A case of sulphasalazine-induced DRESS syndrome with delayed acute interstitial nephritis

Jean-François Augusto1,2,3, Johnny Sayegh1, Amélie Simon1, Anne Croue4, Jean-Marie Chennebault5, Maud Cousin1,3 and Jean-François Subra1,3

1Service de Néphrologie-Dialyse-Transplantation, 2Service de Réanimation Médicale et Médecine Hyperbare, CHU Angers, F-49933, 3UPRES EA 3863, University of Angers, F-49035, 4Département de Pathologie Cellulaire et Tissulaire and 5Département de Maladie Infectieuses et Tropicales, CHU Angers, F-49933, Angers, France

Correspondence and offprint requests to: Jean-François Augusto; E-mail: jfaugusto@chu-angers.fr

Abstract
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a rare and severe drug-induced hypersensitivity syndrome characterized by haematological abnormalities (hypereosinophilia and/or mononucleosis) and multiorgan involvement. Renal failure has been rarely described. We report the case of a 77-year-old female with sulphasalazine-induced DRESS syndrome who improved rapidly on corticosteroid treatment. After prednisone withdrawal, the patient developed renal failure that necessitated a session of haemodialysis. A kidney biopsy showed acute tubulointerstitial nephritis with an intense lymphocytic infiltrate and tubular necrosis. Kidney function normalized after a further 2 weeks of corticosteroid treatment. This is the first histologically proven case of acute tubulointerstitial nephritis in the setting of sulphasalazine-induced DRESS syndrome.

Keywords: acute tubulointerstitial nephritis; DRESS syndrome; HHV-6; sulphasalazine

Introduction
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is a rare and severe drug-induced hypersensitivity reaction characterized by skin rash, fever, eosinophilia and organ involvement [1]. Hepatitis and pneumonitis are frequent visceral manifestations, while kidney involvement is uncommon and has been rarely described. We report a case of typical sulphasalazine-induced DRESS syndrome with delayed onset of renal involvement.

Case report
A 77-year-old women was admitted to hospital with fever (39°C), dyspnoea and a diffuse exanthematous maculopapular rash, 4 weeks after the initiation of sulphasalazine. The patient had no significant past medical history. She developed bilateral ankle pain resistant to an association of paracetamol (3 g/day) with tramadol (300 mg/day) 2 months before admission to hospital.
While no specific disease was identified, sulphasalazine (1.5 g/day) was initiated after a rheumatology consultation.

On admission, blood pressure was 120/70 mmHg and pulse 100/min. She had bilateral basal crackles on pulmonary auscultation and multiple axillary and cervical lymphadenopathies. Blood analysis showed leukocytosis (18.65 g/L), lymphocytosis (5.61 g/L) with hyperbasophilic cells, hypereosinophilia (2.24 g/L) and cytolytic hepatitis (ASAT 852 UI/L, ALAT, 1636 UI/L). BUN was 4.7 mmol/L, serum creatinine was 51 µmol/L and urine sediment was normal. IgM antibodies to HHV -6 and HHV -6 PCR were both positive. Blood cultures and serological tests for other viruses were all negative. A skin biopsy showed a marked infiltration of the dermo-epidermal junction with numerous lymphocytes and keratocytic necrosis (Figure 1).

The clinical and biological features were typical of sulphasalazine-induced DRESS syndrome. A treatment with 80 mg/day prednisone was started. Abnormalities resolved rapidly, and the patient was discharged from hospital. Prednisone was maintained for 20 days.

Two days after corticosteroid treatment withdrawal, the patient was readmitted for asthenia and dyspnoea. Clinical examination was normal. Laboratory investigations showed acute renal failure (BUN 43.5 mmol/L, serum creatinine 904 µmol/L). Urinalysis demonstrated haematuria, leucocyturia and tubular proteinuria of 0.6 g/day. Urine output was preserved. The white cell count was normal without eosinophilia or lymphocytosis. Kidney ultrasound was normal. IgM antibodies to HHV-6 PCR and HHV-6 PCR remained positive. ANA and ANCA were both negative. Despite rehydration, kidney function did not improve and a session of haemodialysis was administrated. The presentation was compatible with acute interstitial nephritis. Prednisone therapy was recommenced and a kidney biopsy was performed.

The anatomopathological study confirmed the diagnosis of acute tubulointerstitial nephritis (Figure 2): the tubules and interstitium showed marked interstitial oedema with an intense inflammatory infiltrate of lymphocytes and plasmocytes. Acute tubular necrosis was present with an infiltrate of polynuclear neutrophils and lymphocytes in the tubules. The immunofluorescence study did not show any specific deposits.

The patient has improved rapidly under corticosteroid treatment. Kidney function recovered progressively over
2 weeks (serum creatinine 67 µmol/L) without need of a further dialysis session.

Discussion

DRESS syndrome was proposed by Bocquet in 1996 to differentiate drug-induced hypersensitivity with haematological and visceral involvement from drug-induced pseudolymphoma [1]. Drug-induced pseudolymphoma has a more insidious onset and is limited to lymph nodes and skin while DRESS syndrome begins acutely during the first 2 months after the drug initiation. The DRESS syndrome has a mortality rate of around 10% mostly secondary to hepatic and pulmonary failure [2].

The pathophysiology of DRESS syndrome remains unclear. The prevailing hypothesis states that the causative drug induces hypersensitivity as a result of abnormalities in the production or in the detoxification of their active metabolites. The toxic effects of these metabolites on cells may trigger the immunological response [3]. An association of DRESS syndrome with HHV-6 reactivation has been reported [4]. HHV-6 reactivation seems to be specifically associated with DRESS syndrome unlike other drug reactions that do not show any increase in anti-HHV-6 antibodies [5]. Primary infection with HHV-6 is usually asymptomatic and occurs before the age of 2 years, and then the virus latently infects monocytes, lymphocytes and salivary glands [6]. The role of HHV-6 in DRESS syndrome is debatable. HHV-6 may act as a trigger of the auto-immune response by interfering with some of the enzymes responsible for drug detoxification.

DRESS syndrome has been reported to be associated with a limited number of drugs: phenytoin, carbamazepin, phenobarbital, dapsone, allopurinol, minocycline, ranitidine and sulphasalazine [1]. Sulphasalazine is a compound of sulphapyridine and 5-aminosalicylic acid (5-ASA). It exerts its therapeutic action primarily through the 5-ASA that is released following bacterial cleavage in the colon. Immunoallergic manifestations following sulphasalazine treatment have been called initially the ‘3-week sulphasalazine syndrome’, with some cases fulfilling the criteria of DRESS syndrome. Previously, it was thought that sulphapyridine was responsible for most of the adverse immunoallergic effects of sulphasalazine. However, reports of hypersensitivity reactions to sulphapyridine free sulphonamides (mesalazine, 5-ASA) have now largely been followed up [7]. Interestingly, there is no report of DRESS syndrome associated with these sulphapyridine-free components.

Nephrotoxicity to sulphasalazine is rare. In a recent retrospective analysis of adverse reactions to sulphasalazine and mesalazine, there were 29 mesalazine-associated acute interstitial nephritis cases, while none were reported with sulphasalazine [7]. Two cases of chronic interstitial nephritis have been reported in patients who have been under sulphasalazine treatment for several years [8]. Only one other case of sulphasalazine-induced DRESS syndrome with kidney involvement has been reported. The patient has developed multiorgan failure with fulminant hepatitis and late kidney failure. Post-mortem histopathology of kidneys showed focal tubulo-interstitial nephritis [9].

In our case, kidney failure developed secondarily when corticosteroid treatment was stopped. We did not observe concomitantly any recurrence of the typical haematological abnormalities of DRESS syndrome. The patient was not treated with any other drugs known to induce interstitial nephritis. Virology screens of other viruses except HHV-6 were negative. Interestingly, HHV-6 has also been studied in renal transplant recipients and can infect renal tubular cells but its pathogenic role is debated [10]. In our case, the lack of viral inclusions on kidney biopsy and the improvement under corticosteroid treatment argue against a direct implication of HHV-6.

The treatment of DRESS syndrome remains empirical. The suspected drug should be stopped immediately. Corticosteroid treatment with gradual withdrawal is proposed in severe forms. As showed in the present case, rapid tapering often causes relapses [1].

In conclusion, we report the first case of acute tubulo-interstitial nephritis in the context of sulphasalazine-induced DRESS syndrome associated with HHV-6 reactivation. Renal lesions have no specific feature. As proposed by other authors, this case supports that corticosteroid treatment should be maintained for a long period to avoid relapses [1].

Conflict of interest statement. None declared.

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Received for publication: 22.3.09; Accepted in revised form: 19.5.09