Journal of Crohn's and Colitis (2011) 5, 457–460

available at www.sciencedirect.com

ScienceDirect

SHORT REPORT

Stevens–Johnson syndrome with sulfasalazine treatment: Report of two cases

Lydjie Tremblay[a,b,*], Guillaume Pineton de Chambrun[b], Bénédicte De Vroey[b], Céline Lavogiez[c], Emmanuel Delaporte[b], Jean-Frédéric Colombel[b], Antoine Cortot[b]

[a] *Pharmacy Department, Centre hospitalier de l'Université de Montréal, Montréal, Canada*
[b] *Gastroenterology Department, Claude Huriez Hospital, Lille University Hospital, Lille, France*
[c] *Dermatology Department, Claude Huriez Hospital, Lille University Hospital, Lille, France*

Received 17 December 2010; received in revised form 25 March 2011; accepted 26 March 2011

KEYWORDS
Sulfasalazine;
Ulcerative colitis;
Stevens–Johnson syndrome;
Side effects

Abstract

We report two cases of Stevens–Johnson syndrome (SJS) associated with the use of sulfasalazine in two ulcerative colitis patients previously tolerant to mesalamine. SJS and toxic epidermal necrolysis (TEN) are very rare adverse cutaneous reactions that can be associated with the use of sulfasalazine. The most severe cases can result in death, and for the others, permanent skin, mucosal or ocular sequelae, which can impair the quality of life in our young IBD patients. Clinicians and patients need to be aware of the signs and symptoms that often precede the appearance of the mucocutaneous lesions in a SJS or TEN, such as fever, influenza-like symptoms, sore throat or burning eyes. For patients with SJS or TEN, immediate withdrawal of the offending medication should be done when blisters or erosions appear in the course of a drug eruption, as this may improve the prognosis.

1. Introduction

Sulfasalazine has been used for over 40 years for the treatment of ulcerative colitis (UC).[1,2] Despite its proven benefits in UC, the usefulness of sulfasalazine is limited by side effects. Exceptionally, adverse skin reactions to sulfasalazine can manifest as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The incidence of SJS and TEN ranges from 0.4 to 1.2, and 1.2 to 6 per million person-years respectively.[3] In spite of the long experience with the use of sulfasalazine, there are only eight cases published in the English and French literature, linking its use

* Corresponding author at: Centre hospitalier de l'Université de Montréal, 1058, Saint-Denis, Montréal, Canada H2X3J4. Tel.: +1 514 890 8000x14886; fax: +1 514 343 2102.
E-mail address: lydjie.tremblay@umontreal.ca (L. Tremblay).

1873-9946/$ - see front matter © 2011 Published by Elsevier B.V. on behalf of European Crohn's and Colitis Organisation.
doi:10.1016/j.crohns.2011.03.014

with SJS or TEN.[4–9] We report here two cases of SJS related to the administration of sulfasalazine in patients with UC previously tolerant to mesalamine.

2. Case reports

Patient 1, a 36-year-old woman, was hospitalized, on September 18th, 2008, for a mucocutaneous reaction suspected to be a SJS. She had been diagnosed with UC in 1996 and was initially treated with mesalamine (Pentasa 3 g/day) and thereafter with corticosteroids. She was referred to our center in October 2000 because of a corticodependant, moderately active UC for which azathioprine was initiated but quickly discontinued due to gastrointestinal intolerance. The patient had a mild flare of her UC in December 2000 which responded to a short course of local and systemic steroids. Mesalamine was continued (3 g/day) and corticosteroids were completely withdrawn in the same month. The patient was then maintained in complete clinical remission with mesalamine alone (2 g/day) until January 2006. Then, as well as in 2008 she presented flares of UC accompanied with peripheral arthropathy diagnosed as UC associated spondylarthropathy. Both of these episodes responded to short courses of corticosteroids. Because of debilitating joint pain, mesalamine was replaced by sulfasalazine 1 g×3/day on September 2nd, 2008.

Eleven days after the introduction of sulfasalazine, the patient developed a painful enanthema of the mouth associated with cervical lymphadenopathy, fever and chills. A diagnosis of pharyngitis was made by a general practitioner, which was treated with telithromycin. The patient also had erythematous and erosive vulvar lesions for which a topical treatment with econazole was prescribed for a presumed vaginal candidiasis. On September 16th, she presented to Emergency because she had developed a morbiliform erythema on the upper trunk and arms with persisting vulvar pain. An allergy to telithromycin was suspected and the drug was changed to amoxicillin–clavulanate and she was sent home. Two days later, the patient returned to the Emergency room for a widespread maculo-papular rash (Fig. 1) with persisting oral and vulvar lesions and the appearance of ocular lesions. She was also complaining of odynophagia with a feeling of lingual and laryngopharyngeal swelling. She had no dyspnea. All medications were immediately discontinued and the patient was admitted to the dermatology unit for a suspected sulfasalazine-induced SJS.

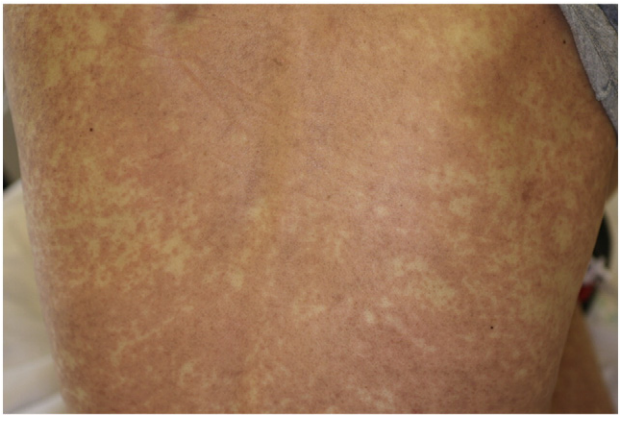

Figure 1.

On admission, she had fever (38.4 °C), but was hemodynamically stable. Other than the previously described cutaneous lesions, the physical exam was normal. Laboratory tests revealed a CRP level×20 N, normal leukocyte (6290/mm^3) and platelet counts (335 000/mm^3). Her hemoglobin level was 8.9 g/dL due to a known previous chronic microcytic anemia. Bacterial and viral infections were ruled out. On September 19th, the morbiliform rash persisted. Nikolsky's sign (minor pressure induces skin separation characteristic of SJS) was positive on the upper trunk and flaccid blisters observed on the left forearm. Skin detachment occurred on less than 10% of the body surface. Further examination revealed a cheilitis with oral and vaginal mucosal erosions and a bilateral pseudo-membranous conjunctivitis and keratitis.

Under symptomatic treatment, mucosal and skin lesions stabilized on day 2 and gradually regressed allowing the patient to be discharged from the hospital on day 8.

Patient 2, a 19-year-old woman, was admitted on March 16th, 2005 for a severe gingivostomatitis. She had been diagnosed with UC in 2000 and treated with aminosalicylates alone (Pentasa 4 g/day tapered to and then 2 g/day). She experienced an acute severe flare of UC in 2001 refractory to intravenous corticosteroids but responsive to cyclosporine and later to azathioprine (2 mg/kg) and mesalamine (Pentasa 2 g/day) as maintenance treatment. The UC remained quiescent but the patient developed recurrent UC-related debilitating arthralgias which led to the replacement of mesalamine by sulfasalazine 1 g×2/day on February 20th, 2005.

Twenty-one days later, (on March 13th), non-umbilicated, non-clustered vesicular lesions appeared on her lips which extended to the whole oral cavity. Sulfasalazine was stopped on the advice of the family physician who suspected a drug allergy. However, lesions worsened, leading to hospitalization three days later. Physical exam upon arrival noticed fever (38.3°), stable hemodynamic parameters, multiple hemorrhagic fibrinoid ulcerations on the lips and tongue, and no lymphadenopathy. A conjunctivitis and a gingivostomatitis were present on examination which were associated with dysphagia and odynophagia indicating a pharyngeal involvement. The cutaneous exam revealed macular and papular palmar lesions and purpuric macular lesions on the trunk. Intravenous acyclovir 5 mg/kg every 8 h was started and azathioprine was discontinued because of a suspected herpetic infection in an immunocompromised patient. Laboratory tests revealed a CRP 1×N, mild leukocytosis (10 700/mm^3), normal platelet count (450 000 mm^3) and a hemoglobin level of 12 g/dL. The chest X-ray was unremarkable.

With such a severe gingivostomatitis, both erythema multiforme caused by a primary herpetic infection, or SJS caused by sulfasalazine were considered as possible diagnoses. Erythema multiforme was ruled out on the basis of negative serology and mouth swab culture for herpes simplex 1 and 2 (IgG and IgM negative serologies on days 0, 8 and 21), and negative serology for *Mycoplasma pneumoniae*. The diagnosis of SJS caused by sulfasalazine was made. The outcome was favorable with improvement of the lesions following symptomatic treatment allowing the patient to be discharged from the hospital on day 9.

3. Discussion

SJS and TEN are acute, life-threatening medical conditions.[10] Most cases of TEN are drug-induced. SJS is caused by drugs in about half of the cases. Infections or combination of infections and drugs have also been implicated.[3,10] With both conditions, symptoms typically begin 1 to 3 weeks after the initiation of the causative medication.[3] The delay between the drug exposure and the appearance of the lesions in both cases reported here, 11 days and 21 days respectively, is consistent with what has been reported in the literature, providing further support of sulfasalazine involvement. Furthermore, other possible etiologies, including infections or other potential causative drugs were excluded. The clinical presentations of SJS and TEN are characterized by fever and influenza-like symptoms unexplained by infectious illness that often precede the cutaneous and mucosal lesions (present in about 90% of patients) by 1 to 3 days.[3]

The characteristic mucosal involvement of SJS was present in both patients, and in the case of the first patient included a positive Nikolsky's sign. With the second patient, the hemorrhagic ulcerations of the lips and tongue were also characteristic of SJS lesions. The first patient had a skin detachment of less than 10% which is also compatible with SJS.[3]

In the case of the first patient, delayed recognition of sulfasalazine induced SJS, despite the presence of a morbiliform rash and vulvar involvement, resulted in a more severe reaction. With the second patient, sulfasalazine was discontinued at the first sign of vesicular lesions on the lips. Thus vigilance is required during clinical assessment, since the signs of SJS and TEN can include flu-like symptoms, oral lesions, dysphagia, or vulvar signs, all of which may lead to erroneous diagnosis. The primary interventions when SJS or TEN is suspected are early recognition and immediate cessation of any potential causative agents and to provide supportive treatment in an appropriate clinical setting. Prompt withdrawal of the drug suspected to have caused the SJS or TEN may reduce mortality and should be done at the first sign of mucosal involvement.[11] The withdrawal of sulfasalazine was followed by the gradual disappearance of lesions and complete recovery without sequelae in both patients.

In patient 1, mesalamine was not reintroduced, whereas it was with patient 2 without further side effects. In both patients, mesalamine treatment received before switching to sulfasalazine was well tolerated, strongly suggesting that the sulfonamide component of sulfasalazine, not the 5-ASA moiety, was responsible for the cutaneous reaction observed.

Two cases of UC patients with suspected 5-ASA induced TEN have been reported in the literature.[12,13] The first case reported by Iemoli et al. is compatible with a TEN caused by balsalazide.[12] The clinical presentation of the second case, reported by Fukunaga et al., does not convince us of the presumed diagnosis of TEN induced by mesalamine.[13]

Clinicians and patients need to be aware of the signs and symptoms that often precede the appearance of the mucocutaneous lesions in a SJS or TEN. These include fever, influenza-like symptoms, sore throat or burning eyes. Prompt intervention in the early course of the disease may improve the prognosis. Patient education is of the utmost importance after an episode of SJS and TEN. It is imperative that the patient be aware of the causative drug, and of other chemically related drugs that have the potential to cross-react with sulfonamide and potentially with sulfasalazine.

Identification of predisposing HLA subtypes could help to predict rare allergic severe adverse cutaneous reactions, such as SJS or TEN, to sulfonamides or other drugs. Studies done in Asian patients have demonstrated an association between specific HLA subtypes, and SJS/TEN induced by allopurinol and carbamazepine.[14,15] However, these findings could not be reproduced in European studies.[16] Ethnicity seems to play an important role in the genetic predisposition to severe adverse cutaneous reactions to drugs.[17] Thus, it is uncertain if pharmacogenomics will help to predict those rare hypersensitivity reactions, at least in the Caucasian population. For now, immediate cessation of drugs suspected to cause SJS or TEN remains the most important measure in clinical practice.

References

1. Baron JH, Connell AM, Lennard-Jones JE, Jones FA. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet* 1962;**1**:1094–6.
2. Misiewick JJ, Lennard-Jones JE, Connell AM, Baron JH, Jones FA. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. *Lancet* 1965;**1**:185–8.
3. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;**331**:1272–85.
4. Ström J. Toxic epidermal necrolysis (Lyell's syndrome). A report on four cases with three deaths. *Scand J Infect Dis* 1969;**1**: 209–16.
5. Maddocks JL, Slater DN. Toxic epidermal necrolysis, agranulocytosis and erythroid hypoplasia associated with sulphasalazine. *J R Soc Med* 1980;**73**:587–8.
6. Pearl RK, Nelson RL, Prasad ML, Orsay CP, Abcarian H. Serious complications of sulfasalazine. *Dis Colon Rectum* 1985;**29**: 201–2.
7. Jullien D, Wolkenstein P, Roupie E, Roujeau JC, Revuz J. Toxic epidermal necrolysis after sulfasalazine treatment of mild psoriatic arthritis: warning on the use of sulfasalazine for a new indication. *Arthritis Rheum* 1995;**38**:573.
8. Martin L, Hazouard E, Michalak-Provost S, Maurage C, Machet L. Épithéliolyse respiratoire toxique fatale. Desquamation suraiguë trachéo-bronchique lors d'un syndrome de Stevens–Johnson. *Rev Pneumol Clin* 2001;**57**:297–301.
9. Borras-Blasco J, Navarro-Ruiz A, Matarredona J, Devesa P, Montesinos-Ros A, Gonzalez-Delgado M. Photo-induced Stevens–Johnson syndrome due to sulfasalazine therapy. *Ann Pharmacother* 2003;**37**:1241–3.
10. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, Mockenhaupt M, Paoletti C, Shapiro S, Shear N, Schöpf E, Kaufman DW. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;**33**:1600–7.
11. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens–Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000;**136**:323–7.
12. Iemoli E, Piconi D, Ardizzone S, Bianchi Porro G, Raimond F. Erythroderma and toxic epidermal necrolysis caused by 5-aminosalicylic acid. *Inflamm Bowel Dis* 2006;**12**:1007–8.
13. Fukunaga K, Ohda Y, Inoue T, Kono T, Miwa H, Matsumoto T. Toxic epidermal necrosis associated with mesalamine in a patient with ulcerative colitis. *Inflamm Bowel Dis* 2007;**13**:1055–6.

14. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CSJ, Wu JY, Chen YT. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A* 2005;**102**:4134–9.
15. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. A marker for Stevens–Johnson syndrome. *Nature* 2004;**428**:486.
16. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, Bouwes-Bavinck JN, Sidoroff A, de Toma C, Schumacher M, Roujeau JC, Hovnanian A, Mockenhaupt M. A European study of HLA-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;**18**:99–107.
17. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, Graf E, Schumacher M, Hovnanian A, Mockenhaupt M, Roujeau JC. A marker for Stevens–Johnson syndrome…: ethnicity matters. *Pharmacogenomics J* 2006;**6**:265–8.