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Exceptional Case

EXCEPTIONAL CASE

Focal segmental glomerulosclerosis associated with the use of the IL-23 inhibitor guselkumab

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ABSTRACT

We report a case of a 38-year-old man who developed a nephrotic syndrome shortly after the start of guselkumab for the treatment of plaque psoriasis. Renal biopsy showed focal segmental glomerulosclerosis (FSGS). The clinical course of our case is highly suspect for drug-induced FSGS since the nephrotic syndrome resolved after cessation of the drug without relapse (2 years of follow-up). To the best of our knowledge, this is the first case describing FSGS lesions associated with the use of an interleukin-23 inhibitor.

Keywords: focal segmental glomerulosclerosis, guselkumab, IL-23

BACKGROUND

Guselkumab is a human monoclonal antibody, Food and Drug Administration (FDA) approved for the treatment of plaque psoriasis. It binds the p19 subunit of interleukin (IL)-23. IL-23 induces and maintains differentiation of T helper 17 (Th17) and Th22 cells which produce pro-inflammatory cytokines involved in the inflammation and epidermal hyperplasia of psoriasis [1]. Th17 cells are involved in a variety of autoimmune diseases, including those affecting the kidney. Guselkumab is a highly efficacious targeted therapy for psoriasis with a favorable safety profile in its phase III trials [2].

Focal segmental glomerulosclerosis (FSGS) describes a lesion on renal histology characterized by focal and segmental scarring in the glomerulus [3]. FSGS is divided into primary (or idiopathic), genetic and secondary FSGS. Secondary forms can be maladaptive, viral or drug-induced. The common pathogenic mechanism of FSGS is podocyte injury and depletion leading to proteinuria. The characteristics of foot process effacement on electron microscopy are helpful in differentiating between primary and secondary FSGS [4]. The clinical presentation of FSGS can vary from subnephrotic proteinuria to overt nephrotic syndrome. We describe a case of secondary FSGS following treatment of plaque psoriasis with guselkumab.

CASE REPORT

We describe a case of a 38-year-old man who presented with new-onset nephrotic syndrome shortly after starting guselkumab for the treatment of therapy-resistant plaque psoriasis. He had no other medical history and was not taking any other medication. Serum creatinine and serum albumin before the start of guselkumab were within the normal range,

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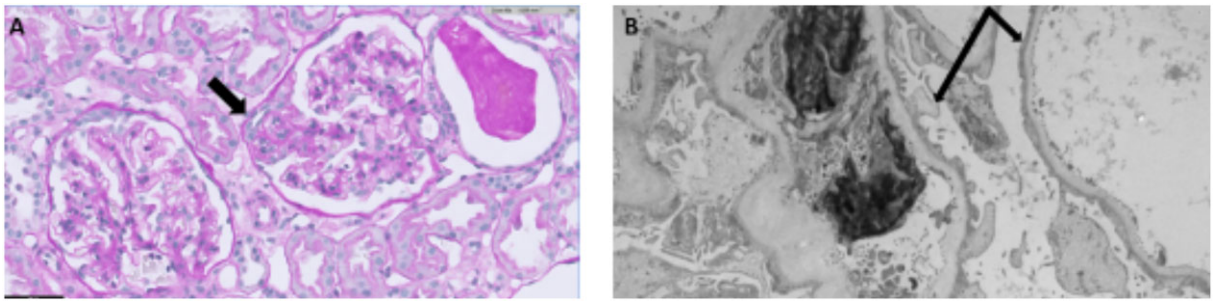

Figure 1: (**A**) Periodic acid–Schiff (400×)—segmental glomerulosclerosis (black arrow); (**B**) electron microscopy (3000×)—diffuse foot process effacement.

respectively 0.88 mg/dL and 47 g/L. Last urine analysis before the start of guselkumab dated from more than 10 years before. He was referred to the outpatient nephrology clinic because of the development of peripheral pitting edema about 14 days after the start of guselkumab. Blood pressure at presentation was high (150/90 mmHg). Spot urine analysis showed gross proteinuria (25 g/L, 10 g/g creatinine), microscopic hematuria (117 red blood cells/µL) and discrete pyuria (30 white blood cells/µL). Serum creatinine was 0.96 mg/dL at presentation. The serum albumin was 20 mg/L. Complement levels (C3–C4) were within the normal range. Antineutrophil cytoplasmic antibodies were positive but anti-myeloperoxidase antibodies and anti-proteinase 3 antibodies were negative, as well as nuclear antibodies. A renal biopsy was performed. The results of the light microscopy revealed the diagnosis of FSGS, with FSGS lesions in 4 of the 22 viable glomeruli (18.2%). The glomerular size was within the normal range. The cellularity of the mesangium was normal. There was no significant tubule-interstitial damage, no signs of vasculitis.

Immunofluorescence microscopy showed discrete depositions of immunoglobulin A (IgA) in the mesangium, however there were no other signs of IgA nephropathy. The diagnosis of FSGS was confirmed by electron microscopy. On electron microscopy, 90.5% of the glomerular capillaries showed a foot process effacement of <80%, suggesting a secondary form of FSGS. Figure 1 shows the results of the light and electron microscopy. Serologic tests for cytomegalovirus (IgM and IgG) and human immunodeficiency virus (HIV-1 and -2 Ab and Ag) were all negative. Epstein–Barr virus IgG was positive but IgM was negative. We promptly stopped the therapy with guselkumab as the time course was very suspect. Low-dose renin–angiotensin–aldosterone system inhibition (ramipril 5 mg) was started in the context of arterial hypertension and proteinuria. Soon after stopping guselkumab, we saw a remission of the nephrotic syndrome with normalization of the serum albumin and spontaneous disappearance of edema. Proteinuria diminished to <3.5 g/day about 3 months after stopping guselkumab. Psoriatic lesions reoccurred and increased in number and severity. Secukinumab, an IL-17 inhibitor, was started. Proteinuria diminished further and became negative. Complete remission remained (2 years of follow-up). Results of genetic testing were all negative, which confirms the assumed diagnosis of secondary FSGS.

DISCUSSION

To the best of our knowledge, this is the first case describing FSGS lesions associated with the use of an IL-23 inhibitor. We searched the publicly available European Medicines Agency and FDA database and found no reported renal adverse events with guselkumab. A Medline search did not reveal a previous case of nephrotic syndrome linked to the use of guselkumab. Th17 cells are known as potent pro-inflammatory cells involved in a variety of autoimmune diseases including renal autoimmune diseases. Furthermore, signs of disintegration of the podocyte cytoskeleton accompanied by increased apoptosis when cultured in the presence of IL-17, a pro-inflammatory cytokine produced by Th17 cells, have recently been described [5]. It is therefore surprisingly that a potent Th17 inhibitor could cause an FSGS lesion. However, the clinical course of our case is highly suspect since the nephrotic syndrome resolved after cessation of the drug. There were no signs of auto-immune disease on the renal biopsy. As soon as proteinuria was subnephrotic, psoriatic plaques reappeared suggesting guselkumab was not therapeutically active anymore.

CONFLICT OF INTEREST STATEMENT

B.S. and A.H.V.C. are members of the *CKJ* Editorial Board.

PATIENT CONSENT

The patient gave informed consent to publish this case.

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