Massive proteinuria for minimal change nephropathy secondary to treatment with D-penicillamine in a patient with Wilson's disease. Case report☆

Proteinuria masiva por nefropatía por cambios mínimos secundaria a tratamiento con D-penicilamina en un paciente con enfermedad de Wilson hepática. A propósito de un caso

Wilson's disease (WD) has a prevalence of 142 cases per million population.[1] It presents an autosomal recessive inheritance pattern with more than 500 different mutations in the ATP7B gene (chromosome 13) This encodes a carrier metalloprotease that leads to the protein deficiency involved in the intrahepatocyte transport of copper, preventing copper from being excreted to the bile canaliculi and the incorporation of copper into apoceruloplasmin, reducing the plasma concentration of ceruloplasmin.[2] It may be asymptomatic or manifest hepatic, ocular and/or neurological symptoms. Some of the therapeutic options available are: D-penicillamine, trientine and zinc salts. Cases of renal involvement have been reported with D-penicillamine therapy. The most common cause is the development of membranous glomerulonephritis.

We present the case of a patient with massive proteinuria in the context of nephrotic syndrome due to minimal change nephropathy secondary to treatment with D-penicillamine.

It is a 50-year-old male patient with a history of type 2 diabetes mellitus and hepatic Wilson's disease receiving treatment with D-penicillamine 1 g/24 h, with stable liver function. Three years after the diagnosis and treatment, he was referred to nephrology with signs of nephrotic syndrome, with generalised oedema, hypoalbuminaemia, dyslipidaemia and proteinuria of 30 g/24 h. Renal function was normal at all times. He was admitted to start depletion therapy with intravenous loop diuretics and suspension of D-penicillamine. A kidney biopsy showed lesions typical of minimal change nephropathy (podocyte oedema, glomeruli intact and podocyte fusion observed by electron microscopy), excluding IgG, C1q and focal and segmental nephropathy from the differential diagnosis. After the diagnosis, the suspension of D-penicillamine continued and zinc acetate was prescribed, one tablet every 8 h, together with antithrombotic treatment with bemiparin and oral diuretics. The nephrotic syndrome remitted, achieving proteinuria of 243 mg/24 h, maintaining normal renal function and observing unaltered analytical parameters after starting the zinc, and no liver function abnormalities before this change (GOT 79 U/l, GPT 191 U/l, GGT 220 U/l, ALP 137 U/l, ceruloplasmin and copper in urine, normal).

D-penicillamine is used in diseases such as rheumatoid arthritis, primary biliary cholangitis and Wilson's disease. Some of its side effects are arthralgia, skin disorders, hypogeusia, leukopenia, thrombocytopenia, haemolytic or aplastic anaemia, lupus-*like* phenomena and, occasionally, renal disorders.[3,4] Membranous nephropathy is the most common renal disorder reported in relation to D-penicillamine. However, cases have also been described with crescentic glomerulonephritis, focal glomerulonephritis, ANCA+ and ANA+ vasculitis that can course with complete or incomplete nephrotic syndrome, but all without massive proteinuria, and some cases of minimal change nephropathy.[5]

The mechanism of action of D-penicillamine is not well understood. It is hypothesised that it could alter immune response, inhibiting mitogen-induced lymphoblastic transformation and reducing immunoglobulin production by stimulated lymphocytes. The complications caused by the drug could be due to a modification of autoantigens, due to the presence of a highly reactive thiol group in the molecule or to interference with Th17 lymphocyte response. It has been reported that it can inhibit *T helper* lymphocyte activity and this could explain its efficacy in the treatment of autoimmune diseases such as rheumatoid arthritis. Ultimately, D-penicillamine could interfere with a regulating immune mechanism, predisposing some patients to develop minimal change nephropathy.

Our case was interesting because it involved the onset of minimal change nephropathy instead of membranous nephropathy, which is the most common associated condition, and due to the intense proteinuria, secondary to the treatment with D penicillamine.

In conclusion, we believe that it is essential to review renal function and proteinuria in patients receiving chronic treatment with D-penicillamine and suspend the drug with the onset of nephrotic syndrome, as there appears to be a possible association between D-penicillamine and minimal change nephropathy (in our case), given that the nephrotic syndrome and the disease remitted when the drug was suspended.

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