Polyclonal Gammopathy

Serum protein electrophoresis (SPEP) is a useful screening test in the evaluation of hypergammaglobulinemia. An elevated gamma globulin level can be suspected in the setting of a patient with an increased total protein, but decreased albumin (e.g. in a comprehensive metabolic profile – CMP). At other times, physicians may order an SPEP as an initial test to “r/o myeloma”. Hypergammaglobulinemia may indeed be the result of a monoclonal gammopathy (in the setting of a plasma cell dyscrasia, lymphoma, amyloidosis or monoclonal gammopathy of undetermined clinical significance - MGUS). Follow-up testing in this case is rather straightforward – immunofixation studies of the serum and/or urine. Polyclonal gammopathy (PG) is another electrophoretic pattern frequently observed in hypergammaglobulinemia. At times, this SPEP interpretation may prompt questions with regard to the clinical significance and whether additional studies are required.

Dr. Robert Kyle and associates published a very helpful review of the Mayo Clinic experience with polyclonal gammopathy. They retrospectively studied all patients during a one year period (1991) at the Clinic who had polyclonal gamma globulin level > 3.0 g/dL. (This value was chose to correspond to the cut-off level they used to help distinguish between MGUS and plasma cell dyscrasia.) The diagnosis was made by visual inspection of cellulose acetate membranes only. Neither immunofixation nor quantitative immunoglobulin studies were performed. (For the purpose of maintaining a uniform study group, 10 patients who had immunofixation or immunoelctrophoresis performed were excluded from the study. Five of these 10 had diminutive M-spikes, too small to quantitate.) The resulting study group numbered 148. The medical records were reviewed to determine the diagnosis most likely responsible for the PG and a total of 167 diagnoses were recorded. In 4 patients, the PG-producing illness could not be determined. The median follow-up was 67 months since the index SPEP. The diagnoses assigned to the patients preceded the PG recognition in 68%, coincided in 28%, and followed in 4%. PG-producing illness in the last group was identified between 2.2 – 27 months following the index SPEP. Six basic disease groups were identified. The clinical findings are summarized below.

### Polyclonal Gammopathy – Clinical Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=148)</th>
<th>Liver (n=79)</th>
<th>CTD (n=28)</th>
<th>HD (n=6)</th>
<th>Malignant (n=4)</th>
<th>Infection (n=8)</th>
<th>Other (n=5)</th>
<th>&gt;1 Dx. (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr.)</td>
<td>58</td>
<td>57</td>
<td>59</td>
<td>66</td>
<td>73</td>
<td>52</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>Age Range</td>
<td>15-86</td>
<td>16-84</td>
<td>15-83</td>
<td>48-80</td>
<td>66-76</td>
<td>31-80</td>
<td>34-73</td>
<td>28-86</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>59</td>
<td>51</td>
<td>86*</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>22</td>
<td>38</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>26</td>
<td>34</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphadenopathy (%)</td>
<td>4.7</td>
<td>1.3</td>
<td>3.6</td>
<td>83</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There was no difference in gamma globulin levels among the 6 groups. Laboratory tests which displayed significant differences between the 6 groups included AST (SGOT), alkaline phosphatase, bilirubin, albumin, hemoglobin, platelets and (Arrrrggghhhh!!!!) the venerable ESR.

### Polyclonal Gammopathy – Laboratory Features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Copyright © 2000 Rex Healthcare/Comprehensive Laboratory Services, Inc. 919/784-3040. All rights reserved.
Liver Disease
The largest category of PG-producing illness was liver disease (either as a single cause or in combination with some other category). Autoimmune hepatitis was the single most common disorder (30%), followed by viral hepatitis (18%), primary biliary cirrhosis (17%), alcoholic liver disease (12%), and sclerosing cholangitis (8%). Some patients had more than one liver disease (e.g. co-infection with hepatitis B and C virus or mixed alcoholic/viral hepatitis). Hypergammaglobulinemia/PG is a common finding in autoimmune hepatitis, but this study illustrates that it is not specific to that type of liver disease.

Connective Tissue Disease
The second most common group of diseases was connective tissue disorders, either alone or in combination with some other disease (usually hematologic or hepatic). In order of decreasing frequency, types of connective tissue diseases included: Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and mixed connective tissue disease. As noted in the first table above, women were disproportionately represented in this group of patients.

Hematologic Disorders
Coming in a somewhat distant 3rd place was the group of hematologic disorders. While only 6 patients had a “pure” hematologic disorder, an additional 7 had associated connective tissue disorders. This category included 2 benign lymphoproliferative disorders (not further specified), 5 low grade lymphomas, 2 high grade T-cell lymphomas, 3 large granular lymphocytic leukemias (!!!), and 1 chronic myelomonocytic leukemia (CMMoL). No patient in this series developed myeloma or a clonal plasma cell disorder. PG has been reported in myelodysplasia (particularly CMMoL) as well as severe hemophilia A, thalassemia major, sickle cell anemia, Fanconi’s anemia, and idiopathic thrombocytopenic purpura.

Nonhematologic Malignancy
Four patients had an isolated non-hematologic malignancy, while 5 had a malignancy in addition to liver disease or connective tissue disease. Perhaps not surprisingly, hepatocellular carcinoma was stated to be the most common malignancy.

Infections
A variety of infections can be associated with polyclonal gammopathy. In this series, 8 patients had an infection (other than viral hepatitis). HIV infection was the most common infection in this series. PG is often observed early in the course of HIV infection, but subsides with the development of AIDS.
Other Illnesses
One patient had a type of hypersensitivity pneumonitis (bird fancier’s lung). The other 4 did not have diseases that could be confidently suspected of producing PG. Two of these developed a lymphoproliferative disorder during the follow-up period, but the authors could not determine if the disease was present (in retrospect) at the time of the index SPEP.

Follow-Up
Many of the patients had a series of SPEPs while being seen at the Clinic. The gamma globulin levels varied over time, and resolved in some patients. Of the 143 patients for whom follow-up was available, 90 (63%) were alive. Specific survival rates for the disease groups was 62% (liver), 89% (connective tissue disease), 33% (hematologic disease), 0% (malignancy), and 57% (infection). By multivariate analysis, significant factors in determining survival were age, albumin concentration, disease group, and platelet count.

Summary
PG is a rather common laboratory finding which may be seen in a variety of disorders. In their review, Dr. Kyle’s group list over 80 specific diseases that have been associated with PG. 3 (The interested reader is referred to Table 4 in that publication.) Nevertheless, the broad categories of liver disease and connective tissue disease account for roughly 80% of PG in the Mayo series. The clinical setting, physical findings, and a few general laboratory tests (LFTs & CBC) should be helpful in suggesting the general category of illnesses responsible for the PG. Specific follow-up testing where indicated (particularly in patients with liver disease) may lead to a more precise diagnosis. Immunofixation/immunoelectrophoresis studies are not necessary. An exhaustive work-up in an otherwise healthy patient with “isolated” PG is probably not indicated. There is no specific therapy for PG, although gamma globulin levels may decline with treatment of the associated disorder. Rarely, PG may produce hyperviscosity-type symptoms, requiring corticosteroids or plasmapheresis.

John D. Benson, MD

References

D-Dimer Case Study

Case Presentation: A 27-year-old female presents to the emergency department with shortness of breath and lethargy. She is 28 week pregnant. Her two previous pregnancies resulted in spontaneous abortions at 12 and 18 weeks respectively. Her CBC is normal except for a mild microcytic, hypochromic anemia. The PT, aPTT and fibrinogen are normal. A SimpliRED (D-dimer test) was positive. Ultrasound evaluation reveals proximal deep vein thrombosis and a ventilation/perfusion scan was positive. Further evaluation by her hematologist shows Protein S deficiency and hyperhomocysteinemia. She is treated with low molecular weight heparin for the duration of her pregnancy. Low molecular weight heparin does not cross the placenta. After a normal delivery at 39 weeks, she is begun on long term warfarin therapy.

Usefulness of the D-Dimer assay: The clinical usefulness of a D-dimer result is in its negative predictive value. A negative result is very helpful in ruling out thrombosis. A positive result is not helpful in making the diagnosis of thrombosis. Positive results are seen in almost all hospitalized and cancer patients, post surgery, pregnancy, in the elderly, burn patients and in the postpartum period. These patients have a hypercoagulable state and subclinical fibrinolysis. A negative D-dimer test in these patients is uncommon. The SimpliRED D-dimer assay has a high sensitivity (94%) and a negative predictive value of 98% for pulmonary embolus. The
SimpliRED test has been available 24 hours a day in the Rex Laboratory since 1997. When the D-dimer test and ultrasound studies are negative, the diagnosis of thrombosis is virtually excluded.

**Case discussion:** The patient has protein S deficiency and hyperhomocysteinemia. Protein S is a relatively strong risk factor for the thrombosis and is an inherited defect in the fibrinolytic system. Since there is a delicate balance between the coagulation and fibrinolytic systems ongoing, a defect such as protein S deficiency can easily result in a hypercoagulable state. When combined with elevated homocysteine levels and pregnancy, venous thrombosis is highly likely. Her two previous pregnancies resulted in miscarriage as a result of her inherited hypercoagulable state causing microthrombi in the placenta and terminating in infarction and fetal death. The hematologist decided to place her on life long anticoagulation because of her clinical history and inherited hypercoagulable state.

Stephen V. Chiavetta, MD

**References**


**Roger Baxter’s Lab Tips (This is a Filler)**

The following tips are quoted from Dr. Roger Baxter’s Oakland, CA Kaiser Permanente quarterly laboratory bulletin (*Lab Tips*) as cited in *CAP Today*.

- False positive and false negative results occur in every laboratory. Lab results that make no sense need to be repeated. Most specimens are held for a week at the laboratory. To add tests and avoid a second phlebotomy, call the clinical laboratory to see if it still has the specimen.
- TSH alone can be used in most cases to screen for both hypothyroidism and hyperthyroidism, and to follow patients on thyroid replacement.
- ANA and rheumatoid factor should be ordered only if there is a moderate suspicion of collagen vascular disease. These make very poor screening tests if the pretest probability is low.
- CBC, thyroid, liver function tests, urinalysis and creatinine are not routine screening tests for young, healthy people.

**References**


**TRH Stimulation Test Discontinued**

Effective immediately, the TRH stimulation test has been discontinued due to ceased production of the protirelin (Thyphinone ®) diagnostic agent. (See second bullet point cited in the preceding article.)