Transient Paraproteinemia: An Intriguing Immunological Anomaly

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Abstract. Serum transient paraproteins are small monoclonal immunoglobulins that are induced by a self-limiting regulatory defect in the control of certain terminally differentiated B-cell clones. Relatively uncommon and ill-defined in the medical literature, such proteins may be regarded as immunologic anomalies. Their clinical significance and potential impact on patient management are poorly understood. To elucidate this phenomenon, we reviewed the serum transient paraproteins that were encountered in a large community hospital during a 12 mo period. Twelve transient paraproteins were identified in a total of 895 serum protein electrophoreses reviewed (1.3% incidence). The relationships of the transient paraproteins to specific diseases were studied. (received 4 March 2003; accepted 27 March 2003)

Keywords: transient paraprotein, electrophoresis, immunofixation, monoclonal protein, autoimmunity

Introduction

Serum protein electrophoresis (SPE) is a diagnostic laboratory test that separates and quantifies several classes of serum proteins and that identifies and characterizes the monoclonal gammopathies (M-proteins). M-proteins are indicative of certain lymphoproliferative conditions, eg, multiple myeloma and Waldenström's macroglobulinemia [1-3]. Serial monitoring of SPE M-protein concentrations is used to evaluate therapeutic responses and disease progression. The widespread use of SPE has revealed a low incidence of potential precursors to lymphoproliferative neoplasia, termed monoclonal gammopathies of undetermined significance (MGUS), most often seen in older adults. In a recent study by Kyle et al [4], the risk of MGUS progressing to multiple myeloma and related disorders was approximately 1% per year.

The clinical utility of SPE extends beyond the monoclonal gammopathies. Alterations in the concentrations of certain protein fractions are typical of various pathological conditions. For example, the acute phase reaction (decreased albumin and transferrin fractions, elevated alpha-1 and alpha-2 globulin fractions) is indicative of an acute inflammatory process. Diffuse (polyclonal) hypergammaglobulinemia is associated with chronic inflammatory disorders, including chronic liver, collagen vascular, and granulomatous diseases. Hypogammaglobulinemia is observed with immune deficiencies, lymphoproliferative neoplasia, and with cytotoxic or immunosuppressive drug therapy. Specific, isolated protein abnormalities, such as alpha-1 antitrypsin deficiency, IgA deficiency, and hyperbetalipoproteinemia may be initially suggested by an abnormal SPE pattern [5].

Occasional SPE patterns contain transient protein bands of uncertain clinical significance. When evaluated further with immunofixation electrophoresis (IFE), many of these prove to be pseudoparaproteins, such as C-reactive protein or fibrinogen [6]. A minority, however, are true transient M-proteins. Of esoteric etiology, these transient paraproteins (TP) pose diagnostic dilemmas to clinical scientists and physicians.

To examine our experience with serum TP, all SPE patterns produced during a 12 mo period were reviewed. TP were defined as small monoclonal immunoglobulins identified in an initial SPE pattern, confirmed by IFE, and absent in follow-up SPE patterns on at least two distinct occasions. Twelve TP were identified in a total of 895 SPE patterns that were reviewed. The major diseases of the 12 patients with TP were tabulated in an attempt to deduce potential relationships.
Methods and Materials

Transient paraproteins (TP) were defined as monoclonal immunoglobulins detected by routine SPE during an initial patient evaluation, but absent in follow-up studies on at least 2 occasions (Fig. 1). Patients with serum TP were followed for at least 6 mo and a maximum (thus far) of 2 yr, with an average follow-up of 18 mo. All TP were confirmed and characterized with serum IFE. Follow-up (negative) SPE patterns for each patient were also correlated with serum IFE analysis to verify the absence of the paraprotein.

All SPE and IFE were performed with the Paragon SPE-II Electrophoresis System (Beckman Instruments, Inc., Fullerton, CA). Serum samples were evaluated at standard dilutions according to the manufacturer’s guidelines. A Beckman Appraise Densitometer was used to quantitate protein fractions. Antisera used for IFE were initially tested against normal controls to ensure the absence of reactivity against normally occurring proteins. Cerebrospinal fluid and urine protein electrophoresis patterns were not included in this study due to their small numbers.

Results

Twelve TP were identified in 895 SPE patterns from a total of 803 patients (age range 3 to 97 yr) produced during a 12 mo period (January to December 2001). Of the TP, 10 were monoclonal and 2 were biclonal. Two separate follow-up SPE patterns were included in the study of each patient with an identified TP. The incidence and distribution of TP according to patient age and sex are compared to the entire study population in Fig. 2. Table 1 lists the 12 patients according to their age, sex, paraprotein subtype and concentration, and primary disease conditions.

A total of 17 patients in the study had a primary diagnosis of an autoimmune disorder (systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, or scleroderma), only 3 of which demonstrated serum TP. The TP identified in the serum of a patient with hepatitis C was a cryoglobulin. This was confirmed by identifying the IgM kappa band in the serum IFE performed at 37°C, with disappearance of this band when the serum sample was cooled to room temperature, centrifuged, and the IFE was repeated.

Eleven patients with SPE patterns suggesting possible TP were lost to follow-up and hence were not included in the study.

Discussion

Transient paraproteins (TP) are an enigmatic laboratory phenomenon, inconsistently defined in the modern literature. Although technically a form of MGUS, these minor M-proteins are typically identified in the serum of patients with a spectrum of acute and chronic inflammatory illnesses.

Whether these proteins imply an increased risk for plasma cell or lymphoid neoplasia has not been established. Their occurrence in the serum of some patients probably represents a self-limiting regulatory defect in the control of fully differentiated B-cell clones [7]. The evanescent nature of these serum proteins in the absence of specific immune suppression or anti-neoplastic therapy suggests that the most are benign.

The SPE that contained TP were generally requested to evaluate a patient with an unexplained elevation of the serum total protein concentration, or an abnormal albumin:total protein ratio (implied hypergammaglobulinemia) that was detected by routine clinical chemistry studies. TP can easily be overlooked when hypergammaglobulinemia is present. Consequently, the true incidence of TP may be underestimated.

Autoimmune diseases (ie, systemic lupus erythematosus, autoimmune hepatitis, and rheumatoid arthritis) were the primary diagnoses in 3 of the 12 patients with serum TP. Autoimmune disorders are manifestations of chronic activation of the immune system by undefined or poorly defined antigenic stimuli. Various pathogens, drugs, and toxins have been implicated as etiological agents [8-10]. A genetic predisposition is suspected in many cases. Due to hyperactivity of the immune system, individuals with autoimmune disorders may, in occasional cases, be predisposed to development of minor paraproteinemia, transient or persistent.
Table 1. Age, sex, and major disease conditions associated with transient paraproteinemia in 12 patients.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yr)</th>
<th>Transient paraprotein(^1) (immunoglobulin type, g/dl)</th>
<th>Associated major disease conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>83</td>
<td>IgG lambda (0.1, 0.1)(^2)</td>
<td>Osteoarthritis (degenerative joint disease)</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>IgM kappa (0.2)</td>
<td>Guillain-Barré Syndrome</td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>IgM kappa (0.2)</td>
<td>HCV(^3) with cryoglobulinemia (type 2)</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>IgG kappa (0.2, 0.1)(^2)</td>
<td>HCV(^3)</td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>IgG kappa (0.1)</td>
<td>Autoimmune hepatitis (ANA = 1:320)(^4)</td>
</tr>
<tr>
<td>F</td>
<td>69</td>
<td>IgG kappa (0.1)</td>
<td>Coronary artery disease with previous cerebral vascular accident</td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>IgG kappa (0.2)</td>
<td>Systemic lupus erythematosus(^5)</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>IgG kappa (0.1)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>F</td>
<td>69</td>
<td>IgG kappa (0.2)</td>
<td>Systemic lupus erythematosus with chronic renal failure(^5)</td>
</tr>
<tr>
<td>M</td>
<td>79</td>
<td>IgG kappa (0.2)</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>M</td>
<td>68</td>
<td>IgG kappa (0.1)</td>
<td>Sepsis, fever of unknown origin</td>
</tr>
<tr>
<td>F</td>
<td>79</td>
<td>IgG kappa (0.1)</td>
<td>Breast cancer (mastectomy 3 yr prior), clinical remission</td>
</tr>
</tbody>
</table>

\(^1\) Determined by serum immunofixation electrophoresis  
\(^2\) Biclonal paraproteins  
\(^3\) Hepatitis C infection (chronic hepatitis)  
\(^4\) Anti-nuclear antibody titer  
\(^5\) Bone marrow biopsy performed

Fig. 1. Immunofixation electrophoresis (IFE) patterns demonstrating a typical transient paraprotein, IgG Lambda, and background polyclonal hypergammaglobulinemia (A), with disappearance of the transient paraprotein in the follow-up IFE performed 3 mo later (B).
Serum paraproteins may be observed in patients with polyneuropathies and peripheral neuropathies [11-13]. The M-proteins may be otherwise subclinical (MGUS) or may be associated with clinically evident disease (e.g., multiple myeloma, amyloidosis, lymphoma). The M-proteins and coexistent polyclonal antibodies may be directed against a variety of human peripheral nerve antigens, including myelin-associated glycoprotein (MAG) and anti-GM1 ganglioside [11]. In our series, the specificity of the transient paraprotein found in a patient with Guillain-Barré syndrome was not characterized, but a previous study has suggested an association with anti-GQ1b IgG antibody [14].

The TP of one patient with chronic hepatitis C infection was a cryoglobulin. Cryoglobulins, immune complexes that precipitate (become insoluble) at temperatures below 37°C, are classified as types I, II, or III, depending on the nature of the immune complexes. Hepatitis C virus (HCV) infection is strongly associated with type II cryoglobulinemia [15-18]. The immune complexes of type II cryoglobulinemia typically consist of monoclonal IgM rheumatoid factor which reacts with polyclonal IgG. HCV virions are concentrated within the cryoglobulins of these patients. Type II cryoglobulinemia appears to be a manifestation of a lymphoplasmacytic disorder, which may be expressed as a multisystem inflammatory response.
to cryoglobulins or as a clinically overt malignant lymphoma [19]. An indolent phase of B-cell lymphoma may exist prior to clinical signs [20].

Bone marrow biopsies were performed to rule out plasma cell neoplasia in only two of our patients, one with chronic renal failure and the other with systemic lupus erythematosus. Both biopsies contained histologically normal populations of plasma cells and lymphocytes. Immunohistochemistry was used to confirm a normal kappa: lambda ratio in the plasma cells present in each biopsy. Flow cytometric immunophenotyping was not performed.

TP must be distinguished from benign pseudoparaproteins, which are also transient and can mimic TP in routine SPE patterns [6]. Common serum pseudoparaproteins include hyperbetalipoproteinemia, fibrinogen, C-reactive protein, hemoglobin-haptoglobin complex (hemolyzed samples), and reactive increases of transferrin or complement C3. IFE is negative for each of these pseudoparaproteins. Quantitative measurement of the suspected pseudoparaprotein can be used to confirm its identity, if clinically relevant.

Certain electrophoretic artifacts can be mistaken for TP [6]. Point-of-application artifact occurs as a thin, discrete line in the application well, and may be particularly prominent in samples containing immune complexes. Cathodal migration artifact may be observed in samples that have undergone prolonged electrophoretic migration (a technique related artifact). In both of these situations, as with pseudoparaproteins, the IFE is negative.

For each of the TP identified in this study, the ordering physicians were contacted to determine their opinion regarding the laboratory findings, and whether or not their awareness of the TP influenced their patient management. Rheumatologists and hematologists/oncologists were inclined to view TP as “aberrant” benign reactive proteins in the serum. However, many clinicians suspected that these proteins could represent an early manifestation of a clandestine malignancy. Pathological/clinical correlation conferences provided an educational opportunity to define TP for clinicians and to emphasize that the TP was an appropriate reflection of a disease process, albeit of uncertain significance.

No instance of TP recurrence was observed. However, the period of follow-up was too brief to conclude that the appearance of TP was necessarily an isolated event in the course of each patient’s disease. Retrospective evaluation of SPE patterns performed in our laboratory prior to 2001 revealed that only 2 patients had previous SPE patterns analyzed, both of which were negative for paraprotein. This study is on-going, and all patients with TP detected in our laboratory are being monitored prospectively for recurrences.

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References