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Case Report

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C1q nephropathy in a patient with Gitelman syndrome

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Abstract
Bartter syndrome can manifest in three different forms and is rarely concomitant with glomerular nephropathies. However, this association is more frequently observed in children. We report the case of a 50-year-old woman with Gitelman syndrome for the past 30 years who also had a nephrotic syndrome of recent appearance. Her renal biopsy revealed hyperplasia of the juxtaglomerular apparatus and mesangial deposits of C1q, with no clinical or serological evidence of systemic erythematous lupus. We have not found any reports of instances of association of Gitelman syndrome and nephrotic syndrome arising from C1q nephropathy in adult patients. Our case suggests the possible existence of an association between hypokalaemic tubular nephropathies and glomerular nephropathies that may cause nephrotic syndrome.

Keywords: Bartter syndrome; C1q nephropathy; Gitelman syndrome; nephrotic syndrome

Background

Bartter syndrome is an autosomal recessive tubulopathy related to different genetic disorders. It presents as three clinically and biochemically similar entities: neonatal, typical Bartter syndrome and Gitelman syndrome. One of its features is hyper-reninaemic hyperaldosteronism, with hyperplasia of the juxtaglomerular apparatus. Although it is uncommonly associated with glomerulonephritis, there are published reports of cases of Bartter syndrome with focal and segmental glomerulonephritis, proliferative glomerulonephritis and diffuse mesangial hypercellularity [1, 2]. Some rare cases of Bartter syndrome and C1q nephropathy have been described in children.

We present the case of a 50-year-old female with observed Gitelman syndrome for 30 years who presented with a nephrotic syndrome due to C1q nephropathy.

Case report

A 50-year-old female was diagnosed with Gitelman syndrome at the age of 20 years. She was treated with spironolactone (100 mg/day), magnesium lactate (1.2 g/day), potassium chloride (5.4 g/day) and indometacin (25 mg/day).

The patient was recently admitted to our Nephrology Department with oliguria and progressive facial and lower limb oedema 15 days in duration. Her blood analyses showed urea 60 mg/dL, creatinine 0.93 mg/dL, Na 138 mmol/L, K 3.3 mmol/L, Cl 98 mmol/L, Mg 2.1 mg/dL, Ca 8.2 mg/dL (ionic 1.08), P 3.1 mg/dL, total proteins 4.5 g/dL, albumin 1.7 g/dL, bicarbonate 30.1 mmol/L, cholesterol 441 mg/dL, triglycerides 151 mg/dL, high-density lipoprotein 101 mg/dL, low-density lipoprotein 339 mg/dL. Anti-nuclear antibodies, antineutrophil cytoplasmic antibodies and serologic tests for hepatotropic virus, human immunodeficiency virus and treponema were negative, and her complement system, haemogram and thyroid function were normal. Urinalysis findings were proteinuria 11.7 g/day, Na 74 mmol/L, K 152.6 mmol/L, Ca 5.7 mg/dL (136.8 mg/day) and Mg 3.8 mg/dL. A renal biopsy showed: subendothelial and mesangial segmental C1q deposits, mainly located in the distal areas of the capillary loops (Figure 1), with discrete mesangial proliferation, slight interstitial fibrosis and hyperplasia of the juxtaglomerular apparatus (Figure 2).

Her definitive diagnosis was nephrotic syndrome secondary to C1q nephropathy, probably minimal change type. Treatment with steroids at a dose of 1 mg/kg/day was started. The nephrotic syndrome resolved after 6 weeks of treatment.

Discussion

Gitelman syndrome is a variant of Bartter syndrome and is commonly diagnosed in adolescence or adulthood. Its underlying causes are various mutations of the SLC12A3 gene, which encodes the thiazide-sensitive cotransporter of the Na–Cl distal tubule. Dysfunction of the cotransporter induces saline loss, hypovolaemia, hypokalaemia, metabolic alkalosis, stimulation of the renin–angiotensin–aldosterone system, hyperplasia of the juxtaglomerular apparatus and hypersecretion of quinines and prostaglandins (PG E2), with a vasodilatory effect that explains the absence of hypertension [2]. The diagnosis of Gitelman syndrome is established mainly on the basis of clinical findings, among which the most common are normal arterial pressure and

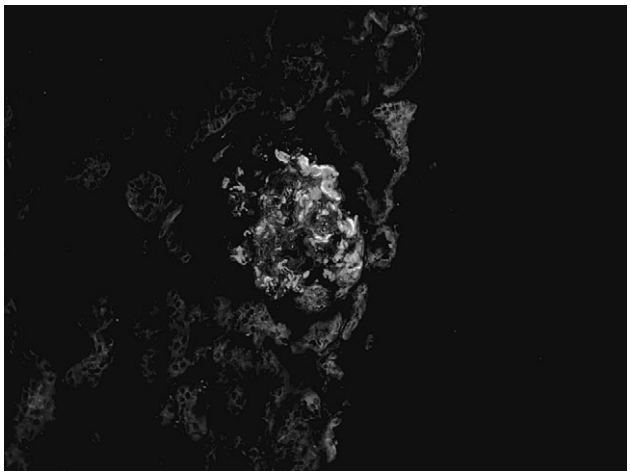

Fig. 1. Immunofluorescence which shows subendothelial and mesangial segmental C1q deposits, mainly located on the peripheral areas of the capillary loops.

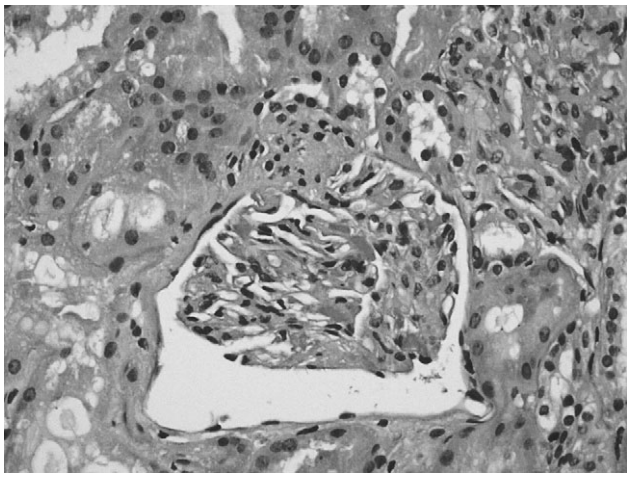

Fig. 2. Haematoxylin–eosin staining in which we appreciate hyperplasia of the juxtaglomerular apparatus and discrete mesangial proliferation.

shivering limbs, tetany, fatigue, polyuria and nocturia due to hypokalaemia and hypomagnesaemia.

C1q nephropathy appears with proteinuria, usually within the nephrotic range. Histological evidence of mesangial proliferation is seen frequently. Immunofluorescence shows mesagial deposits of C1q. A poor response to steroid therapy is a common feature [3]. Histological variants of C1q nephropathy are: focal and segmental glomerulosclerosis, minimal-change glomerulonephritis or mesangial hypercellularity [4]. These patients with C1q nephropathy do not present clinical or serological signs of systemic erythematous lupus [5].

The coexistence of Bartter–Gitelman syndromes and a glomerular disease is very rare and described only in children. Some cases of Bartter syndrome associated with glomerular nephropathies have been reported, such as diffuse mesangial hypercellularity, proliferative glomerulonephritis and focal and segmental glomerulosclerosis [6]. As is known, the constant stimulation of the renin–angiotensin–aldosterone system, with the subsequent increase of angiotensin II, induces glomerulosclerosis. It is unknown, however, whether these tubulopathies might precipitate a glomerular disease, such as C1q nephropathy. A possible explanation might be that a constant increase of angiotensin II induces hyperplasia of the juxtaglomerular apparatus and a secondary renal sclerosis due to the stimulation of cytokines, such as tumour necrosis factor-α and tumour growth factor-β. Although these cytokines do not lead to complement deposits, they induce mesangial hypercellularity because of the close proximity of the juxtaglomerular apparatus to the vascular pole. Hypothetically, the genetic alteration of the Na–Cl channel, responsible for the symptoms of Bartter–Gittelman, could be an antigenic stimulus that leads to an immune response with C1q deposit [7].

We have not found any previously reported case of C1q nephropathy that responded satisfactorily to steroid treatment in a patient with Gitelman syndrome for 30 years. The association of the two pathologies might be coincidental, but our case, as those described in children (two boys with Bartter syndrome and one girl with Gitelman syndrome, all three under 10 years old), supports the theory that there is a causal relation between hypokalaemic tubulopathies and rare glomerulopathies, such as C1q nephropathy.

Conflict of interest statement. None declared.

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