CASE REPORT

Pauci-immune crescentic glomerulonephritis associated with use of trimethoprim–sulfamethoxazole

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Abstract Drug-induced pauci-immune crescentic glomerulonephritis has been described with several agents, including propylthiouracil, minocycline, D-penicillamine, and hydralazine. We present the case of a 60-year-old man who presented with rapidly progressive glomerulonephritis in the setting of recent use of trimethoprim–sulfamethoxazole complicated by the development of the Stevens–Johnson syndrome, and was found to have biopsy-proven pauci-immune crescentic glomerulonephritis and undetectable anti-neutrophilic cytoplasmic antibodies. We review the existing literature on the potential association between sulfonamides and hypersensitivity polyangiitis.

Keywords Trimethoprim–sulfamethoxazole · Rapidly progressive glomerulonephritis · Pauci-immune crescentic glomerulonephritis

Introduction

Since its approval in the US by the Food and Drug Administration in 1973, the antimicrobial drug combination trimethoprim–sulfamethoxazole (TMP–SMX) has

been used for a wide range of infections. It is the antibiotic of choice for community-acquired soft tissue infections [1] and uncomplicated urinary tract infections [2]. Elderly persons and patients with pre-existing chronic kidney disease in the setting of hypertension, diabetes mellitus, and vascular disease are more vulnerable to the adverse effect of this antibiotic combination [3]. While commonly reported kidney-related adverse effects of this drug include allergic acute interstitial nephritis, acute tubular necrosis, hyperkalemia, and spurious elevation in serum creatinine [4–8], there are no published reports of TMP–SMX associated proliferative glomerulonephritis.

We review the case of a 60-year-old man with normal kidney function who presented with severe rapidly progressive glomerulonephritis two weeks after having developed the Stevens–Johnson syndrome due to TMP–SMX used for the treatment of a toe infection, which was secondary to biopsy-proven pauci-immune crescentic glomerulonephritis with nonreactive anti-neutrophilic cytoplasmic antibodies. We review the existing literature on the association between these two disorders.

Case report

A 60 year old morbidly obese man with known hypertension, hyperlipidemia, atrial fibrillation (on warfarin therapy), stroke and alcoholic cirrhosis with prior hepatitis B virus infection was prescribed TMP–SMX orally for a toe infection. Five days later, he presented to an outside hospital with a rash and blisters over his lower extremities, and was diagnosed with the Stevens–Johnson syndrome. He was hospitalized at a Burn center for 10 days. At the time of his presentation to the Burn center, the serum creatinine was 1.4 mg/dL with an estimated GFR of 52 mL/min/

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1.73 m², and at time of discharge, it was 1.3 mg/dL with an estimated GFR of 59 mL/min/1.73 m². One week later, he presented to an outside hospital complaining of a two-day history of gross hematuria. The urinalysis and automated sediment revealed 3+ blood and 3+ protein with >50 red blood cells/high-power field. The serum creatinine was up to 1.9 mg/dL. He underwent a CT scan of the abdomen and pelvis without radiocontrast, which was negative for nephrolithiasis. The hematuria was initially ascribed to a supratherapeutic INR of 3.5, and he was discharged home. Five days later, he presented back to the hospital with worsening dyspnea, persistent hematuria and decreased urine output. He had noted an 8-kg weight gain over the prior two weeks. He denied taking non-steroidal anti-inflammatory drugs. He was hypoxemic with an oxygen saturation of 70 % on room air. Vital signs were otherwise unremarkable. He weighed 130.6 kg with a body mass index of 41 kg/m². On examination, he had diffuse rales over both lung fields and had significant bilateral lower extremity pitting edema. The chest X-ray revealed pulmonary vascular congestion consistent with pulmonary edema. The blood urea nitrogen and serum creatinine were 103 and 11.8 mg/dL, respectively, and the serum potassium was 7 mEq/L. The urinalysis revealed large blood and 2+ protein with greater than 50 red blood cells/high-power field. Urine eosinophils were negative. A random urine protein-to-creatinine ratio was 5.3 g/g. He underwent emergent hemodialysis for the severe hyperkalemia in the setting of acute kidney failure. Due to concerns of rapidly progressive glomerulonephritis, the patient underwent an extensive serological work-up that was unrevealing, including negative ANA screen, normal serum complement levels, nonreactive hepatitis B surface antigen, reactive anti-hepatitis B core antibody with undetectable hepatitis B DNA titer, nonreactive anti-hepatitis C virus antibody, nonreactive anti-neutrophilic cytoplasmic antibodies (ANCA) (both anti-proteinase 3 and anti-myeloperoxidase antibody), nonreactive anti-glomerular basement membrane antibody, and nonreactive anti-DNase and anti-streptolysin D antibody. A kidney ultrasound revealed no hydronephrosis. He underwent multiple hemodialysis sessions. On day 4, he underwent a kidney biopsy, which revealed crescentic glomerulonephritis with pauci-immune cellular crescents present in 45 % of the viable glomeruli (Fig. 1a–d). Light microscopy consisted of 37 glomeruli, of which 1 was globally sclerosed, 1 glomerulus showed segmental sclerosis, and some glomeruli were slightly hypoperfused. Proliferative changes with or without focal fibrinoid necrosis of the tuft were observed in 16 glomeruli. The non-involved segments revealed normal thickness and texture of glomerular capillary loops with only segmental wrinkling. The ANCA screen was repeated and confirmed to be negative. He was treated with a pulse dose of

Fig. 1 Kidney biopsy findings of pauci-immune crescentic glomerulonephritis and time course of disease. **a** Top right and bottom left glomeruli contain small cellular crescents with fibrinoid necrosis. Tubules reveal evidence of acute injury with distention by red blood cells and cellular debris (PAS stain, $\times 100$). **b** A cellular crescent with fibrinoid exudate in the extracapillary space and compression of the glomerular tuft (PAS stain, $\times 400$). **c** No significant reactivity for immunoglobulin G is seen on direct immunofluorescence microscopy ($\times 400$). **d** Time course of the serum creatinine and daily urine output over the course of the hospitalization. Solid line indicates the serum creatinine (mg/dL), and hatched line indicates the daily urine output

methylprednisolone (1000 mg) intravenously daily for three days followed by oral prednisone 100 mg once daily. On day 10, he was transferred to our hospital for consideration of plasmapheresis as an adjunctive therapy. Oral cyclophosphamide 150 mg once daily was added to his immunosuppressive regimen. On day 12, he was initiated on plasmapheresis, and received five sessions with no improvement in his kidney function. Figure 1d displays the serum creatinine values over the hospital course of therapy with hemodialysis, immunosuppressive therapy and

plasmapheresis. On day 17, he was discharged to a long-term acute care facility, dialysis dependent, on a course of prednisone 80 mg daily, cyclophosphamide 125 mg daily, and atovaquone 750 mg daily (for prophylaxis against *Pneumocystis jiroveci* pneumonia), with the goal of tapering the immunosuppressive regimen. Unfortunately, 10 weeks later, he was hospitalized with febrile neutropenia and septic shock and expired. He was still dialysis dependent and remained on cyclophosphamide and prednisone.

Discussion

Worldwide, TMP–SMX is one the most widely used antibiotics for the treatment of a variety of bacterial infections, and it is featured on the World Health Organization's List of Essential Medicines [9]. Well known potential kidney-related adverse effects of TMP–SMX include SMX-induced acute allergic interstitial nephritis and crystal-induced acute tubular necrosis, TMP-induced hyperkalemia due to tubular sodium channel blockade, and spurious elevation in the serum creatinine due to inhibition of creatinine tubular secretion by TMP [4–8]. Drugs known to be associated with the development of pauci-immune crescentic glomerulonephritis include propylthiouracil, benzylthiouracil, methimazole, D-penicillamine, minocycline, ciprofloxacin, and hydralazine [10]. While most of the reported cases of drug-induced pauci-immune crescentic glomerulonephritis have a circulating ANCA, antibody positivity has not been observed for minocycline and D-penicillamine associated crescentic glomerulonephritis [11].

To our knowledge, we report the first case of TMP–SMX associated ANCA-negative, pauci-immune crescentic glomerulonephritis, likely representing drug-induced hypersensitivity polyangiitis. While a review of the literature identifies a rare association between TMP–SMX and the development of vasculitis, most published reports are old, focusing on sulfonamides, which include both antimicrobial and non-antimicrobial agents. In 1948, Van Rijssel and Meyler first described seven patients who presented with sulfonamide-associated necrotizing vasculitis and developed nephritis [12]. In 1962, Symmers described four cases of connective tissue disease, two cases of biopsy-proven polyarteritis, and two cases of thrombotic purpura associated with the use of sulfonamides [13]. In 1976, Wahlin and Rosman described a patient with nodular cutaneous vasculitis, affecting the small vessels of the dermis, which developed four days after initiating oral cotrimoxazole; these authors documented seven additional similar cases, but did not provide clinical details [14]. Although sulfonamides were originally incriminated in the

pathogenesis of polyarteritis nodosa, the Advisory Committee on Safety of Medicines has not substantiated this concern [14]. A recent review of drug-induced glomerular diseases documents case reports of ANCA-associated vasculitis following use of sulfadiazine with evidence of glomerulonephritis, and elevated anti-MPO, anti-DS DNA, and anti-lactoferrin antibody titers [15].

While the pathogenesis of drug-induced vasculitis is unknown, postulated mechanisms include the drug or a metabolite serving as hapten for the induction of auto-antibodies [16]. Our patient did not have circulating anti-MPO antibodies, however, the induction of other types of antibodies cannot be ruled out. Neutrophils are likely to play a major role in ANCA-negative pauci-immune crescentic glomerulonephritis. Neutrophil activation in this setting is accomplished by other auto-antibodies such as anti-endothelial cell antibodies [3]. Such antibodies were not measured in our patient. Circulating antibodies against lysosome-associated membrane protein 2 (LAMP-2) have also been found in 90 % of patients with pauci-immune crescentic glomerulonephritis [17]. A strong homolog has been found between a major epitope of the human LAMP-2 and an adhesion molecule found in Gram-negative bacteria, suggesting that bacterial infections in susceptible individuals might induce auto-antibodies, resulting in pauci-immune crescentic glomerulonephritis [17]. Our patient had a previous toe infection, which was confounded by the development of the Stevens–Johnson syndrome as a result of taking TMP–SMX, making this postulated mechanism less likely. We cannot rule out the possibility that the TMP–SMX-induced Stevens–Johnson syndrome might have triggered the crescentic glomerulonephritis.

Patients with ANCA-negative pauci-immune crescentic glomerulonephritis have a shorter interval from onset of disease to diagnosis, likely reflecting a more ‘fulminant’ form of kidney injury [18, 19]. Our patient experienced a rapid decline in kidney function and became soon after anuric (Fig. 1). No randomized controlled trials have been conducted for the treatment of patients with ANCA-negative pauci-immune crescentic glomerulonephritis. Treatment protocols are, therefore, usually based on those for patients who are ANCA-positive. Patients with ANCA-negative pauci-immune crescentic glomerulonephritis tend to have worse kidney outcomes compared to those with ANCA-positive disease [3, 4]. Our patient received pulse doses of corticosteroids, cyclophosphamide, and five plasmapheresis sessions; unfortunately, there was no meaningful improvement in his kidney function, and he remained dialysis dependent. Sepsis is a major predictor of survival in patients with pauci-immune crescentic glomerulonephritis [3]. This finding illustrates the need for early diagnosis and treatment. Delay in diagnosis likely resulted in more severe kidney disease in our patient, and

the more aggressive immunosuppressive treatment strategy likely resulted in a higher predisposition to a serious and potentially fatal infection.

In conclusion, to our knowledge, this is the first case reporting an association between the use of TMP–SMX and the development of ANCA-negative pauci-immune crescentic glomerulonephritis. A high index of suspicion for crescentic glomerulonephritis is required in patients with unexplained acute kidney injury in the setting of recent use of TMP–SMX.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

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