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Clinical relevance of trace bands on serum electrophoresis in patients without a history of gammopathy

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Non-standard abbreviations:
IFE – immunofixation
MGUS – monoclonal gammopathy of undetermined significance
SMM – smoldering multiple myeloma
SPE – serum protein electrophoresis
TFS – trace, faint, suspicious

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ABSTRACT

Serum protein electrophoresis (SPE) and immunofixation is commonly used to screen for plasma cell dyscrasias. Interpretation of these tests is qualitative by nature and can yield trace, faint, or scarcely visible immunoglobulin bands (TFS), which can be difficult to classify. Whether these bands should be reported at all is challenging given their unknown clinical significance.

In the present study, we retrospectively analyzed 14,036 physician-ordered protein SPE and immunofixation electrophoresis (IFE) tests on serum and urine specimens (from 4,091 patients) during the period of 2000-2010. We found that 17% of all IFE results evaluated for the presence of monoclonal gammopathies (2,389 out of 14,036) contained TFS bands, representing 4.2% (173 out of 4091) of all patients evaluated. Sixty of these patients (42%) had no previous history of gammopathy, and were clinically evaluated over a mean period of up to five years from the original diagnosis of plasma cell pathology.

None of these patients had progressed to multiple myeloma, lymphoplasmacytic lymphoma, plasmacytoma, or leukemia. The remaining 82 patients (58%) had a previous history of gammopathy, but had not progressed to any symptomatic plasma cell dyscrasia. Evaluation of these patients was followed for a median period of 4.3 years, with a mean of 21.5 IFE tests per individual.

These data suggest that for patients without a previous history of gammopathy, the presence of TFS bands on serum protein electrophoresis does not warrant frequent follow up investigation as commonly practiced. Routine follow up of patients with a prior history of gammopathy, conversely, are warranted and may contribute to overall survival with multiple treatment options now available. For those interpreting IFE results, it may be worth considering these data when composing comments regarding suggested repeat testing frequency by SPE/IFE or alternate test methods.

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INTRODUCTION

Serum protein electrophoresis (SPE) is commonly used as a diagnostic tool to screen for plasma cell dyscrasias including multiple myeloma, macroglobulinemia, and amyloidosis[1]. Screening by SPE is then commonly followed by immunofixation electrophoresis (IFE) to confirm and classify the specific paraprotein present (IgG, IgA, IgM, IgD, or IgE). Interpretation of both SPE and IFE by trained reviewers is qualitative by nature. In our experience, both SPE and IFE assays can yield faint, or scarcely visible immunoglobulin bands that may be equivocal and difficult to interpret. While these patterns technically fall in the category of "monoclonal gammopathies of undetermined significance," they are truly at the threshold of visual detection and subject to intense debate amongst those who review them daily. We've previously identified, as others have, that this threshold commonly varies from reviewer to reviewer to some extent[2].

Ultimately, the debate centers on whether these faint / equivocal bands should or should not be reported and whether they are of clinical significance. If they are not clinically relevant, they may be the cause for ongoing testing that may extend, on average, 15-20 years beyond initial diagnosis[3], which could prove costly and potentially require unnecessary labor, analysis, and patient risk. If they are of clinical relevance, then they should be identified so that patients may be appropriately monitored, diagnosed, and treated as necessary. Thus, the present study was conducted to determine the clinical significance of these trace or equivocal bands and their correlation to the development of monoclonal gammopathy.

MATERIALS AND METHODS

Study design

This retrospective study included data from 14,036 serum and urine specimens (from 4,091 patients) analyzed by the McLendon Laboratories at the University of North Carolina (UNC) Hospital for physician-ordered protein SPE and immunofixation electrophoresis (IFE) tests during the period of 2000-2010. The subjects' ages ranged from (31 to 90; mean = 62$\pm$0.9 years of age) (Table 1). Forty-four percent of subjects were female with 61% Caucasian and the remaining 39% comprised of African-Americans, Hispanics, Asians, Native-Americans, and other races. This study was reviewed and approved by the UNC at Chapel Hill School of Medicine Human Research and Ethics Board (IRB No. #11-0639).

Table 1 Demographic and racial distribution of patients displaying trace/faint/suspicious (TFS) bands during testing

Race	Patients with TFS bands (%)	Gender (males; females)	Mean age at first diagnosis (yrs)	Patients with unequivocal bands >3 g/dl	Relative risk	Confidence interval	p-value
African American	54 (31%)	32; 22	58±1.5	2 (40%)	0.98	0.92-1.0	0.54
Asian	2 (1%)	1; 1	59±1.4	0	0.85	0.51-1.4	0.54
Caucasian	105 (61%)	57; 48	65±1.1	2 (40%)	-	-	-
Hispanic	6 (3%)	4; 2	58±4.8	1 (20%)	0.85	0.59-1.2	0.37
Native American	2 (1%)	2; 0	45±1.5	0	0.85	0.51-1.4	0.54
Other	4 (2%)	1; 3	58±8.7	0	0.92	0.69-1.2	0.59
Total	**173**	**97; 76 (56% Male)**	62±0.9	**Out of 5 total patients (Group 8)**	-	-	-

The relative risk (and confidence interval) for a given racial/ethnic group to display unequivocal bands > 3g/dl during SPE/IFE analyses are provided. Risk is calculated with respect to the Caucasian group as reference. Of the total number of patients diagnosed with unequivocal bands >3g/dl (N=5), the percentage listed indicates representation from that racial/ethnic group.

Methodology for serum protein electrophoresis and immunofixation testing

Serum protein electrophoresis and immunofixation testing was performed using the Sebia Hydrasys System (Norcross, GA) or the Beckman Coulter Paragon Electrophoresis System (Brea, CA), according to the manufacturer's directions, as previously described[4-7].

Of the 173 IFE gels identified as having trace, faint, suspicious bands, thirteen were assessed on the Beckman Paragon (used 1990-2002), 160 were run on the Sebia Hydrasys II (2003-2011), and one was run on an unknown system in 1989 (records of the technology used are not available).

Quantitation of monoclonal immunoglobulins

Monoclonal immunoglobulins were quantitated using a combination of the serum total protein (Vitros® 5600 - Ortho Clinical Diagnostics;

Total Protein dry slides, which rely on the biuret reaction) and the % area of the abnormal band determined by scanning densitometry (Sebia, Phoresis Software). At UNC, it was determined experimentally that 0.3 g/dL was the threshold for reproducible, accurate, quantitation of the monoclonal protein using serial dilution of 3 different patient's monoclonal immunoglobulins (undiluted concentration was >5 g/dL). If a monoclonal immunoglobulin was determined to be below 0.3 g/dL, it was not quantitated and defined as *"too low to quantify."* Monoclonal proteins in the alpha and beta regions, or in the presence of a high concentration of polyclonal immunoglobulins were reported on a case-by-case basis.

Inclusion and exclusion criteria

The study focused on identifying patients that had very low concentration abnormalities in serum, as outlined in Figure 1. For inclusion in the present study, both SPE and IFE results were required. In addition, serum immunofixation interpretations had to contain one or more of the following descriptive key words: *Trace; Faint; Suspicious; Possible; Small; Questionable; Equivocal; "?Ig"; Band of restricted mobility; Suggestive of;* and *Weak.* These are heretofore referred to as trace/faint/suspicious (TFS) bands. We excluded urine electrophoresis results, those with a monoclonal protein >0.3 g/dL, results without preceding or subsequent tests, and those without any abnormalities. Any results designated with TFS nomenclature that satisfied the exclusion criteria were also omitted.

Figure 1 shows the study design and inclusion/exclusion criteria. The first row, all protein electrophoresis tests, represents every available SPE or UPE result for a 5 year time period. To define the relevant data, UPE results were excluded (Figure 1, row 2) as were results that indicated a quantifiable monoclonal gammaopathy (Figure 1, row 3). Results were also excluded where there was an absence of serial results, abnormalities, or unequivocal bands (Figure 1, row 4). The remaining dataset included 434 results from 173 unique patients, which were subsequently classified into group (described below).

Classification of patients with TFS bands

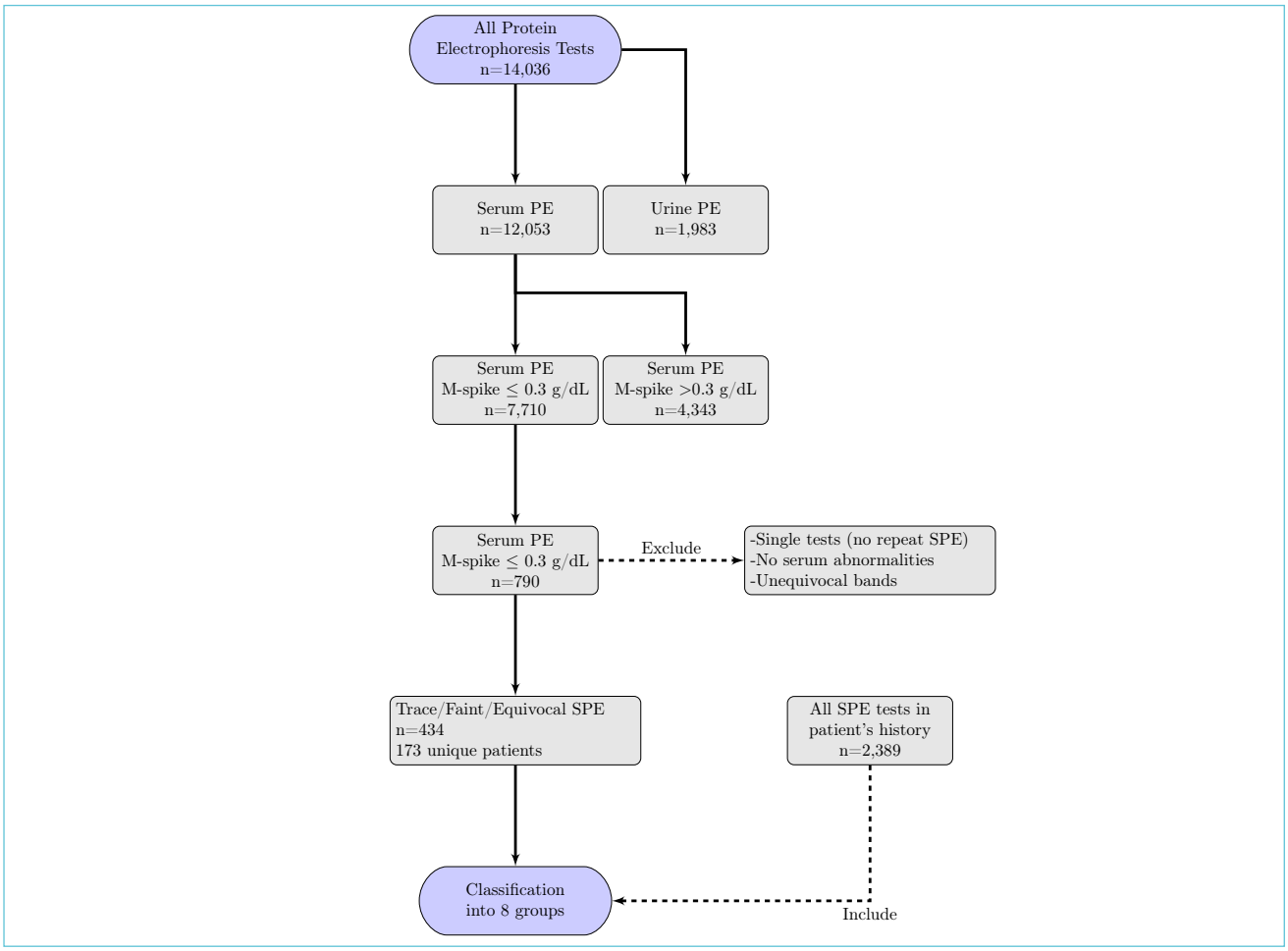
Results that met the inclusion criteria (N=434) were categorized into Groups (I – VIII) as defined in Table 2. Groups are based on the clinical history and concentration of preceding and subsequent monoclonal abnormalities by IFE at UNC that were mined from the SOFT electronic laboratory system; follow up and history of patients were determined by both the laboratory SOFT and the hospital electronic medical record (WebCis). The data include 173 distinct patients. In order to evaluate the clinical significance of the TFS bands in these patients, the complete electrophoretic history from the SOFT electronic laboratory system and the hospital electronic medical record of each patient was included in the final analysis, yielding a total of 2,389 tests.

RESULTS

We identified that 17% of all IFE results assessed at UNC Hospitals and evaluated for the presence of monoclonal gammopathies (2,389 out of 14,036) contained TFS bands, representing 4.2% (173 out of 4091) of all patients evaluated. These patients were further subdivided into two groups based on previous history of gammopathy. In all, 82 patients had an IFE result classified as having a TFS band and history of gammopathy; 60 patients had an IFE result classified as TFS without a history of monoclonal gammopathy.

All patients with TFS bands were sub-grouped according to the concentration of any previous or subsequent abnormal bands. The characteristics and outcomes of each group are indicated

Figure 1 **Experimental design, inclusion and exclusion criteria, of trace, faint, or scarcely visible immunoglobulin bands***



**analyzed by the McLendon Laboratories at the University of North Carolina Hospital for physician-ordered protein SPE and immunofixation electrophoresis (IFE) tests during the period of 2000-2010.*

in Table 2 and Table 3. Patients in Groups I to IV had no prior history of gammopathy. Patients in Group I had a TFS band, but no subsequent abnormality by IFE, while those in Group II did have a subsequent TFS band or unequivocal band that remained below the detection limit (<0.3 g/dL). Patients in Groups III and IV had subsequent unequivocal bands that were quantifiable at concentrations of <0.3g/dL and >0.3g/dL, respectively. In Group I patients, serial testing ceased after a single normal IFE test, whereas patients in Group II had repeat SPE/IFE tests or were no longer followed due to insufficient clinical evidence for a monoclonal gammopathy. None of these patients had a record of progression to myeloma or had an IFE test with an unequivocal band as of their most recent available record. Similarly, no patients in either Groups III or IV progressed to myeloma as of the most recent report. One individual in Group IV progressed to a "low-intermediate" risk category, according to 2010 International Myeloma Working Group guidelines (patient with just one risk factor for progression, in this case the monoclonal gammopathy)[8]. Patients in Groups V-VIII all had a previous history of monoclonal gammopathy, and were

Table 2 Group characteristics of serum protein electrophoresis testing with trace/faint/suspicious (TFS) monoclonal protein

Group	History	Description	Subsequent gammopathy [concentration]	Prior gammopathy [concentration]
I	No history of gammopathy	Subsequent testing yielded no serum or monoclonal protein		
II		Subsequent testing yielded TFS bands with ultimately no unequivocal, quantifiable band	Trace, Faint, Suspicious Bands	
III		Subsequent testing yielded TFS with ultimately no unequivocal, quantifiable bands	<0.3 g/dL	
IV		Subsequent testing reveal unequivocal monoclonal bands that were quantifiable	>0.3 g/dL	
V	Previous history of gammopathy	Previous serum PE with unequivocal bands that are not quantifiable		<0.3 g/dL
VI		Previous serum PE with unequivocal, quantifiable bands		0.3 to < 1.5 g/dL
VII		Previous serum PE with unequivocal, quantifiable bands		1.5 to <3.0 g/dL
VIII		Previous serum PE with unequivocal, quantifiable bands		>3.0 g/dL

classified according to the concentration of monoclonal protein detected in previous IFE tests. Patients in Group V had unequivocal bands that were not quantifiable (i.e. <0.3 g/dL). Patients in Groups VI, VII, and VIII displayed unequivocal bands that were quantified between 0.3 to 1.5 g/dL, 1.5 to 3.0 g/dL, and > 3.0 g/dL, respectively. Patients from Group V will require further monitoring over time to determine the significance of the unquantifiable TFS bands, and the probability of progression to myeloma. Likewise, patients from Groups VI and VII

Table 3 Retrospective summary of group outcomes of patients with trace/faint/suspicious (TFS) monoclonal protein

Group	Mean age at initial testing (years)	No. unique patients	Median no. serum PE/IFX	Median testing period (years)	Results of additional testing/summary outcome
I	63.0±5.1	8	3 (3 to 5)	5 (0.8 to 5.0)	Testing ceased after the first normal serum PE
II	63.2±2.2	35	2 (2 to 13)	0.72 (0.1 to 7.4)	Patients are still monitored with repeat serum PE or are no longer followed due to insufficient clinical evidence. None of these patients have a record of progression to myeloma or have ever had a serum PE that resulted in an unequivocal band as of their most recent record.
III	64.3±2.9	12	5 (2 to 13)	2.66 (0.2 to 6.4)	Nome of these patients has progressed to myeloma as of their most recent record.
IV	71.2±4.4	5	13 (5 to 29)	5.5 (3.9 to 7.4)	No patients progressed to myeloma. One patient progressed to a "low-intermediate" risk category (according to 2010 IMWG guidelines)
V	59.2±1.3	60	14 (2 to 84)	3.4 (0.1 to 11.0)	Require further evaluation to determine the significance of the unquantifiable TFS bands, and the probability of progression to myeloma.
VI	58.4±3.4	11	15 (3 to 56)	4.4 (1.4 to 9.5)	Require further evaluation to determine if the TFS band is a result of post-treatment remission for myeloma or is of no clinical significance.
VII	60.2±7.6	6	26 (12 to 69)	5.5 (2.3 to 14.7)	Require further evaluation to determine if the TFS band is a result of post-treatment remission for myeloma or is of no clinical significance.
VIII	60.6±4.7	5	31 (12 to 80)	3.8 (0.8 to 13.2)	Displayed unequivocal protein bands indicative of multiple myeloma and will require further evaluation to determine clinical significance.

Groups defined in Table 2; additional testing obtained by retrospective chart review.

will require further monitoring to ascertain if the TFS band is a result of post-treatment remission from myeloma, or if significant risk of persistent or returning myeloma exists.

Patients with unequivocal monoclonal protein > 3.0 g/dL (Group VIII) and a previous history of gammopathy (and treatment) have an increased risk of developing multiple myeloma,

despite improvements in therapy options and increased survival[9, 10]. These five patients must be closely followed with on-going SPE/IFE to determine the clinical significance of the present TFS band findings, and the probability of progression to multiple myeloma.

DISCUSSION

In the present study, we evaluated the significance of TFS bands on serum IFE tests from patients being investigated for plasma cell disorders. Of the 12,053 IFE tests assessed, 434 (4%) had TFS bands (M-spike >0.3 g/dL), representing 142 distinct patients. Sixty of these patients (42%) had no previous history of gammopathy, and were clinically evaluated over a mean period of up to five years from the original diagnosis of plasma cell pathology. None of these patients had progressed to multiple myeloma, lymphoplasmacytic lymphoma, plasmacytoma, or leukemia as of their most recent record. The remaining 82 patients (58%) had a previous history of gammopathy, but had not progressed to any symptomatic plasma cell dyscrasia. In the case of patients with previous tests displaying M-spikes > 3.0 g/dL, there is a higher risk of development of multiple myeloma, but no evidence that this has yet occurred. Patients in this latter group have undergone evaluation for a median period of 4.2 years, with a mean of 21.5 IFE tests per individual.

Serum and urine protein electrophoresis are the front line tests used for workup of any suspected plasma cell dyscrasia. They require a balance between clinical sensitivity and specificity so as to not miss patients with disease, but not over-diagnose those who are healthy or who have a benign condition. While the consequences of identifying an isolated monoclonal gammopathy in a healthy individual are generally low, there is some patient risk for unnecessary bone marrow biopsy and additional blood draws over the ensuing years. There is also an associated cost to continuous follow-up to both the patient and healthcare system. The objective of this study was to provide some information as to the clinical progression of patients with very faint abnormal bands identified by serum IFE by assisting the practicing electrophoresis results interpreter in putting their cases into context. The debate between different interpreters seeing or not seeing a particular abnormal band is likely to continue, but evidence from the current study supports that very low concentration bands are unlikely to progress to anything associated with a symptomatic disease state in a short time period (<5 years). Of course, one must consider other testing modalities, such as serum free light chains, and the rare aggressive plasma cell clone. Low concentration B-cell clones may produce toxic monoclonal immunoglobulins that cause severe tissue damage despite being difficult to detect by routine electrophoresis testing[11]. Examples of these include light-chain amyloidosis, light-chain deposition disease, and monoclonal cryoglobulinemia, which may cause irreversible tissue damage. Likewise, it is reported that multiple myeloma can occur despite a scarcely detectable monoclonal component[12]. Collectively, these data suggest that repeat serum IFE testing in patients with TFS bands may not be informative in the short run. In cases where there are TFS bands, but remaining concern for disease, it is probable that other testing modalities, such as serum free light chains and urine protein electrophoresis are appropriate.

All of the patients in this study of low concentration bands effectively meet the criteria for *monoclonal gammopathy of unknown significance* (MGUS). MGUS is defined by production of small amounts of monoclonal protein (< 3g/dL) in the absence of symptoms of myeloma, such as renal insufficiency, hypercalcemia or bone lesions that may be attributed to plasma cells

pathologies. MGUS is significantly more common than myeloma and the incidence increases with age, affecting ~3% of individuals aged 70 and older[13]. Though MGUS is believed to be a pre-myeloma condition, not all patients with MGUS develop myeloma. About 30-40% of individuals with MGUS, given sufficient time, may progress to myeloma, with the risk of progression approximated at 1% per year[3]. The objective of this study was to examine the progression of patients that are at the border of no monoclonal abnormality and MGUS. Given that plasma cell dyscrasias are a continuum from MGUS to myeloma, it is plausible that patients with very low concentration abnormalities are at risk for progression. In the available time frame (median 5 years), it appeared that none of the patients progressed. Based on the 1% progression rate reported by Kyle et al.[3] for MGUS, we might expect that 1-2 of the 142 patients included in this study might progress to myeloma per year. While more time is needed to monitor these patients, it is possible that lower concentration abnormalities are at lower risk for progression. Indeed, some of these low concentration abnormalities failed to persist over time let alone progress. It is unknown whether the TFS bands identified represent a pre-malignant state at all or some other immunological process entirely, such as a targeted immune response.

Marked differences in the incidence of MGUS and multiple myeloma have been reported in both African-Americans and Africans compared to Caucasians (see recent review Greenberg et al., 2012)[14]. The prevalence of MGUS in African-Americans has been reported to be higher than that of Caucasians in patients residing in North Carolina. Cohen et al, (1998) studied 1,732 subjects >70 years of age and found that 8.4% of African-American patients had a monoclonal protein compared to 3.8% of white patients ($p<0.001$), increasing in prevalence with age and greater in men vs. women[15]. In the present study, 31% of patients with a previous history of gammopathy and the presence of TFS bands were black, compared to 61% white patients. Indeed, the percentage of patients with unequivocal bands >3 g/dL were comparable between African-Americans (40%) and whites (40%), despite the lower representation of African-Americans in this study (Table 1). Twenty percent of Hispanic patients displayed quantifiable bands in this category, with no observations for unequivocal bands for Asian, Native American or other patients. Thus, in addition to age, the race of the patient should play a factor concerning the decision to pursue further testing, and determining the likelihood for progression to malignancy, particularly for African-American patients.

For those individuals with a previous history of gammopathy and with serum monoclonal protein >3 g/dL, *smoldering multiple myeloma* (SMM) becomes an important consideration. Similar to MGUS, SMM is characterized by plasma cell proliferation, and is asymptomatic with respect to end-organ damage, but presents with serum monoclonal protein levels higher than that of MGUS. Patients diagnosed with SMM are believed to have a higher incidence of progression to multiple myeloma than those with MGUS, accounting for 10-15% of new cases of multiple myeloma; however, the risk of progression declines significantly over time[3], therefore requiring a shorter period of post-evaluation from the initial determination.

Only some patients with clearly identifiable MGUS will progress to the stage of multiple myeloma. In a study of 241 patients diagnosed with MGUS, 64 individuals (26%) eventually developed multiple myeloma, amyloidosis, Waldenström's macroglobulinemia, immunoglobulin light chain amyloidosis, or some lymphoproliferative disorder[3]. However, these patients were further observed for a median period of 10.4 years before

being diagnosed for a proliferative cell disorder. Similarly, in a larger, population-based study in Minnesota, 115 of 1,384 patients (8%) diagnosed with MGUS and followed over a median period of ~15 years progressed to a proliferative cell disorder[16]. The median age at initial diagnosis of MGUS was 72 years old[16].

Though little is known regarding the mechanism by which progression to a plasma cell malignancy occurs, certain conditions have been suggested as predictive of progression. The following have been reported to correlate with an increased rate of malignant progression from MGUS: serum monoclonal protein values > 2.5g/dL; the presence of an IgM or IgA monoclonal protein; having more than 5% bone marrow plasma cells; an abnormal free light chain ratio[3]. For SMM, progression to malignancy may occur progressively, with gradual increases in serum monoclonal protein levels (termed evolving SMM), or abrupt increases in monoclonal protein values (non-evolving SMM). The rate of progression to malignancy is dependent upon the number or proliferation rate of circulating plasma cells[17].

Despite extensive analysis over a prolonged period, this study has a few limitations that should be considered when interpreting the data. The study includes a maximum of 10 years of follow up for any given patient (median follow-up was 4 $\pm$ 0.4 years) such that the time frame may be too short to identify patients that progress to symptomatic disease slowly. The analysis did not include serum free light chains or urine protein electrophoresis data except where available for the 142 patients included; serum protein electrophoresis was unavailable for the first several years of the time included in the study. Lastly, we have previously reported on the variability between interpreters and methods, which could factor into the classification of results by IFE[4]. Three different platforms were used over the course of the study data and at least 8 different interpreters reported results over the ten-year period.

Collectively, the data in this study suggest that for patients without a previous history of gammopathy, the presence of TFS bands on serum protein electrophoresis does not warrant frequent follow up investigation as commonly practiced (Groups I-IV in the current study). Routine follow up in those with a prior history of gammopathy, conversely, are warranted and may contribute to overall survival with multiple treatment options now available. For those interpreting IFE results, it may be worth considering these data when composing comments regarding suggested repeat testing frequency by SPE/IFE or alternate test methods.

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