**Immunotactoid glomerulopathy is one of several renal disorders characterized by the extracellular deposition of nonamyloid fibrillary deposits.** There is considerable debate as to whether immunotactoid glomerulopathy should be distinguished from fibrillary glomerulonephritis, a closely related entity. Currently, the distinction is based on fibril size and arrangement. We report the case of a 59-year-old woman in whom a diagnosis of immunotactoid glomerulopathy was made after a 2-year history of proteinuria. Electron microscopy of her renal biopsy showed randomly arranged microtubular subepithelial and mesangial deposits, which measured 34 nm in average diameter. She was later discovered to have circulating immunoglobulin G heavy chains without associated light chains (\(\gamma\)-heavy-chain disease) and, subsequently, non-Hodgkin lymphoma, follicular lymphoma, grade I (World Health Organization classification). Approximately 100 cases of \(\gamma\)-heavy-chain disease have been reported in the literature since it was originally described by Franklin in 1964. However, while there are 10 reports in the literature of heavy-chain disease, none fit the criteria for immunotactoid glomerulopathy. (Arch Pathol Lab Med. 2004;128:689–692)

A large number of glomerulopathies are characterized by the presence of organized glomerular deposits at the ultrastructural level. Among them is immunotactoid glomerulopathy, a newly described entity that is distinguished (by some investigators) from the closely related entity fibrillary glomerulonephritis by the presence of large microtubular deposits that are arranged in parallel arrays. We report the case of a 59-year-old woman diagnosed with immunotactoid glomerulopathy after a 2-year history of proteinuria, who subsequently was found to have \(\gamma\)-heavy-chain disease and follicular lymphoma.

**REPORT OF A CASE**

A 59-year-old woman with a history of hypertension and aortic stenosis was noted to have proteinuria during a routine insurance examination. A follow-up 24-hour urine protein measurement showed 822 mg protein per day and a urinary microalbumin level of 118 mg/dL. Symptoms at the time included low back, periumbilical, and groin pain; joint tightness; and dry eyes and mouth. Family history was significant for a mother and sister with Sjögren syndrome.

The patient was referred for evaluation of her proteinuria. Subsequent urinalyses showed microhematuria as well. Results of additional testing, including serum creatinine levels, a Westergren erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and a renal ultrasound were normal. A urine screen revealed no Bence-Jones protein. Tests for anti-SS-A and anti-SS-B antibodies and antineutrophil cytoplasmic antibodies were negative, and complement levels (C3 and C4) were in the normal range. Testing for human immunodeficiency virus and viral hepatitis was negative, as were tests for cryoglobulins.

Almost 2 years after the patient’s initial presentation, a renal biopsy was performed, which showed immunotactoid glomerulopathy. To investigate the possibility of an associated hematologic or lymphoid malignancy, chest and abdominal computed tomographic scans, nuclear whole body bone scan, and serum protein electrophoreses were performed. The abdominal computed tomographic scan showed multiple enlarged lymph nodes in the mesentery and the retroperitoneum. A mixed sclerotic and lytic lesion was noted in the right scapula also. A bone scan showed multiple areas of abnormal increased skeletal uptake of radiotracer, as well as increased uptake in the left kidney. Follow-up plain radiographs of the pelvis and left femur were nondiagnostic. Serum protein electrophoresis and immunofixation revealed an abnormal band and a pattern suggestive of immunoglobulin (Ig) G heavy-chain disease, respectively. Urine remained negative for Bence-Jones protein. A repeat erythrocyte sedimentation rate was elevated at 70 mm/h. Lactate dehydrogenase was in the normal range.

The patient’s symptoms progressed to include episodic bone and muscle pain; hot flashes; decreased energy; insomnia; loss of appetite without weight loss; frontal headaches; generalized weakness; migratory pains in her shoulders, arms, legs, and ribs; as well as intermittent swelling of her submandibular lymph nodes. She displayed discrete point tenderness over bones. She had no palpable lymphadenopathy. She also complained of blurred vision and dry eyes.

Approximately 8 months later, a repeat computed tomographic scan of the chest and abdomen showed progression of her retroperitoneal lymphadenopathy, as well as renal abnormalities characterized by enlargement of the kidneys and parenchymal heterogeneity. A bone marrow examination was nondiagnostic by morphology and flow cytometry. A fine-needle aspirate of 1

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of the enlarged retroperitoneal lymph nodes was performed, which along with flow cytometry, revealed non-Hodgkin lymphoma, follicular lymphoma, grade I (World Health Organization classification). Presently, the patient is receiving chemotherapy for non-Hodgkin lymphoma.

**PATHOLOGIC FINDINGS**

**Light Microscopy**

Light microscopy of the renal biopsy revealed focal basement membrane thickening and “spike” formation accompanied by focal and segmental glomerular hypercellularity. A small number of glomeruli showed segmental endocapillary proliferation (Figure 1). The capillary walls showed increased thickness, and the mesangial matrix was focally increased (Figure 2). Jones silver stains highlighted the basement membrane spikes in some, but not all, glomerular capillaries (Figure 3). A minimal amount of interstitial fibrosis was associated with rare atrophic tubules and minimal intimal and medial thickening in the small arteries and arterioles.

**Immunofluorescence**

Frozen sections exposed to fluorescein-labeled antibodies directed against IgG, IgM, IgA, C3, C1q, fibrinogen, and polyvalent immunoglobulins revealed moderately intense granular fluorescence in the glomeruli with the anti-IgG, -C3, and -C1q conjugates. The fluorescence outlined the majority of the glomerular capillary loops in a granular pattern and was located in the mesangium in some tufts.

**Electron Microscopy**

Epithelial foot process effacement with microvillous transformation was present. Numerous subepithelial deposits associated with the basement membrane spikes were noted. These deposits consisted of large (34 nm), randomly arranged microtubules (Figures 5 and 6). These deposits were nonuniform in their distribution in the glomerular capillaries. Elsewhere, the basement membrane architecture was intact. The mesangium was expanded and contained occasional microtubular deposits similar to those observed in the basement membranes. (Fibril diameter measurements were obtained from images acquired at a magnification of ×30,000. Ten fibers in cross-section were measured [range, 29.4–37.5 nm] and averaged.)

**Immunofixation of Serum**

Immunofixation showed a broad and heterogeneous monoclonal IgG component, which was consistent with heavy-chain disease (Figure 4).

**Fine-Needle Aspiration of Retroperitoneal Lymph Node**

The specimen showed a predominant population of small lymphocytes, many of which had irregular nuclear contours, consistent with follicular lymphoma, grade 1.

**Flow Cytometry of Retroperitoneal Lymph Node**

Approximately half of the gated cells were B lymphocytes (CD19⁺, CD20⁺, CD22 dim, HLA-DR⁺), which were CD45⁺ dim. Neither κ nor λ light chains were detectable on the surface of most of the CD19⁺ B cells. CD10 was coexpressed on the CD20⁺ B cells. These cells were FMC-7⁺ and showed minimal expression of CD23. These results were interpreted as consistent with the diagnosis of non-Hodgkin lymphoma of B-cell lineage and follicular origin.

**COMMENT**

A large number of glomerulopathies are characterized by ultrastructurally organized glomerular deposits.¹ One subset of these is immunotactoid glomerulopathy, a term that was coined in 1980 by Schwartz and Lewis.² They observed glomerular deposits that were composed of microtubular structures grouped in parallel arrays. Understanding of immunotactoid glomerulopathy and fibrillary glomerulonephritis is complicated by differences in nomenclature, as well as the debate regarding the validity and importance of subclassifying these diseases as 2 distinct clinicopathologic entities.³ Both diseases are characterized by extracellular nonamyloid fibrillary deposits, typically within the mesangium but also involving basement membranes.² Both entities are uncommon. In a recent series of 67 cases of fibrillary glomerulonephritis and immunotactoid glomerulopathy, fibrillary glomerulonephritis comprised 0.6% of total native kidney biopsies and immunotactoid glomerulopathy was 10-fold more rare (0.06%).⁴ Both fibrillary glomerulonephritis and immunotactoid glomerulopathy showed female predominance and were more common in whites.⁴ The deposits may be located in the subendothelial or, less commonly, subepithelial regions. The diagnosis is based on ultrastructural findings. Fibrillary glomerulonephritis is generally defined as having fibrils that are solid and randomly arranged, with a diameter of about 18 to 22 nm.¹ Immunotactoid glomerulopathy is characterized by microtubular deposits focally arranged in parallel bundles, usually with a diameter of more than 30 nm³ and typically with a visible lumen (microtubules).² However, these morphologic patterns can overlap.³ In our case, nonamyloid subepithelial and mesangial deposits were randomly arranged and measured 34 nm in average diameter. Accordingly, this patient fit the diagnostic criteria for immunotactoid glomerulopathy. Some investigators have cautioned against subclassifica-

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Figure 1. Basement membrane thickening with focal and segmental glomerular hypercellularity. A few glomeruli show segmental endocapillary proliferation. The mesangial matrix is expanded (hematoxylin-eosin, original magnification ×60).

Figure 2. Thickening of glomerular capillary walls (periodic acid–Schiff, original magnification ×60).

Figure 3. Spikes projecting from the basement membrane in some glomerular capillaries (arrows) (Jones silver, original magnification ×60).

Figure 4. Serum immunofixation demonstrating a broad monoclonal IgG band.

Figure 5. Electron microscopy demonstrating 34-nm, randomly arranged subepithelial deposits (original magnification ×15,000).

Figure 6. Electron microscopy demonstrating subepithelial deposits (original magnification ×30,000).
tion based on ultrastructural appearance alone. A few patients with chronic lymphocytic leukemia or related B-cell lymphoma have been found to have monoclonal microtubular immunoglobulin deposits with a microtubule diameter smaller than that commonly observed in immunotactoid glomerulopathy.5 Both fibrillar glomerulonephritis and immunotactoid glomerulopathy have features that overlap with hepatitis C virus–induced cryoglobulinemic glomerulonephritis, and some investigators require the presence of an associated cryoglobulin to be excluded before a diagnosis of fibrillar glomerulonephritis or immunotactoid glomerulopathy is made.6 Cryoglobulinemia is defined by the presence of serum cryoglobulins, which were absent in this patient. In general, cryoglobulinemia is a systemic disease characterized by skin rash, arthritis, and renal manifestations clinically,7 which were lacking in this patient. She also did not have hypocomplementemia or hepatitis C virus infection, which are commonly associated with cryoglobulinemia. In the kidney, the pattern of involvement is that of membranoproliferative glomerulonephritis with subendothelial and intraluminal deposits.7 By electron microscopy, these may be organized deposits, but are typically smaller than those of immunotactoid glomerulopathy.7

The most important clinical problem of immunotactoid glomerulopathy is the association with autoimmune disease or lymphoproliferative disorders.1 In a review of 186 patients with fibrillary glomerulonephritis and immunotactoid glomerulopathy, when patients with circulating or urinary paraproteins were included the incidence of malignancy was 33% in patients with immunotactoid glomerulopathy, compared to 7% in patients with fibrillary glomerulonephritis.8 When patients with a paraprotein were excluded, the incidence of malignancy in each group was less than 7%.1 Other series have confirmed that patients with immunotactoid glomerulopathy have a significantly higher incidence of serum or urine monoclonal gammopathy (67% vs 15%), underlying lymphoproliferative disease, and hypocomplementemia than patients with fibrillary glomerulonephritis.4 In our patient, the diagnosis of immunotactoid glomerulopathy led to a search for an underlying malignancy. Serum protein electrophoresis and immunofixation revealed the presence of circulating heavy chains without associated light chains. While immunofluorescence of the renal biopsy revealed moderately intense granular fluorescence in the glomeruli with anti-IgG, -C3, and -C1q conjugates, staining of the biopsy for κ and λ light chains was negative. The flow cytometry performed on the retroperitoneal lymph node aspirate revealed an immunophenotype consistent with non-Hodgkin lymphoma of B-cell lineage and follicular origin. Morphologic evaluation of the lymph node aspirate supported the diagnosis of follicular lymphoma. Neither κ nor λ light chains were detectable on the surface of most of the CD19+ B cells on flow cytometry.

Since γ-heavy-chain disease was described in 1964 by Franklin, approximately 100 cases have been reported in the literature.8 γ-Heavy-chain disease most often presents as a lymphoproliferative disorder with lymphadenopathy, splenomegaly, and constitutional symptoms.8 Heavy-chain disease can be thought of as a variant type of non-Hodgkin lymphoma that secretes an abnormal immunoglobulin heavy chain.9 Most γ-heavy-chain proteins are clones of truncated heavy chains, which are 50% to 75% the normal length, and all have a truncated C1 region.9 Heavy-chain deposition disease with immunoglobulin deposits in the kidney is very rare, and to our knowledge only 10 cases have been reported in the literature to date.10 One other reported case of heavy-chain deposition disease with mesangial nonamyloid fibrils seen on electron microscopy also demonstrated strong mesangial IgG immunofluorescence without significant light-chain labeling.11

Autoimmune diseases are found in about one quarter of patients with γ-heavy-chain disease.8 There have been very rare case reports of Sjögren syndrome associated with γ-heavy-chain disease.12 Our patient had Sjögren syndrome–like symptoms and a family history of Sjögren syndrome. However, serologic testing for autoimmune disease was negative.

The serum protein electrophoresis pattern of heavy-chain disease is extremely variable. In approximately 40% of patients, the abnormal protein is undetectable by electrophoresis.9 If a localized band is detected, it is most commonly in the β1 and β2 region.9 Serum protein evaluation of our patient revealed an abnormal band and a broad, heterogeneous monoclonal IgG component on immunofixation, which was interpreted as consistent with heavy-chain disease. A urine sample was negative for monoclonal IgG protein.

In conclusion, we report a unique case of immunotactoid glomerulopathy associated with γ-heavy-chain disease and follicular lymphoma. The known association between immunotactoid glomerulopathy with lymphoproliferative disorders initiated the search for an underlying malignancy in our patient. While several cases of heavy-chain disease with nonamyloid fibrillary deposits in the kidney have been reported previously, these cases did not fit the diagnostic criteria for immunotactoid glomerulopathy.

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References