP) was stamped on the report. It has been the policy in this institution for more than 15 years that before any additional test is ordered after the finding of an M-protein in SPE, an IEP should be performed. Indeed, when a physician received an SPE report showing a tall spike and he wanted to investigate this abnormality further, a serum IEP would be requested. Therefore, the absence of a serum IEP order was taken to signify that the physicians ignored the SPE report. To verify this assumption, charts of random patients with M-proteins in the electrophoregrams but who did not have serum IEP performed were reviewed for evidence of tests or notes written as a consequence of the finding of M-proteins. Since SPE and IEP have different charges, and since IEP is an expensive laboratory test that requires expert interpretation, serum IEP was not performed by the laboratory unless specifically ordered. The results were reported one to two days after the patients' admission to the hospital.

All SPE reports for six consecutive years were retrospectively reviewed, and those showing M-proteins were separated by year, from 1976 through 1981. If a patient had more than one SPE performed, only the first one was counted. For each patient with M-protein on SPE, a corresponding serum IEP was searched for in the yearly records of IEP, and the patients without a corresponding IEP were considered to have the SPE report ignored by the physicians. Serum IEP was performed by a standard microtechnique with use of

* Corning, Medfield, MA.
agar gel in barbital buffer, pH 8.6. Monospecific antibodies to heavy and light chains of the five immunoglobulins classes were used for IEP.†

Results

During the six years reviewed in this study, 73,630 SPE's were performed and 881 (1.19 percent) of them showed M-proteins. Of these latter, 74 (8.9 percent) were in the beta region only, 764 (91.1 percent) were in the gamma region, and 43 (4.8 percent) SPE's had two or three M-proteins. Of the 881 patients with M-proteins, 549 did not have a serum IEP performed and 33 patients had only a urine IEP performed. Therefore, it is assumed that 59 percent of SPE reports that showed M-proteins were ignored by physicians (table I).

Of the specimens with M-proteins on electrophoretograms and with which a serum IEP was performed, 71 percent had a monoclonal IgG, 15.5 percent an IgA, 12.8 percent an IgM, and 0.8 percent had a monoclonal IgD. The ratio \( \kappa/\lambda \) for the monoclonal immunoglobulins was 1.6 for IgG, 1.5 for IgM, and 1.0 for IgG.

† Cappel-Worthington, Malvern, PA.

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<th>M-proteins in Serum Protein Electrophoresis (SPE) of Hospitalized Patients</th>
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*Percentage in parentheses.

Discussion

The term M-protein or M-component seems to have been coined in 1948 to denote a tall and narrow peak in the serum electrophoretogram. Later, these spikes, which represent in fact homogeneous proteins, were defined as having the height at least four times higher than their width at mid-point between the base and the top. The M initially stood for multiple myeloma, macroglobulinemia of Waldenström's, and malignant lymphoma, i.e., diseases in which M-proteins were most often found. M-proteins (later thought to also mean monoclonal) were also found in SPE of patients with various non-malignant diseases as well as in serum of clinically normal individuals (the so-called benign monoclonal gammapathies), but it is often thought that M-proteins found in an SPE of a hospitalized patient may signify a grave disease. In fact, the most important clinical indication for performing SPE is the detection of monoclonal immunoglobulins, i.e., M-proteins. Other abnormalities seen in SPE, for example, the decrease of albumin or gamma globulins and the increase of gamma globulins, are routinely detected by use of multiple parameter chemistry analyzers. It was assumed by us that finding an M-protein in SPE required a follow-up action. Indeed, M-spikes in SPE are the most obvious and conceivably the most serious abnormality in this assay, such that ignoring an M-protein in an SPE is tantamount to ignoring the whole SPE.

How physicians respond to abnormal laboratory results is of importance. Previously, the failure of a substantial proportion of physicians to respond to abnormal laboratory tests has been reported, e.g., low serum cobalamin levels, abnormal fasting blood sugar, low hemoglobin and abnormal urinalysis. Perhaps these abnormal parame-
ters are less likely to herald a poor prognosis than are M-proteins in SPE of patients with suspected lymphocytic malignancies. From our study, it appears that a large proportion of physicians also ignore abnormal results of SPE.

Several questions can be raised: Is the absence of ordering a follow-up serum IEP in a patient with M-protein in SPE a valid indication of physicians ignoring the results or SPE? If this were so, what is the explanation for their lack of action? The separate, large forms of SPE were not buried among other results and could not have been ignored. As observed from reviewing random charts, bone marrow aspiration and/or X-ray bone survey were not performed on the basis of a single SPE showing M-protein. Still, there is no firm assurance that other tests were not performed in some patients without serum IEP because of the finding of an M-protein on SPE (since we did not review charts of all these patients). The existence of so-called benign monoclonal gammopathies, i.e., the presence of M-proteins in serum of asymptomatic individuals, could explain why physicians might choose to ignore the SPE findings in patients without signs and symptoms suggestive of one of the malignant lymphoproliferative diseases commonly associated with M-proteins. This view is, however, to be challenged since symptoms in a patient with multiple myeloma, for example, usually appear when the tumor burden reaches a mass of 1 Kg, whereas with sensitive electrophoretic techniques an M-protein in the serum can be found when the tumor mass is only several hundred grams or as low as 100 g.

The frequency of M-proteins in SPE was reported mainly for normal individuals (e.g., blood donors) and less for hospitalized patients or clinic patients. In normal subjects, the prevalence of M-proteins depends on the geographic factors as well as on the age; the frequency of M-proteins is higher in older individuals. In blood donors, who are presumed to be healthy individuals, the frequency of M-proteins was between 0.10 and 0.34 percent. Higher frequencies of monoclonal proteins, similar to our findings, have been reported in hospitalized patients. It should be mentioned that the frequency of M-proteins is also dependent on the electrophoresis technique; it is higher when agarose gel is used instead of cellulose acetate as the supporting medium for electrophoresis. In a small number of hospitalized patients, the prevalence of small spikes in SPE was up to 65 percent when high resolution electrophoresis was used. Not all of these spikes were, however, monoclonal proteins. The distribution of M-proteins among the four classes of immunoglobulins was similar in our study with that in other studies. Ratios of \( \kappa/\lambda \) above one were consistently reported for monoclonal IgG, IgM, and IgA. In contrast, our findings showed a ratio of one for IgA, i.e., an increase of monoclonal IgA-\( \lambda \). Similar findings were reported by Pick et al.

Most of the patients with M-proteins were not followed after the discharge from the hospital and their final diagnosis and their outcome are not known. Therefore, it is not known how many patients with M-proteins in SPE developed lymphoid malignancies. From the present review of SPE performed during six years, it is concluded that SPE is not valuable for screening newly admitted patients at least since the most important finding in this test, M-proteins, is often ignored by physicians. (The predictive value of SPE for certain diseases was not studied). For this reason, offering SPE as an admission screening test in our institution has been discontinued. The SPE is now specifically requested in certain
patients and the frequency of M-proteins is now about 10 percent of the total SPE performed. All sera showing M-proteins in SPE now have a follow-up IEP ordered by physicians.

Acknowledgments
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References