ADAMTS-13 deficiency: can it cause chronic renal failure?

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Abstract

We describe a case of a 45-year-old woman with progressive chronic kidney disease (CKD), macrocytic anaemia without fragments or thrombocytopenia, and thrombotic microangiopathy on renal biopsy. ‘A disintegrin and metalloprotease, with thrombospondin-1-like domains’ (ADAMTS-13) deficiency was detected, and genotyping revealed single-nucleotide polymorphisms known to be associated with reduced ADAMTS-13 secretion and activity. Congenital thrombotic thrombocytopenic purpura was diagnosed with unusual features of late presentation and absent neurological involvement. ADAMTS-13 deficiency should be considered a cause of CKD when features of thrombotic microangiopathy are present on renal biopsy.

Keywords: ADAMTS-13 deficiency; chronic kidney disease; thrombotic thrombocytopenic purpura

Background

Thrombotic microangiopathies are syndromes involving microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. Traditionally, a diagnosis of thrombotic thrombocytopenic purpura (TPP) requires the presence of a ‘pentad’ of signs, including thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological signs and renal impairment.

Recently, major advances in our understanding of the underlying pathophysiology have been made, leading to a novel classification of thrombotic microangiopathies dependent on the presence or absence of von Willebrand factor (vWF)-cleaving protease activity, or ‘a disintegrin and metalloprotease, with thrombospondin-1-like domains’ (ADAMTS-13). ADAMTS-13 is a plasma metalloprotease that cleaves vWF multimers soon after excretion by endothelial cells [1]. In its absence, large vWF multimers, in conditions of high shear, cause spontaneous platelet activation in the microvasculature. Levels of ADAMTS-13 are <5% of normal in 80% of patients clinically diagnosed with TTP [2]. Homozygous or double heterozygous mutations in the corresponding gene have been identified in inherited cases [3], and acquired cases are caused by circulating antibody [2].

Since the discovery of ADAMTS-13, an increasingly wide spectrum of associated clinical syndromes has been described [4]; however, TTP has not been associated causally with chronic kidney disease (CKD). We describe the case of a patient with inherited ADAMTS-13 deficiency presenting in adulthood with CKD, who progressed to end-stage renal failure within 3 years, without any episodes of acute renal failure or apparent triggers for deterioration.

Case report

Investigations for anaemia in a 45-year-old woman revealed a serum creatinine of 120 μmol/L (MDRD eGFR 40 mL/min/1.73 m²) and 24-h urinary protein excretion of 0.5 g with no evidence of haematuria or leucocyturia. She had a previous history of pre-eclampsia before 37 weeks complicating two pregnancies, but was normotensive with no family history of kidney disease and no exposure to nephrotoxins. A kidney biopsy showed a subacute thrombotic microangiopathy, characterized by fragmented red blood cells in a few glomerular capillary loops, and foci of mesangiolysis (Figure 1). Silver-stained sections showed short segmental splits in the glomerular capillary walls (Figure 2). There was focal acute tubular injury, focal tubular atrophy and focal interstitial fibrosis. No immune complex and complement deposition were seen, but staining for von Willebrand factor antigen and CD61 (platelet glycoprotein-IIIa) was positive.

D-dimers were elevated (1274 μg/L), and haemoglobin was 9 g/dL with low erythropoietin levels, but platelet count and blood film, coagulation screen, serum ferritin, autoantibody screen, immunoglobulins, antiphospholipid
antibodies, C3, C4 and CD59 levels, direct antiglobulin test, and blood glucose were normal. Her anaemia resolved with epoetin-beta therapy. Her kidney function deteriorated (serum creatinine 157 μmol/L and eGFR 33 mL/min/1.73 m²), so a second kidney biopsy was undertaken a year later which again showed subacute thrombotic microangiopathy with progressive fibrosis and tubular atrophy. A third biopsy 2 years later (serum creatinine 240 μmol/L and eGFR 20 mL/min/1.73 m²) showed extensive interstitial fibrosis without microangiopathy. Three years after presenting, she commenced dialysis.

In view of the unexplained thrombotic microangiopathy, ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, 13) deficiency was investigated, while she was stable; she had low levels (<5%) without evidence of an inhibitor. She was homozygous for three single-nucleotide polymorphisms (SNPs)—C19T (R7W), C1342G (Q448E) and C1852G (P618A)—and heterozygous for one SNP—C2699T (A900V). Factor H levels were above normal [0.68 g/L (range 0.35–0.59 g/L)], no anti-factor H autoantibodies were detected, and no mutations were found in membrane cofactor protein (MCP), factors H or I genes.

Five years after presenting, the patient presented with massive gastrointestinal haemorrhage. She was found to have liver cirrhosis intraoperatively and on further imaging. Despite a subtotal gastrectomy and supportive care, she developed multiorgan failure and died.

Discussion

Inherited or acquired deficiency of ADAMTS-13 has been identified as the cause of most cases of TTP, with a pentad of signs including neurological manifestations, fever, MAHA, thrombocytopenia and kidney disease. This is the first report where ADAMTS-13 deficiency has been associated with chronic thrombotic microangiopathy without characteristic non-renal manifestations.

Although mild kidney involvement occurs in 50% of acquired TTP [5], acute kidney injury is a minor feature of inherited ADAMTS-13 deficiency classically presenting in childhood with a relapsing–remitting course sometimes requiring long-term dialysis [6], but always associated with recurrent thrombocytopenia, MAHA and neurological manifestations. Other unusual features of our case were late age at presentation, rapid progression of kidney failure and the absence of hypertension.

Those with inherited deficiencies of ADAMTS-13 may first present during pregnancy and are at risk of pre-eclampsia due to placental thromboses; in hindsight, our patient’s pre-eclampsia may have been due to such phenomena.

Although the major site of ADAMTS-13 synthesis is the liver, ADAMTS-13 secretion has also been demonstrated with thrombospondin type 1 motif, 13) deficiency was investigated, while she was stable; she had low levels (<5%) without evidence of an inhibitor. She was homozygous for three single-nucleotide polymorphisms (SNPs)—C19T (R7W), C1342G (Q448E) and C1852G (P618A)—and heterozygous for one SNP—C2699T (A900V). Factor H levels were above normal [0.68 g/L (range 0.35–0.59 g/L)], no anti-factor H autoantibodies were detected, and no mutations were found in membrane cofactor protein (MCP), factors H or I genes.

Liver cirrhosis was identified at the same time as gastrointestinal haemorrhage prior to the patient's death and was not formally investigated. It is possible that cirrhosis was another manifestation of TTP, but unfortunately this cannot be confirmed.

In conclusion, we have described inherited ADAMTS-13 deficiency presenting in adulthood with chronic kidney disease as the only clinical manifestation. Further studies are required to assess whether ADAMTS-13 deficiency is a common cause of chronic thrombotic microangiopathy without non-renal manifestations.
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References

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Apparent renal disease due to elevated creatinine levels associated with the use of boldenone

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Abstract
The widespread use of reporting estimated glomerular filtration rate (eGFR) alongside serum creatinine has led to a heightened appreciation of renal disease. However, creatinine is recognized as an insensitive marker of true GFR and therefore can lead to misdiagnosis of renal dysfunction in the absence of true pathology. We report the case of a 37-year-old male referred due to abnormal eGFR and creatinine in the absence of clinical signs, symptoms or other biochemical abnormalities of renal disease. Subsequent investigations based on a high index of suspicion for exogenous substance abuse led to a novel observation of significantly raised creatinine due to the presence of boldenone, an equine anabolic steroid commonly abused in body building.

Keywords: anabolic steroids; boldenone; disproportionately high creatinine

Case report
A 37-year-old male admitted to hospital was referred to the medical take due to perceived abnormal renal function. His GP had checked his bloods 5 days previously as part of routine screening for his repeat prescription of citalopram and found his creatinine elevated at 338 μmol/L, equating to an estimated GFR of 18 as calculated by the laboratory. He had started citalopram 3 months earlier after suffering from an acute episode of depression at which time his creatinine was 109 μmol/L.

A detailed history yielded little extra information. He had been to Thailand 4 months previously and had a diarrhoeal illness for 1 week, but no other symptoms including weight loss, dry eyes, rash, joint pains or arthralgia were elicited. There was no NSAID usage, and he vehemently denied illicit drug use. He was self-employed as a business manager and did body building for a