

Clinical Report

Progressive chronic kidney disease secondary to tubulointerstitial nephritis in primary biliary cirrhosis

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Abstract

Primary biliary cirrhosis (PBC) is an autoimmune disease characterized by the presence of anti-mitochondrial antibodies (AMA). Whilst asymptomatic distal tubular acidosis (DTA) is the commonest renal lesion reported in PBC, tubulointerstitial nephritis (TIN) has also been reported as a rare association. Although PBC could be a familial disorder, there have been no previous reports of familial chronic TIN in association with PBC. We report a case of progressive chronic kidney disease (CKD) due to TIN in a mother and daughter known to suffer from PBC and review the previously reported literature. Both showed good response to steroids.

Keywords: chronic kidney disease; familial; primary biliary cirrhosis (PBC); tubulointerstitial nephritis

Background

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic liver disease characterized by destruction of small- to medium-sized bile ducts. It is an autoimmune disease characterized by circulating anti-mitochondrial antibodies (AMA). Asymptomatic distal tubular acidosis (DTA) is the most common renal lesion associated with PBC and may occur in up to one-third of patients with the disease [1]. More rarely Fanconi syndrome, membranous nephropathy, microscopic polyangiitis and tubulointerstitial nephritis (TIN) have also been reported in patients with PBC [2–5].

TIN is a disorder characterized by inflammatory infiltrate which occurs mostly in the tubules and interstitium. Chronic tubulointerstitial nephritis (CTIN) is associated with a number of diseases of diverse aetiology and is characterized by tubular cell atrophy, flattening of epithelial cells and tubular dilatation, interstitial fibrosis and areas of mononuclear cell infiltration within the interstitial compartment and between the tubules. DTA is one of the typical manifestations of CTIN. The association between TIN and PBC was first reported in 1987 by Macdougall *et al.* although it appears to be an extremely rare association with only a handful of cases published in the literature since then [5–10].

PBC is not considered to be an inherited disorder, although there have been reports of multiple cases occurring in a single family [11]. To our knowledge, TIN leading to chronic kidney disease (CKD) in genetically linked patients with PBC has not been previously reported. We report a case of CKD due to CTIN occurring in both mother and daughter who have liver biopsy-

proven PBC and review the current literature of TIN in patients with PBC.

Case report

A 46-year-old female patient was referred for nephrology assessment in October 2011 for progressive CKD with a creatinine level of 207 $\mu\text{mol/L}$ (estimated glomerular filtration rate, eGFR 22 mL/min/1.73 m²). Her creatinine level was 145 $\mu\text{mol/L}$ (eGFR 36 mL/min/1.73 m²) in 2009. She had previously been diagnosed with PBC on liver biopsy in 2004 and was under regular follow-up with a hepatologist. She was otherwise well and was in full-time employment as an office manager. She was a non-smoker and only occasionally drank alcohol. She had no known allergies and only took amitriptyline for fibromyalgia. She had received no new drugs or antibiotics recently. Her mother was also diagnosed with PBC on liver biopsy in 1997 and underwent renal biopsy for progressive CKD in 2001 at another tertiary centre which showed TIN. The patient's mother was treated with long-term low-dose steroid therapy for CTIN which had successfully stabilized her renal function.

Systemic examination of the patient was unremarkable, blood pressure was 119/72 mmHg, and urine dipstick showed no blood or protein. Blood tests showed raised alkaline phosphatase at 209 IU/L (30–130 IU/L) and γGT 252 IU/L (0–40 IU/L). Full blood count was normal. Auto-antibody screen for AMA showed a positive M2 pattern strongly suggestive of PBC. The rest of the immunology screen including anti-nuclear antibody-Hep2, centromere antibody, anti-smooth muscle antibodies and liver kidney

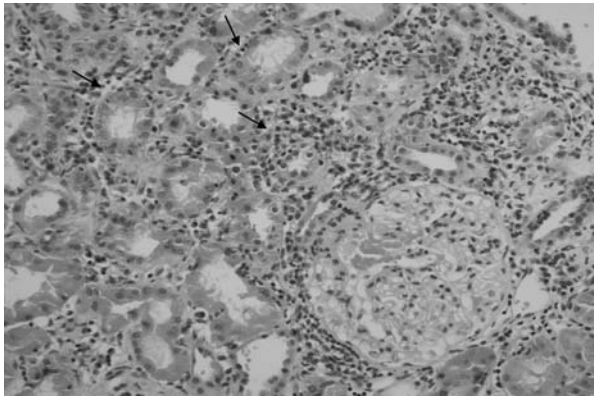


Fig. 1. Light microscopy of kidney biopsy showing tubulointerstitial nephritis.

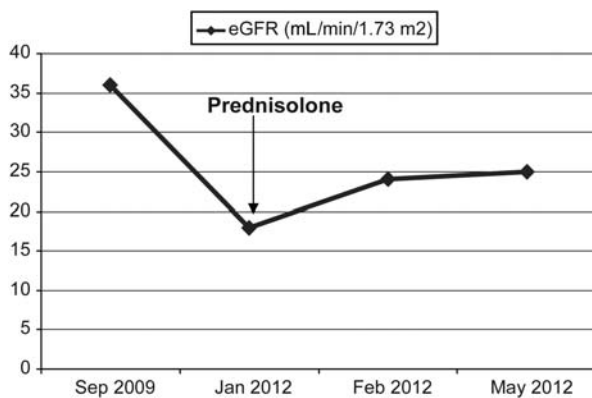


Fig. 2. Patients' eGFR (modification of diet in renal disease) before and after treatment.

microsomal antibody was negative. Her anti-neutrophil cytoplasmic antibodies indirect immunofluorescence screen was negative. Her serum complements were within the normal range. Her dsDNA IgG was 14 IU/mL (0–55 IU/mL). Serum and urine protein electrophoresis was normal. Abdominal ultrasound showed normal appearance of kidneys, liver, spleen and pancreas.

A kidney biopsy was performed to establish a diagnosis and revealed a chronic active TIN associated with mild oedema and moderately widespread established fibrosis (Figure 1). Electron microscopy and immunohistochemistry were unremarkable. The patient was started on 40 mg of oral prednisolone that has now been tapered off to a maintenance dose of 5 mg daily. Her renal function has improved on steroids and she currently has stable CKD (Figure 2).

Discussion

PBC is an autoimmune cholestatic liver disease characterized by highly specific AMA. Occurrence of multiple cases in a single family is well recognized and different series have shown prevalence of familial PBC ranging from 1.33% to 5.5%. This familial predisposition to PBC is complex and polygenic [11]. HLA association of PBC is well recognized and many loci have been identified. An association has been suggested between PBC and

haplotypes HLA-DR8 and HLA-DPB1. In patients with familial PBC, maternal inheritance is most common and might be linked to mitochondrial DNA that is always maternally inherited [8].

Various renal lesions in association with PBC have been described in the literature. One-third of patients with advanced PBC are recognized to have DTA that normally has no clinical significance [5]. Membranous nephropathy and microscopic polyangiitis have also been described in patients with PBC. TIN, an inflammatory renal disease characterized by lymphocytic infiltration of interstitium and tubules, has rarely been described in these patients. In a review of the literature, Lino *et al.* identified four patients with TIN and PBC. Two patients also had associated Fanconi syndrome. They suggested a possible role of AMA in the pathogenesis of renal disease during PBC. It has also been postulated that familial PBC has an associated abnormal lymphocyte function [12]. Lino *et al.* suggested that abnormal antigen expression may occur in renal tubular cells and this may lead to infiltration of the renal interstitium by autoreactive T-cells causing TIN [5].

In our patient, there was no evidence of associated renal tubular acidosis. More recently, Komatsuda *et al.* reviewed 5955 renal biopsies performed over a 30-year period in a single centre and identified four patients with TIN associated with asymptomatic PBC [10]. Kidney biopsy in all four cases showed severe tubulointerstitial cell infiltration, tubulitis and mild-to-moderate interstitial fibrosis and tubular atrophy. In the review of the literature, they identified nine biopsy-proven cases of TIN in association with PBC (including four reported in their case series). Eight patients had an abnormal renal function, seven of whom showed a good clinical response to a moderate dose of steroids (25–30 mg prednisolone). In the remaining two patients, histology showed progressive glomerulosclerosis and interstitial fibrosis in spite of steroid therapy. TIN is now identified as a rare but important extra-hepatic manifestation of PBC.

To our knowledge, there are no previous reports of familial presentation of TIN in association with PBC. The incidence of CKD in familial PBC is not reported in the literature owing to the rarity of this occurrence. It is also not clear how long steroids should be continued. In our case, it is worth noting that the mother's kidney function deteriorated when steroids were withdrawn and improved when steroids were restarted, and therefore, we have made an elective decision to maintain our patient on long-term low-dose steroids. Further case reports and registry-based data could help to establish the familial inheritance of TIN in PBC and management strategies in these patients.

Conflict of interest statement. None declared.

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