Immunotactoid glomerulopathy with extrarenal deposits in the bone, and chronic cholestatic liver disease

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Immunotactoid glomerulopathy represents a newly recognized, distinct clinical entity which is characterized histologically by subendothelial and mesangial, Congo red negative, amyloid-like deposits in the glomeruli. As revealed by electron microscopy, the deposits consist of organized fibrils and tubules reactive for immunoglobulins; hence the coining of the term immunotactoid glomerulopathy [1, 2].

Up until now, these deposits have been demonstrated almost exclusively in the kidney. There is one case report of a female patient with immunotactoid glomerulopathy having died of pulmonary haemorrhage, where fibrillary deposits in the interstitium of the lung were detected on autopsy [3], and another report of a male patient with amyloidosis-like glomerulopathy and deposition of an amyloid-like material in the liver [4].

We describe a young patient with immunotactoid glomerulopathy rapidly progressing to end-stage renal disease, a chronic liver disease closely resembling primary biliary cirrhosis without assessment of antimito-
ochondrial antibodies, and deposition of an amyloid-like material in the bone marrow cavity and around the bone vessels.

Case report

A 30-year old female Caucasian patient was admitted to our hospital for evaluation of a nephrotic syndrome and marked intrahepatic cholestasis. Her family and personal history were essentially unremarkable. Eight years before admission, a caesarean section had been performed due to a narrow pelvis after an otherwise uneventful pregnancy. For a couple of years, she had been taking various oral contraceptives which she had terminated two months before admission. At this time, she noticed diffuse swelling of the ankles and eye-lids, and she complained of weakness, fatigue, and a generalized pruritus. Physical examination revealed moderate pitting oedema of both lower legs, and scratch marks on the trunk, but no jaundice. Liver and spleen were enlarged, and there was a small amount of ascites detected by ultrasound.

On admission, renal function was slightly impaired with a serum creatinine level of 1.4 mg/dl, correspond-
ing to a creatinine clearance of 55 ml/min. Excessive proteinuria (11.2 g/24 h), hypoproteinaemia with 4.9 g/dl, and marked hyperlipidaemia with a total chole-
terol level of 487 mg/dl, and a triglyceride level of 371 mg/dl were indicative of a severe nephrotic syn-
drome. Paraproteinemia was excluded by immunoel-
ctrophoresis. C3c level was 106 mg/dl (normal range 50–90) and C4 19 mg/dl (normal range 10–40). Arterial blood gas examination revealed mild metabolic acidosis with a pH of 7.31, partial pressure of carbon dioxide of 41 mm Hg, partial pressure of oxygen of 95 mm Hg, and a bicarbonate level of 19.9 mEq/l.

Measurement of liver enzymes showed a marked intrahepatic cholestasis with a gamma glutamyl trans-
ferase of 220 U/l, an alkaline phosphatase of 785 U/l; aspartate aminotransferase (SGOT, 41 U/l) and alan-
ine aminotransferase (SGPT, 27 U/l) were only slightly elevated. Serum bilirubin was 1.0 mg/dl. Repeated analyses for anti-neutrophil cytoplasmic antibodies (ANCA), antibodies against glomerular basement membrane (AGBMA), anti-nuclear antibodies (ANA), and anti-mitochondrial antibodies (AMA) remained negative, as were analyses for the subsets of ANA and AMA. A test for circulating cryoglobulins was negative. Antibodies against hepatitis A, B, and C virus, cytomegalovirus, and human immunodefici-
ency virus were not detectable. The patient’s serum was positive for Epstein-Barr virus IgG antibodies.

Ultrasound revealed kidneys of normal size and structure. Intra- and extrahepatic bile ducts were not thickened or beaded and showed therefore no evidence
of primary sclerosing cholangitis, as demonstrated by endoscopic retrograde cholangiopancreatography. Portal vein thrombosis was excluded by duplex sonography. Endoscopic examination of the upper and lower gastrointestinal tract disclosed no sign of chronic inflammatory bowel disease or hyperplasia of the lymphoid tissue that would have indicated a mucosa-associated lymphoma.

As a Jehovah’s Witness, the patient initially refused any invasive examination associated with even a small risk of bleeding. After a tentative six weeks’ course of oral prednisolone (1 mg per kg of body weight) without any significant effect on proteinuria or liver enzymes, she finally agreed to undergo a liver biopsy. Histologic examination of the liver specimen (see Figure 1) revealed a loss of normal interlobular bile ducts, extensive proliferation of small bile ducts, a marked fibrosis of the portal regions with extension of fibers into the liver parenchyma, and a dense mononuclear and granulocytic infiltration of the portal regions. As a consequence of chronic bile stasis, adjacent hepatocytes demonstrated feathery degeneration of the cytoplasm and contained bile pigmentation. There were no destructive lesions of the bile ducts and no granulomatous infiltration of the portal regions. Amyloidosis was excluded by the light microscopic appearance and by a negative Congo red stain. A diagnosis of chronic, non-suppurative cholangitis with ductopenia and partial regeneration of intrahepatic bile ducts compatible with incipient primary biliary cirrhosis or idiopathic adulthood ductopenia was made. In the meantime, the cholestatic parameters increased to a maximum of alkaline phosphatase 2006 U/l, and gamma glutamyl transferase 770 U/l. Serum bilirubin remained in the normal range throughout. Oral therapy with ursodeoxycholic acid was established.

A few weeks later, with renal function deteriorating progressively, she consented to a renal biopsy. Microscopic examination showed large deposits of an amorphous, eosinophilic mass in the mesangium and along the basement membranes of the glomeruli, strongly resembling amyloid (see Figure 2A). Nevertheless, a Congo red stain and an anti-amyloid-A stain were likewise negative (not shown). By immunohistochemistry, IgM κ and C3 were identified in the deposits (see Figure 2B). Finally, electron microscopy revealed large arrays of partly organized fibrils and tubules in the mesangium and subendothelially (see Figure 2C), with a mean diameter of 20 nm.

To exclude a malignant lymphoma, bone marrow aspiration was performed and disclosed a slightly hypercellular, regular haematopoesis, and no lymphocytic or plasmocytic infiltration. In the bone biopsy taken from the iliac crest, extensive deposition of a homogenous, eosinophilic material along the marrow fibers and especially along small vessels and capillaries (similar to that found in the kidney biopsy) was seen. In accordance to the findings in the glomeruli, a Congo red stain was negative, and an immunohistochemical stain for IgM was positive (see Figure 3A). Ultrastructural examinations of some parts of the bone biopsy exhibited loosely arranged fibrils and microtubules clearly thicker in diameter (40 nm) than the fibrillar material found in the kidney specimen. Although these fibrils appear somewhat disorganized, the deposited material suggests immunotactoids within the bone marrow (see Figure 3B).

During the following months, an irreversible decline

![Fig. 1. Low-power micrograph of liver biopsy (chrome-anilin-blue stain, x 340). Fibrosed portal tract showing a moderate infiltration with lymphocytes and histiocytes. The mononuclear cells infiltrate the bile duct shown in the center of the portal tract (arrow-head).](https://academic.oup.com/ndt/article-abstract/11/8/1619/1859695)
of the patient's renal function occurred. In spite of a marked improvement in cholestatic parameters, the subsequent course of her liver disease was complicated by the development of an intractable ascites and recurrent pleural effusions. To enable a continuous paracentesis and ascitic fluid reinfusion, a peritoneo-venous shunt (Denver shunt) was inserted. The patient underwent several ultrafiltration sessions to avoid volume overload. Finally, as uraemic symptoms like wasting, vomitus, symptomatic renal anaemia, and severe metabolic acidosis developed, chronic maintenance haemodialysis was established. For the time being, the patient is functioning well on dialysis. The excessively elevated cholestasis parameters continue to show a remarkable decline without deterioration of liver function (gamma glutamyl transferase 29 U/l, alkaline phosphatase 210

Fig. 2A. Low-power micrograph of kidney biopsy (hematoxylin-eosin stain, × 180) with glomeruli demonstrating amyloid-like deposits without cellular proliferation.

Fig. 2B. Immunohistochemical demonstration of IgM deposits within the glomerular capillary walls and the mesangium (avidin biotin complex method, × 180).
U/l). Due to her religious beliefs, the patient refuses categorically to be enrolled in a transplantation program. For the same reasons, she does not consent to a repeat liver or bone biopsy either.

**Discussion**

Immunotactoid glomerulopathy is a newly described kidney disease with unique ultrastructural features. Aetiology and pathogenesis of this disorder still remain to be elucidated. Though there is a striking resemblance to amyloidosis by light microscopy, Congo red stain and, more specifically, anti-amyloid A stain are invariably negative. The ultrastructure, as demonstrated by electron microscopy, consists of organized fibrils and tubules with a diameter of approximately 20–40 nm. By definition, they are composed of—probably abnormal—immunoglobulins, and there is some evidence that these large protein molecules may crystallize into ‘tactoids’ in a hyperosmotic milieu [5]. Immunotactoid glomerulopathy should therefore be distinguished from other fibrillary glomerulopathies that are encountered in, for instance, amyloidosis, systemic lupus erythematosus, cryoglobulinemias, and diabetes mellitus [6]. However, there is not a unanimous consensus on how to differentiate immunotactoid glomerulopathy from fibrillary glomerulonephritis [7–9]. It has been suggested by some that fibril size and/or morphology alone can distinguish immunotactoid glomerulopathy from fibrillary glomerulonephritis [10]. Given the wide range of fibril size described so far in immunotactoid glomerulopathy, the immunoglobulin content of the deposits seems to be a better criterion for differentiating these entities.

In most instances, deposition of immunotactoid material is almost exclusively restricted to the glomeruli. This may be due to the unique hyperosmotic milieu prevailing in the glomerular capillary loops. So far, two case reports have been published demonstrating extrarenal deposition of Congo red-negative material in immunotactoid glomerulopathy: in one patient having died from pulmonary haemorrhage, immunotactoid deposits were found in the lungs at autopsy [3]; and in another patient with immunotactoid glomerulopathy, Congo red-negative material was detected in the liver [4]. In our patient, amyloid-like depositions were discerned in the bone marrow space and around small vessels of a bone biopsy taken from the iliac crest. Remarkably, no such material was found in the otherwise highly diseased liver of our patient. The striking difference in diameter of the fibrillary deposits in the kidney (20 nm) and the bone marrow (40 nm) may be explained by varying microenvironmental factors, for example osmolality. Moreover, the occurrence of differently sized, but histochemically identical immunotactoid material in the same patient provides strong evidence against a classification of fibrillary glomerulopathies according to fibril size.

Immunotactoid glomerulopathy bears a relatively poor renal prognosis. Approximately 40% of the patients are expected to develop end-stage renal disease within 1–6 years [2,5,6]. The rapid loss of renal function in our patient may thus be explained by the natural course of the underlying kidney disease.

The manifestation of an anicteric cholestatic liver disease resembling primary biliary cirrhosis, and immunotactoid glomerulopathy at approximately the same time suggests a related pathogenesis. Primary biliary cirrhosis is an autoimmune disease of unknown origin.
characterized by distinct histopathological features and the occurrence of autoimmune antibodies directed against mitochondrial constituents. Renal involvement is relatively uncommon in primary biliary cirrhosis, and has been reported on only five times in medical literature: two cases associated with membranous nephropathy [11,12], one case with interstitial nephritis [13], one case with glomerulosclerosis [14], and one with focal proliferative glomerulonephritis [15].

Though highly suggestive of incipient primary biliary cirrhosis, the histological examination of the liver biopsy of our patient did not reveal all the typical features of this autoimmune disease. The lack of antimitochondrial antibodies would not fully exclude this diagnosis. Nevertheless, in our view, this patient's chronic cholestatic liver disease should be better classified as 'idiopathic' adulthood ductopenia [16], a syndrome characterized by progressive loss of

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Fig. 3A. Histologic specimen of bone biopsy taken from the iliac crest demonstrating amyloid-like deposits in the marrow space and around vessels staining for IgM (avidin biotin complex method, × 180).

Fig. 3B. Electron micrograph of the bone marrow specimen containing fibrils and microtubules ('immunotactoids'), which are thicker in diameter (40 nm) than the glomerular deposits (arrow heads). This part of the section corresponds to the area exhibiting Congo red-negative, but IgM positive material in the light microscope (× 5300).
interlobular bile ducts that may occur under a variety of circumstances [17]. The differential diagnosis of idiopathic adulthood ductopenia comprises drug-induced cholestatic liver disease. Prolonged cholestatic liver disease with loss of interlobular bile ducts even after withdrawal has been reported for several drugs, for example amitriptyline [18], ajmaline [19], carbamazepine [20], and ciproheptadine [21], but not for oral contraceptives. The only drugs our patient had been ingesting for a couple of years before the onset of anicteric cholestasis were oral contraceptives. Though rather unlikely, we cannot exclude that these drugs might have elicited an immunoallergic process in the liver leading to the vanishing of bile ducts and the marked intrahepatic cholestasis.

Immunotactoid glomerulopathy is an intriguing new kidney disorder which, in most cases reported to date, seems to be a genuinely renal disease. In rare instances, however, the immunotactoid material may be deposited in other organs, too, pointing to the apparently systemic character of this disease. The association between our patient’s liver disease and immunotactoid glomerulopathy remains speculative.

References


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