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Case Report

Granulomatous Interstitial Nephritis Secondary to Stelara (Ustekinumab) Use in A Patient With Crohn's Disease

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2. Keywords

CD; GIN; Infliximab; Ustekinumab

1. Abstract

1.1. Background: Granulomatous interstitial nephritis (GIN) is a rare pathological entity detected in 0.5–0.9% of all native kidney biopsies. We report a case of GIN secondary to stelara (ustekinumab) use in a patient with Crohn's disease (CD).

1.2. Case presentation: A 35 years-old Kuwaiti man, with a 5-years history of CD was presented with rising serum creatinine following the use of stelara (ustekinumab) for treatment of CD. His serum creatinine had increased to 350 umol/L from 52 umol/L recorded on November 2013 before the start of CD medications. He had been treated with mesalamine, Infliximab and azathioprine for his CD in the preceding 5 years. On August 2016, serum creatinine increased to 169 umol/L and mesalamine was discontinued. On July 2018, serum creatinine increased to 260 umol/L and Infliximab was discontinued and a novel biological drug stelara (ustekinumab) started on August 2018, but unfortunately, serum creatinine increased to 350 umol/L. All immunology and virology tests were negative. Kidney biopsy was performed and the pathological diagnosis was acute GIN with non-caseating granulomas on top of chronic tubule-interstitial nephritis. A Quantiferon Gold assay and Ziehl– Neelsen staining of the biopsy were negative for tuberculosis. Immunoglobulin G (IgG), IgM and IgA were normal. Serum angiotensin-converting enzyme was normal. Antinuclear antibodies, anti-neutrophilic cytoplasmic antibodies were negative. Computed tomography of the chest and abdomen were normal. Ustekinumab) was discontinued and 60 mg coticosteriod was prescibed. His kidney function improved and stabilized at a serum creatinine of 260 umol/L. To our knowledge, our case is the first case report GIN secondary to ustekinumab use in a patient with well controlled CD.

1.3. Conclusion: Stelara (ustekinumab) use in patients with CD can be associated with GIN, warranting, the necessary of following the kidney function and urine abnormalities while the patients with CD on ustekinumab treatment.

3. Introduction

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury (AKI) [1, 2]. The presence of granulomas with AIN is rare [3, 4]. Granulomatous interstitial nephritis (GIN) has been linked to several antibiotics such as cephalosporins, vancomycin, nitrofurantoin and ciprofloxacin. It is also associated with non-steroidal anti-inflammatory drugs and granulomatous disorders such as sarcoidosis, tuberculosis, fungal infections and granulomatosis with polyangiitis (GPA) [3, 4].

Extra intestinal manifestations of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis, probably reflect systemic inflammation, autoimmune susceptibility and/or drug-related toxicities [5]. Although these manifestations are prevalent, parenchymal renal disease as such is considered rare. However, kidney biopsies from patients with IBD can reveal a wide spectrum of pathologies most commonly af-

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fecting the glomerular and tubule-interstitial compartments [6].

Found GIN in 5% of kidney biopsies from patients with IBD, the occurrence of which was linked to current or recent or past exposure to 5-aminosalicylic acid (5-ASA) preparations or in relation to the CD [7]. We report a 35 years-old male Kuwaiti patient with 5-years history of well controlled CD, who recently developed rising of serume creatinine with bland urine analysis after the use of stelara (ustekinumab; IL-12 and IL-23 inhibitors) and kidney biopsy revealed GIN with improvement of kidney function after discontinuation of stelara (ustekinumab) and receiving corticosteroids 60 mg daily.

4. Case presentation

A 35 years-old Kuwaiti man, with a 5-years history of CD (November, 2013), was referred to nephrology clinic, Al-Adan hospital, Kuwait, with rising serum creatinine following the use of stelara (ustekinumab) for treatment of CD. There was no fever, nausea, vomiting, infection or diarrhea. His serum creatinine had increased to 350 umol/L from 52 umol/L recorded on November 2013 before the start of CD medications. He had been treated with mesalamine, Infliximab (TNF-**α** inhibitor) and azathioprine for his CD in the preceding 5 years and azathioprine was discontinued due to development of pancreatitis. On October 2015, although serum creatinine increased to 101 umol/L, mesalamine and Infliximab continued. On August 2016, serum creatinine increased to 169 umol/L and mesalamine was discontinued. On July 2018, serum creatinine increased to 260 umol/L and Infliximab was discontinued and a novel biological drug stelara (ustekinumab) 90 mg SC started on August 2018, but unfortunately, serum creatinine increased to 350 umol/L. On examination, his BP was 130/70 mmHg, HR 80/min and temprature 37.2; chest, heart and abdomen examination were normal with no lower limb oedema. Chemistry values showed serum creatinine 350 umol/L, blood urea nitrogen 16.3 mmol/L, serum potassium 4.6 mmol/L, serum sodium 136 mmol/L and albumin 35 g/L. Total Ca 2.21 mmol/L, phosphorous 1.24 mmol/L. White blood count was 5.54 × 10 7 /L, hemoglobin 112.00 mmol/L, hematocrit 0.35 L/L, platelet 318.00 × 10 7 /L. Erythrocyte sedimentation rate was 74 mm/h. Total cholesterol 5.3 mmol/L, high density lipoprotein-cholesterol 2.12 mmol/L and triglycerides 2.13 mmol/L. Liver enzymes were normal. The urine sediment contained 0-2 red blood cells and 2-3 white blood cell/hpf and 24 urinary proteins was 165 mg/day. All immunology and virology tests were negative (Table 1). Abdominal ultrasound revealed normal both kidneys in position and size with grade 1 echogenecity and maintained corticomedullary differentiation. Chest X-ray and echocardiography were normal. The professional differential diagnosis was kidney injury as an extraintestinal manifestations of CD [glomerulonephritis (GN), acute tubule-interstitial nephritis (ATIN), amyloidosis, kidney stones and drug-induced Interstitial nephritis]. Kidney biopsy was performed in order to establish the diagnosis.

Table 1: Time course of laboratory investigations.

Variables	11/2013	10/2015	8/2016	7/2018	9/2018	11/2018
S. creatinine (umol/L)	52	101	169	260	350	260
mesalamine	started	DC	DC	DC	DC	DC
Infliximab	started	continued	continued	DC	DC	DC
Azathioprine	started	DC	DC	DC	DC	DC
Stelara (ustekinumab)				started	DC	DC
ANA	-ve				-ve	
RF					-ve	
ANCA-PR3					-ve	
ANCA-MPO					-ve	
HbsAg					-ve	
HCV ab					-ve	
HIV					-ve	
TB gold test					-ve	
ACE					N	
Chest x ray					N	
CT chest, abdomen					N	
Echo-heart					N	
24 h urine protein (mg/day)				140	165	
Kidney biopsy					GIN	

5. Kidney Biopsy

With light microscopy, there was a core of renal tissue containing up to 26 glomeruli, 6/26 (23%) glomeruli are globally sclerosed and the viable glomeruli are within nomal limits. Tubules and interstitium: There is a diffuse interstitial inflammatory cell infiltrate comprising plasma cells, lymphocytes, esinophils and a few neutrophils. A well formed non necrotizing granuloma is present (**Figure 1**). Occasional tubules containing neutrophils casts are noted. There are foci of tubulitis and evidence of tubular injury with regenerative changes. There is moderate –severe interstitial fibrosis and tubular atrophy (50-60%). Vessels: One patially sampled, tangentially cut, artery is sampled which appears unremarkable. Arterioles show mild sclerosis but no hyalinosis is seen. Special stains for mycobatrial and fungal organisms are negative. With immunohistochemisty, Immunoglobulin (Ig) A, IgM, IgG, C3C, C1q were negative. The pathological diagnosis was acute GIN with non-caseating granulomas with modeate to severe interstial fibrosis and tubular atrophy.

He subsequently underwent an extensive evaluation for tuberculosis (TB), including a Quantiferon Gold assay and Ziehl– Neelsen staining of the biopsy, these were negative. Immunoglobulin G (IgG), IgM and IgA serology were normal. His serum angiotensin-converting enzyme (ACE) was normal (normal 20–70). Antinuclearr antibody (ANA), *Anti-neutrophil cytoplasmic antibodies* proteinase 3 (ANCA PR3) *and ANCA* myeloperoxidase (ANCA MPO) were negative. Computed tomography of the chest, abdomen and pelvic regions were normal. Stelara (ustekinumab) was discontinued and 60 mg coticosteriod was prescibed. His kidney

function improved and stabilized at a serum creatinine of 260 umol/L.

ANA, antinuclear antibody; RF, rheumatoid factor; ANCA-PR3, anti-neutrophilic cytoplasmic antibodies; ANCA-MPO, ANCA myelopeoxidase; HbsAg, hepatitis B surface antigen; HCV ab, hepatitis C virus antibodies; HIV, human immunodeficiency virus; TB gold test, tuberculosis gold test; ACE, angiotensin converting enzyme; CT, Computed tomography; DC, discontinued; GIN, granulomatous interstitial nephritis.

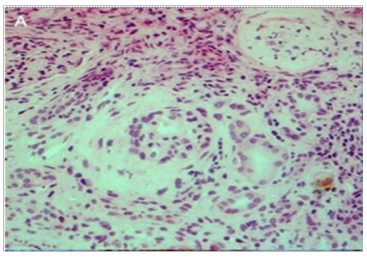

Figure 1: Renal biopsy revealing granulomatous interstitial nephritis (A; haematoxylin and eosin, 200×).

6. Discussion

GIN occurs in 0.5–0.9% of native kidney biopsies [8-13]. In a report by Mignon et al. [9] of 32 cases, 28% were due to drugs, 16% were caused by GPA and 9% were attributed to sarcoidosis and tuberculosis. In the series presented by Viero and Cavallo [12], 25% of cases were due to drugs, sarcoidosis and infections each. Bijol et al. [10] reviewed 9779 biopsies between January 1987 and July 2004 to describe cases of GIN. They found 38 GIN cases. Seventeen patients had drug-induced GIN, 11 patients had sarcoidosis-related GIN and 2 had GPA. Javaud et al. [14] evaluated 40 kidney biopsies between January 1991 and February 2004 with GIN defined as the presence of at least one epithelioid granuloma in the interstitium. The majority of their cases were linked to sarcoidosis (50%), where medications (17.5%) and tuberculosis (7.5%) accounted for fewer cases [14]. The variability in these series can be explained by both sampling and publication bias of these cohorts.

Crohn's disease, oxalosis and intravesicular bacillus Calmette–Guerin have also been responsible for causing GIN in a few cases [10,12,14]. The etiology for GIN remains obscure in 10% of cases [10,14].

We report a 35 years-old male Kuwaiti patient with 5-years history of well controlled CD, who recently developed rising of serum creatinine with bland urine analysis after the use of stelara (ustekinumab) and kidney biopsy revealed GIN with improvement of kidney function after discontinuation of stelara (ustekinumab) and receiving corticosteroids 60 mg daily.

This patient's exposure to stelara (ustekinumab) was followed by AKI resulting in a biopsy-proven diagnosis of GIN. Although the patient was exposed to mesalamine and Infliximab prior to kidney biopsy, the last patient's laboratory derangements were traced after the initiation of stelara (ustekinumab).

Renal manifestations of AIN typically occur within 3 weeks of starting the offending drug in 80% of cases, where the average delay is 10 days with antibiotics [15]. The patient's exposure to mesalamine and Infliximab preceded this recent presentation by years; therefore, it is less likely that these drugs were responsible for GIN, but may be responsible for the underlying chronic tubule-intestitial nephritis [16]. Stelara (ustekinumab) was initiated about 4 weeks prior to the patient's rise in serum creatinine, which would be the cause of interstitial nephritis with granulomas.

The role of kidney biopsy was critical in excluding a progressive GN and in delineating the extent of inflammation, fibrosis and eosinophilic infiltration. The findings of mild tubulointerstitial fibrosis are associated with a more favorable response to corticosteroid therapy [17]. On Kidney biopsy, granulomas with non-necrotizing features are associated with drug-induced GIN and sarcoidosis, whereas, necrotizing granulomas are common in patients with GPA, fungal or tuberculosis-induced GIN [10, 14]. Drug-induced GIN leads to more loose appearing aggregates of epithelioid macrophages, but granulomas in sarcoidosis tend to be rather well defined [10,18]. Although these findings are suggestive of certain diagnosis, they are not absolute. Joss et al. [11] found no correlation between the degree of inflammation or fibrosis and the underlying etiology. The concentration of eosinophils cannot direct one to a particular diagnosis. Bijol and coworkers [10] demonstrated that drug-induced GIN had more diffuse interstitial involvement with a higher concentration of eosinophils and neutrophils. In contrast, Javaud et al. [14] noted that drug-induced GIN should be considered when granulomas are present and when eosinophils are not seen in the inflamed interstitium. This difference surrounding the presence of eosinophils may reflect the timing of when biopsies are performed or the various medications implicated.

Drug-induced AIN is most likely related to immune reactions as few patients exposed to a particular drug develop AIN. The response is not dose dependent, and it can be associated with extrarenal signs of hypersensitivity [15]. Furthermore, AIN can recur when patients are re-introduced to the inciting agent or a very similar agent. In experimental models, AIN can occur due to an immune response against an antigen that originates within the kidney or an extrarenal antigen that is deposited in the kidney [19-21]. Potentially, a drug can bind to part of the tubular basement membrane and act as a hapten. Alternatively, the drug can mimic an antigen in the tubular basement membrane or intersitium where via molecular mimicry an immune response targets both the drug and the similar antigen [15]. The response is

most likely cell mediated in nature given the number of lymphocytes and macrophages seen on light microscopy specimens and the paucity of immune deposits seen on immunofluorescence. GIN has been attributed to a delayed type hypersensitivity reaction and cell-mediated response type 1 helper T cells [15].

Although drug-induced nephrotoxicity by 5-ASA has been considered an aetiological factor in tubulo-interstitial nephritis with [22-24] or without granulomas [25, 26], or focal segmental glomerulosclerosis [27], there is no clear relationship between the duration and dose and the development of renal disease.

Infliximab is a chimeric anti-TNF-**α** monoclonal antibody. Infusion related reactions and infection are well known side effects of infliximab; however, renal complications have not been well recognized. ATIN after treatment with infliximab for CD has been reported. Kidney biopsy indicated that ATIN was probably induced by drug, considering significant infiltration of eosinophils [28, 29].

It has also been proposed that binding of infliximab to TNF-**α** on the lymphocyte plasma membranes might induce apoptosis, releasing immunogenic nucleosomal antigens that promote anti-dsDNA antibody formation [30]. Moreover, the induction of ANA, anti-dsDNA and ANCA from TNF-**α** inhibitors may give rise to either lupus-like immune complex GN or ANCA-related necrotizing and crescentic GN in susceptible individuals [31].

Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin (IL) 12 and 23, is a novel pharmacotherapy for CD patients. It is approved for use in psoriasis and psoriatic arthritis. Renal complications with this novel biological drug have not been reported [32 - 34]. To our knowledge, our case is the first case report of development of GIN secondary to ustekinumab use in a patient with well controlled CD.

The kidney constitutes a target organ involved in the CD-induced systemic disorders. Furthermore, many drugs and their metabolites are condensed in situ and excreted in the urine, so the kidney is susceptible to the nephrotoxicity of these drug with low incidence reported so far. Our observation would emphasize the need for increasing awareness of the kidney function and the presence of urine abnormalities during the management of IBD with mesalamine, sulfasalazine, mesalazine or 5-ASA, Infliximab and ustekinumab.

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