Proteinaceous (Angiocentric Sclerosing) Lymphadenopathy: A Polyclonal Systemic, Nonamyloid Deposition Disorder

By Joseph Michaeli, Ruben Niesvizky, David Siegel, Marc Ladanyi, Philip H. Lieberman, and Daniel A. Filippa

Proteinaceous lymphadenopathy with hypergammaglobulinemia (PLWH) is an exceedingly rare disease of unknown etiology. Described primarily as a pathologic entity, relatively little is known about its clinical manifestations or its response to therapy. The disease is often referred to and treated as an unusual form of plasma cell dyscrasia or light chain deposition disease. We have recently encountered a young patient with PLWH who presented with generalized lymphadenopathy, marked liver function abnormalities, hypocomplementemia, cryoglobulinemia, decreased T4/T8 ratio, and ophthalmopathy. Contrary to the notion that PLWH is a clonal disorder, we found no evidence of clonality in this patient. The most characteristic finding in this and in another patient, previously seen at our institution, was marked angiocentric hyaline sclerosis of the small and mid-sized blood vessels of involved lymph nodes and organs. Based on these findings, we propose the term angiocentric sclerosing lymphadenopathy, which more accurately defines this clinicopathologic entity that appears to be distinct from light chain deposition disease and other plasma cell dyscrasias. © 1995 by The American Society of Hematology.

DEPOSITION OF extracellular Igs, in the absence of amyloidosis has been described in association with plasma cell dyscrasias. These deposits may involve many tissues including the kidneys, lungs, and bone marrow. This disorder is invariably associated with the deposition of a clonal light or heavy chain in these tissues. In this report, we describe the clinical and pathological features of a rare systemic disorder characterized by a nonamyloid polyclonal Ig deposition, manifested primarily as generalized lymphadenopathy and severe liver dysfunction. This variant deposition disorder is clearly distinguishable from the clonal deposition disorder associated with plasma cell dyscrasias and amyloid.

MATERIALS AND METHODS

Immunochemical studies. Serum and concentrated urine samples were studied by high-resolution electrophoresis and immuno fixation. The immunologic studies were performed with monoclonal antibodies (Abs) specific for kappa and lambda light chains.

Molecular studies. Analysis of antigen receptor genes was performed by Southern blotting. Genomic DNA was extracted from snap-frozen tissues on an automated DNA extractor (Model 340A; Applied Biosystems, Foster City, CA). Southern blots of both EcoRI and HindIII digests of genomic DNA were performed on a semiautomated blotting system (Probe Tech II; Oncor, Gaithersburg, MD). Placental DNA was used as germline, ie, normal, control. The filters were hybridized overnight with probes radiolabeled to a high specific activity by random priming. The probes used included, for the Ig heavy chain gene (IgH), a 5.6-kb HindIII-BamHI fragment spanning the entire J region and, for the T-cell receptor beta gene, a 0.6-kb EcoRI fragment of the constant region or a combination of J beta 2 and J beta 3 (Oncor). After hybridization, the filters were washed at high stringency and exposed to film for 1 to 4 days.

RESULTS

Case no. 1. A 38-year-old woman was referred to our hospital for evaluation of a systemic illness of 18 months in duration. Her past medical history was remarkable for polycystic ovaries and intermittent episodes of elevated intracranial pressure. She had a well-documented episode of pseudotumor cerebri 4 years before the onset of her current symptoms. The patient had sought medical attention before her referral because of intermittent low-grade fever, night sweats, myalgia, malaise, and pruritus. Physical examination showed bilateral painless cervical and supraclavicular lymph node enlargement (2 cm × 2.5 cm). The liver was palpable 5 cm below the right costal margin. Eye examination disclosed subepithelial corneal infiltrates and bilateral orbital inflammation. The remainder of the physical examination was unremarkable.

The urinalysis was normal. The hematocrit was 42.8%, and the white cell count was 8.1 × 10^9/L with 65% neutrophils, 30% lymphocytes, 3% eosinophils, 1% monocytes, and 1% basophils. The platelet count was 286 × 10^9/L, and the erythrocyte sedimentation rate was 66 mm/h. The abnormal blood chemistry values at presentation are given in Table 1. Human immunodeficiency virus Abs hepatitis B surface antigens, hepatitis C antigen, and hepatitis A and hepatitis C Abs were also negative. Purified protein derivative and Venereal Disease Research Laboratory tests were negative as were serologies for toxoplasma, Q-fever, and Epstein-Barr virus. The patient had high serum anticytomegalo virus (anti-CMV) IgG antibody titer, but IgM anti-CMV titers were negative. Protein electrophoresis showed a gamma fraction of 1.47 g/dL (range, 0.7 to 1.6 g/dL). Immunofixation showed a polyclonal increase in Igs and no evidence of a monoclonal gammopathy. Nephelometry showed an elevated IgM (330 mg/dL; normal range, 70 to 280 mg/dL), low IgA (76 mg/dL; range, 90 to 480 mg/dL), and normal IgG (855 mg/dL; range, 800 to 1,900 mg/dL). Serum cryoglobulins were positive. Urine protein electrophoresis was normal. Beta-2 Microglobulin was 2.0 mg/L (range, 1.1 to 2.4 mg/L). C-reactive protein and lactate dehydrogenase were normal. A comprehensive workup for possible autoimmune disorder was negative. Serology for rheumatoid factor was negative. Surface marker analysis of peripheral blood showed a decreased T4:T8 ratio of 0.5 (normal, 1 to 4). Skelet survey was normal. Computerized tomography (CT) of the abdomen showed mild hepatosplenomegaly and multi-

From the Division of Hematologic Oncology and the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY.

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Address reprint requests to Joseph Michaeli, MD, Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

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Table 1. Laboratory Findings

<table>
<thead>
<tr>
<th>Variable (normal range)</th>
<th>At Presentation</th>
<th>18 Months Later</th>
<th>7 Months on Steroid Treatment</th>
<th>6 Months After Termination of Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.0</td>
<td>2.3</td>
<td>0.9</td>
<td>2.5</td>
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<tr>
<td>Serum aspartate aminotransferase (ASAT) (15-35 U/L)</td>
<td>67</td>
<td>52</td>
<td>49</td>
<td>519</td>
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<tr>
<td>Alkaline phosphatase (38-126 U/L)</td>
<td>590</td>
<td>900</td>
<td>364</td>
<td>793</td>
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<tr>
<td>Serum alanine aminotransferase (10-60 U/L)</td>
<td>49</td>
<td>72</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>Gamma glutamyl transpeptidase (10-60 U/L)</td>
<td>867</td>
<td>1535</td>
<td>565</td>
<td>1679</td>
</tr>
<tr>
<td>C3 complement (70-176 mg/dL)</td>
<td>ND</td>
<td>36</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>C4 complement (16-45 mg/dL)</td>
<td>ND</td>
<td>7</td>
<td>ND</td>
<td>12</td>
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<tr>
<td>Total hemolytic complement CH50 (50-110 U/L)</td>
<td>ND</td>
<td>NMA</td>
<td>NMA</td>
<td>NMA</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not determined; NMA, no measurable amount.

ple small retroperitoneal and pelvic lymph nodes. CT of the chest was unremarkable. Bilateral bone marrow (BM) aspiration and biopsy specimens showed a normocellular BM with complete maturation of all hematopoietic lineages. No excess of plasma cells or extracellular deposits were observed.

BM marker studies showed no evidence of B- or T-cell clonal excess. IgH gene and T-cell receptor β gene rearrangement studies performed on DNA extracted from the patient’s BM also showed no evidence of clonality. The BM showed a normal karyotype. A right cervical and supraclavicular lymph node biopsy disclosed an identical marked, diffuse depletion of lymphoid cells, with a pronounced hyaline sclerosis of small- and mid-sized vessels extending concentrically in an “onion skin” pattern around each vessel, uniformly replacing the lymphoid tissue (Fig 1). Immunohistochemistry showed no identifiable deposition of kappa or lambda light chains or of heavy chains. There was no binding of monoclonal Abs against collagen type IV or laminin by the sclerosing material. Abs to factor VIII and CD-34 positively stained the cells lining the markedly reduced lumina of the concentrically sclerosed vessels. There was no evidence of amyloid deposits by Congo red staining or by electron microscopic examination. Special stains showed that this material is formed largely by dense, concentric bundles of fine reticulin fibers in the vessel wall and outward in concentric rings (Fig 2). The few plasma cells identified did not show either kappa or lambda light chain excess. A liver biopsy specimen disclosed portal fibrosis with foci of concentrically arranged sclerotic material, around the small vessels in the portal spaces. Foci of hepatocellular necrosis (without “piece meal” appearance) were also observed. No Mallory bodies or steatosis was found.

A therapeutic trial with prednisone (100 mg/d) was initiated. Within 25 days of therapy, the patient reported marked subjective improvement in her performance status. Prednisone was then gradually tapered to 50 mg/d. Four months after initiation of treatment, the patient had no detectable peripheral lymphadenopathy. Three months later, there was a marked improvement of liver functions (Table 1). Complement levels remained low, and cryoglobulins were still positive; however, the polyclonal gammopathy was no longer detectable. The IgG, IgA, and IgM were 915 mg/dL, 73 mg/dL, and 237 mg/dL, respectively. An eye examination showed marked reduction of both the corneal and the orbital inflammation. However, 3 months later, steroids were dis-

Fig 1. High-power view of a lymph node largely replaced by dense sclerotic tissue is shown. Notice the vessels with amorphous dense sclerotic tissue replacing the vessel wall and extending in concentric rings to the adjacent tissue.

Fig 2. A reticulin stain shows that the amorphous material is composed of bundles of fine fibrils in a concentric pattern.
continued because of emotional changes and a herpes zoster infection involving the trigeminal nerve. Immunoelectrophoresis at that time showed no gammapathy, and cryoglobulins were not detected. C3, C4, and C5 were 53 mg/dL, 21 mg/dL, and unmeasurable, respectively. Physical examination 6 months after discontinuation of steroids showed mild ascites and numerous telangiectasis on the chest. Liver function tests were markedly abnormal (Table 1). A polyclonal increase in IgM (402 mg/dL) reappeared. An abdominal CT again showed pelvic adenopathy and hepatomegaly. The patient has been followed up for a total of 23 months. She remains extremely debilitated and anorexic. Moderate pruritis, low-grade intermittent fever, and night sweats persist.

Case no. 2. In 1966, a 77-year-old woman presented with a history of weight loss, diarrhea, anorexia, and generalized weakness. Physical examination showed generalized diffuse lymphadenopathy and splenomegaly. The urinalysis was normal. The hematocrit was 37%, and the white cell count was 9.1 × 10^9/L with normal differential. The platelet count was 266 × 10^9/L. The total protein was 5.7 g/dL, and the albumin was 4.1 g/dL; protein electrophoresis was not performed. The hospital course was characterized by progressive cachexia and continued diarrhea. The patient died suddenly. The most striking finding at autopsy was that virtually all of the lymph nodes were firm, grey-white, and of homogenous consistency. Most of these nodes were discrete and measured up to 7 cm. Microscopic sections disclosed virtual replacement of the lymph nodes by dense sclerotic tissue with a concentric pattern. Similar foci of sclerosis with identical angiocentric pattern were also found in the gastrointestinal tract, heart, spleen, and liver (Fig 3). Congo red staining was negative.

**DISCUSSION**

This report describes a patient with generalized lymphadenopathy, polyclonal hyperglobulinemia, severe liver function abnormalities, hypocomplementemia, cryoglobulinemia, and reversed T4/T8 ratio. In 1966, another patient with similar systemic progressive illness, generalized lymphadenopathy and liver involvement, was seen in our institution. Lymph node examination disclosed the characteristic features of the so-called "proteinaceous lymphadenopathy" originally reported by Osborne et al in 1979. These investigators described three patients with polyclonal hypergammaglobulinemia and generalized lymphadenopathy. One of these patients presented with intermittent fever, night sweats, chest pain, nonproductive cough, and weight loss. Lymph node biopsy specimens from all these patients showed extensive deposition of an nonamyloid material obliterating the architecture of the involved nodes. Notably, these nodes contained only few foci of lymphocytes and plasma cells. As shown in Fig 2, this material is formed by dense concentric bundles of fine reticulin fibers along the involved vessel walls. Hence, it appears that the term angiocentric sclerosing lymphadenopathy (ASL) more accurately describes the underlying pathologic feature of this disorder. Most of the reported cases of ASL/proteinaceous lymphadenopathy with hypergammaglobulinemia (PLWH) subsequent to Osborne's description are of patients with monoclonal nonamyloid light chain deposition disease (LCDD) or overt multiple myeloma (MM). Although it is conceivable that systemic deposition of proteinaceous material can be triggered by both monoclonal nonamyloid gammapathies as well as by the polyclonal systemic disorder described here, the typical pathologic and immunologic features of LCDD and MM are readily distinguishable from those of ASL/PLWH. The deposits observed in LCDD disease or MM are typically restricted to a single light chain, whereas there is no light chain predominance in the polyclonal form of ASL/PLWH. The lymph nodes involved in LCDD or MM are typically normocellular, containing primarily lymphocytes and plasma cells and, occasionally, giant cells and asteroid bodies that are not present in the nonclonal ASL/PLWH. The disseminated angiosclerotic changes in lymph nodes (Fig 1) and other organs are typically absent in LCDD or MM.

The clinical features of ASL/PLWH are also distinct from those of nonamyloid LCDD. These include systemic symptoms such as intermittent low-grade fever, myalgia, anorexia, cachexia, and pruritis. Whereas the kidneys are almost invariably involved in all patients with nonamyloid LCDD, only one patient with presumed proteinaceous lymphadenopathy and renal involvement has been described. The most striking finding in patient no. 1 was the profound liver function abnormalities. A liver biopsy specimen showed hepatocellular necrosis, portal fibrosis, and focal deposition of the sclerotic material. Patient no. 2 had milder liver function abnormalities and a milder inflammatory reaction but showed pronounced sclerotic lesions (Fig 3). Liver function abnormalities were also noted in two patients described by Osborne et al and in one of the patients described by Banerjee et al. Conversely, liver dysfunction in patients with LCDD is uncommon. Most cases are asymptomatic, occasionally with a mild to moderate disturbance of the liver function tests. Hypocomplementemia, cryoglobulinemia, and inverted T4/T8 ratio have not been previously described.
in conjunction with ASL/PLWH. Banerjee et al., though, described a patient with ASL/PLWH with a 14-year history of hypocomplementemic vasculitis.

Several pieces of circumstantial evidence would imply that these deposition states result from some host-related characteristic extrinsic to the protein itself. First, both light and heavy chain deposition diseases occur with similar systemic manifestations. Animal models of deposition implicate both host factors as well as the monoclonal Ig's. However, in ASPL/PLWH there is no direct evidence that an excessive production of a polyclonal globulin is the basic defect. It is equally plausible that a systemic host defect makes individuals susceptible to deposition of reticulin fibers synthesized in situ by perivascular cells and that the modest increase in serum globulins is merely an epiphenomenon.

Although the etiology of ASL/PLWH remains unknown, it is likely to be triggered by an infectious or an inflammatory process. The possibility of chronic persistent CMV infection could not be confirmed by specific serological tests. In light of the hypocomplementemia, cryoglobulinemia, and the response to steroid treatment, an inflammatory etiology is more conceivable. In this regard, it is noteworthy that “onion skinning” around blood vessels, as was observed in the involved lymph nodes of patient no. 1 (Fig 1), can also be observed in spleens of patients with systemic lupus erythematosus. We have shown that this polyclonal disorder is amenable to corticosteroid therapy as attested to by the disappearance of the peripheral lymphadenopathy, the polyclonal gammopathy, and the serum cryoglobulins. There was also a steroid-related improvement of liver functions, as well as amelioration of the orbital and corneal inflammation. Similarly, one patient in Osborne’s series also responded to steroid treatment.

In summary, ASL/PLWH appears to represent a distinct clinicopathologic entity, characterized by disseminated angiocentric sclerosis of lymph nodes and other organs. To date, only five patients with polyclonal ASL/PLWH have been described, three of whom have had a more complicated course with systemic symptoms and liver disease, which, in patients tested, has responded to corticosteroid treatment. The diagnosis of ASL/PLWH has to be included in the differential diagnosis of unexplained lymphadenopathy with systemic manifestations and must be considered as a unique form of systemic nonneoplastic deposition disorder.

REFERENCES

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