Tiopronin-induced membranous nephropathy in a patient with refractory familial cystinuria

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Introduction

Familial cystinuria is an inherited condition characterised by recurrent formation of cystine stones, which can lead to significant morbidity. Tiopronin is indicated for the prevention of these stones in patients who are refractory to urinary alkalinisation and hydration. Tiopronin, also known as 2-mercaptopropionyl glycine, has been reported to cause nephrotic syndrome. So far, 33 cases have been reported but histology results were only available in 13 of these. Children receiving the maximum recommended dose of tiopronin at 50 mg/kg/day were initially reported to be at the highest risk. The underlying pathogenesis is not yet understood, but cessation of therapy typically leads to resolution of the nephrotic syndrome. This article presents a case of a 16-year-old-boy who developed nephrotic syndrome 16 months after initiation of tiopronin.

Case report

A 16-year-old boy presented with bilateral lower limb oedema and genital swelling. He denied other symptoms such as fever, rashes or shortness of breath. The patient had been diagnosed with familial cystinuria at 14 years of age, after presenting with cystine stones. The patient had experienced recurrent stones despite potassium citrate and oral hydration, leading to an atrophic non-functional right kidney. He had subsequently been started on tiopronin 250 mg three times daily (12 mg/kg/day), with good clinical response 16 months before his presentation with oedema. His baseline creatinine level at the time of initiation of tiopronin was 88 µmol/litre (normal range 62–106 µmol/litre). He had no other comorbidities of note.

Initial investigations revealed an acute kidney injury with a creatinine level of 208 µmol/litre. His serum albumin level was 17.6 g/litre (normal range 34–48 g/litre), lipid levels were elevated with a total cholesterol level of 9.50 mmol/litre (normal range 2.0–5.0 mmol/litre) and a low-density lipoprotein level of 7.27 mmol/litre. 24-hour urine protein collection confirmed nephrotic range proteinuria of 6 g/day. Urinalysis on admission was positive for proteins and erythrocytes but negative for leukocytes and nitrites. Urine microscopy on admission showed rare cellular casts but was otherwise unremarkable.

A hepatitis screen was negative. Vasculitic and autoimmune screens were unremarkable, with negative antineutrophil cytoplasmic antibodies, antinuclear antibodies, anti-glomerular basement membrane antibody and normal complement levels. An ultrasound showed the shrunken right kidney, an 8 mm calculus in the lower pole of the left kidney, and no evidence of obstruction or renal vein thrombosis. Computed tomography confirmed the sonographic findings.

Nephrotic syndrome was diagnosed, and the patient managed conservatively with angiotensin-converting enzyme inhibitors, statins, diuretics and thromboprophylaxis. With no underlying cause for the nephrotic syndrome identified, tiopronin was suspected to be the most likely culprit and the drug was stopped.

A renal biopsy showed normal glomerular morphology on light microscopy (Figure 1). Immunohistochemistry revealed a slight staining of IgG and C3. Electron microscopy showed extensive podocyte foot process effacement (Figure 2), with occasional subepithelial immune deposits (Figure 3), consistent with membranous nephropathy, likely drug-induced.

The patient's symptoms improved after cessation of tiopronin and he was discharged after a few days. His creatinine level improved to 117 µmol/litre and albumin:creatinine ratio to 47.7 mg/g (normal range 1–20 mg/g) within 2 months of presentation. His serum albumin and lipid levels had also normalised by this time. The patient was maintained on potassium citrate and oral hydration, but continued to have problems with recurrent nephrolithiasis leading to established chronic kidney disease.

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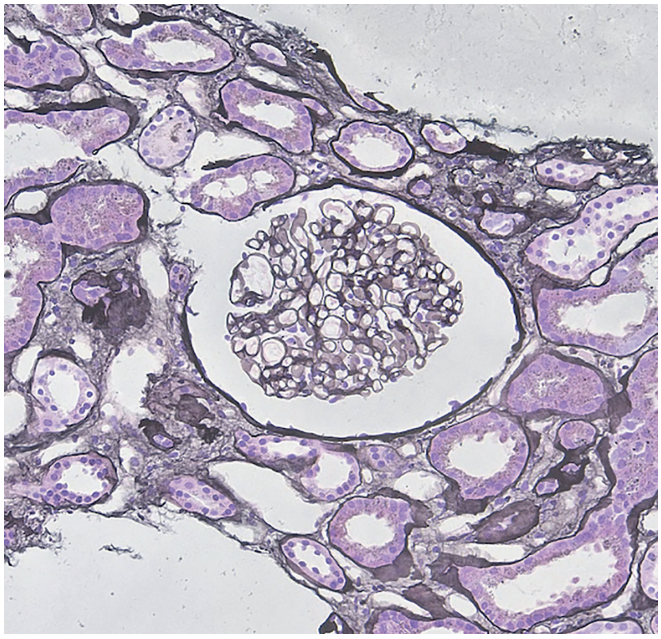

Figure 1. Normal-looking glomerulus under light microscopy using Jones' methenamine silver stain. Morphology appears normal with open capillary loops and no cellular proliferation.

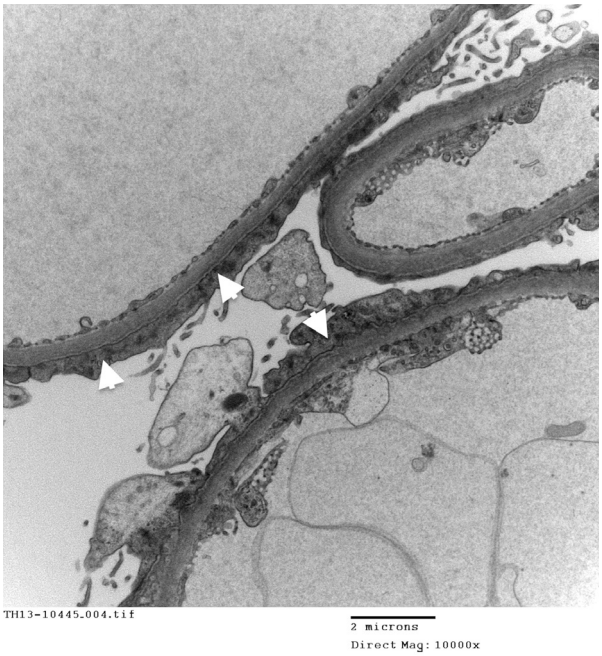

Figure 2. Electron microscopy showing extensive podocyte foot effacement (arrowheads).

Discussion

Cystinuria is an autosomal recessive condition characterised by impaired tubular reabsorption of cystine leading to precipitation in the urine. Recurrent cystine stones lead to significant morbidity and impairment of renal function as a result of repeated infection and obstruction.

The mainstay of treatment is optimisation of urine volume and pH. Increasing hydration to achieve a urine output of 2.5–3.0 litres per day dilutes urinary cystine concentrations. Alkalinisation of the urine to a pH of 7.0–7.5 using potassium citrate or sodium bicarbonate makes cystine more soluble, thus preventing stone formation (Leslie et al, 2021). In

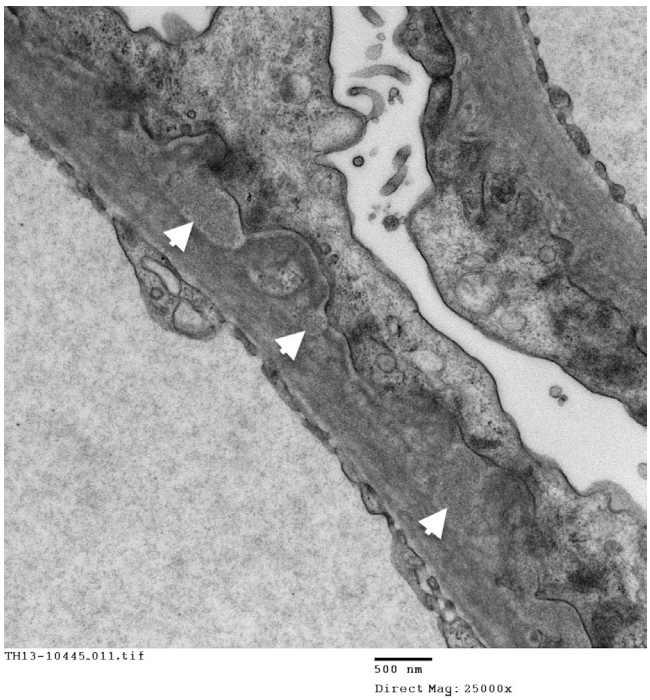

Figure 3. Occasional sub-epithelial immune deposits (arrowheads), supporting a diagnosis of membranous nephropathy, likely drug-induced.

Learning points

- The mainstay of treatment in familial cystinuria is hydration and urinary alkalinisation; in refractory cases, sulfyhydryl agents such as tiopronin and penicillamine are indicated.
- In patients who develop nephrotic syndrome secondary to tiopronin use, histology is mostly in keeping with membranous nephropathy.
- The time of onset of nephrotic syndrome may vary, and may even occur 16 months after starting therapy, as demonstrated by this case. This effect does not appear to be dose dependent.
- Regular surveillance for proteinuria should be carried out in all patients on tiopronin, and treatment stopped if the patient develops significant proteinuria.
- Patients should be managed using supportive measures such as fluid restriction, angiotensin-converting enzyme inhibitors, diuretics, statins and thromboprophylaxis as necessary. Cessation of tiopronin leads to resolution of the nephrotic syndrome in most cases.

refractory cases, sulfyhydryl agents such as tiopronin and penicillamine are indicated. Tiopronin, a glycine derivative, acts as a reducing agent, forming a mixed disulphide of tiopronin-cysteine that is water soluble and therefore less likely to form stones (Carlsson et al, 1993). Tiopronin is associated with fewer side effects than penicillamine, so tends to be the preferred option (Knoll et al, 2005).

The first case of tiopronin-induced nephrotic syndrome was reported in 1978. To the authors' knowledge, 33 cases of tiopronin-induced nephrotic syndrome have been reported at the time of writing (Zheng et al, 2014; Aksoy and Cakar, 2020; Zhong et al, 2019; Vidović et al, 2021), with nephrotic syndrome most commonly occurring within 1 year of therapy. Histology was available in 13 cases, with membranous nephropathy being the most common pattern observed. Other patterns of injury observed included mesangioproliferative glomerulonephritis (Ferraccioli et al, 1986) and minimal change disease (Lecoules et al, 1999; Zhong et al, 2019). Acute interstitial nephritis was also noted in one patient on concomitant tiopronin and non-steroidal anti-inflammatory drugs (Vidović et al, 2021). This case demonstrates that nephrotic syndrome may occur as late as 16 months after initiation of tiopronin, and at a much lower dose than that originally suggested (Rizzoni et al, 1979).

The incidence of tiopronin-induced nephrotic syndrome is unknown. In one study of 50 patients who were taking tiopronin to treat rheumatoid arthritis, four patients developed nephrotic syndrome (Ambanelli et al, 1982). The underlying mechanism remains unclear, although one hypothesis is drug interference with podocyte function (Tasic et al, 2011). Discontinuation of the drug and supportive measures for nephrotic syndrome are often sufficient. All patients on tiopronin should have regular urine surveillance with cessation of the drug if significant proteinuria occurs.

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