DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME) ASSOCIATED WITH SULFASALAZINE AND HUMAN HERPESVIRUS 6 INFECTION SUCCESSFULLY TREATED WITH STEROID THERAPY

DRESS SYNDROME ASSOCIE A LA PRISE DE SULFASALAZINE ET A UNE INFECTION A HERPESVIRUS HUMAIN QUE 6 INFECTION TRAITE AVEC SUCCES PAR UNE CORTICOTHERAPIE.

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Summary

We report a case of a 30-year-old man who developed a generalized erythematous skin eruption, fever, lymphadenopathy, hepatic cytolysis and eosinophilia probably due to sulfasalazine. Indirect immunofluorescence assay for Human herpesvirus-6 (HHV-6) was positive, supporting recent HHV-6 infection. The patient was successfully treated with dexamethasone.
The case is reported with a review of the literature. DRESS syndrome mechanisms and management are also discussed.

Keys words : DRESS syndrome – sulfasalazine – HHV6

Résumé

Nous rapportons l'observation d'un homme âgé de 30 ans qui a développé une éruption érythémateuse généralisée accompagnée de fièvre, d'adénopathie, de cytolyse hépatique et d'éosinophilie secondaire à la prise de sulfasalazine.
L'immunofluorescence indirecte pour herpesvirus-6 Humain (HHV-6) était positive en faveur d'une infection récente à HHV-6. Le malade était par la déxaméthasone avec une évolution favorable.
A partir d'une revue de la littérature, nous discutons les mécanismes et les modalités thérapeutiques de ce syndrome.

Mots clés : DRESS syndrome – sulfasalazine –HHV6

INTRODUCTION

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an acute and a potentially fatal multiorgan-system reaction characterized by fever, rash, lymphadenopathy, eosinophilia and hepatitis [1]. The syndrome typically begins within 2-6 weeks after initiation of a number of different drugs [2]. This long interval between drug introduction and onset is characteristic. Antiepileptic drugs and sulphonamides are the most common cause [1]. But many other drugs have been associated with DRESS syndrome, including sulfasalazine, allopurinol, dapsone, trimethoprim, minocycline, metronidazole, nevirapine and abacavir [3]. Human herpesvirus-6 (HHV-6) has been suggested to be involved in this syndrome [2, 4-6].

We report herein a new case of DRESS syndrome associated with HHV-6 infection with a favorable evolution following withdrawal of sulfasalazine and corticoid therapy. Based on a literature review, the role of HHV-6 infection and the management of this syndrome are discussed.

CASE REPORT

A 30-year-old man was admitted because of fever and cutaneous rash. History of ankylosing spondylitis treated by anti-inflammatory drugs has occurred two years earlier. There was no history of allergy neither recent travel nor exposure to sick persons. Twenty-five days before admission, patient received sulfasalazine (2g twice a day), indomethacine (100 mg twice a day) and paracetamol (1.5g per day) for bilateral sacroiliitis.

Arthritis has disappeared, but twelve days after, fever and vomiting developed with worsening epigastric pain and myalgias. Indomethacine and paracetamol doses were reduced. Two days later, cutaneous rash developed.

Initial physical examination, while sulfasalazine was continued, showed a temperature at 39.5°C, the pulse rate was 95 beats /mn, the breathing rate was 16/mn and the blood pressure was 130/70 mm Hg. A generalized maculopapular rash and edema with pustular lesions of the face were observed (Figure 1).

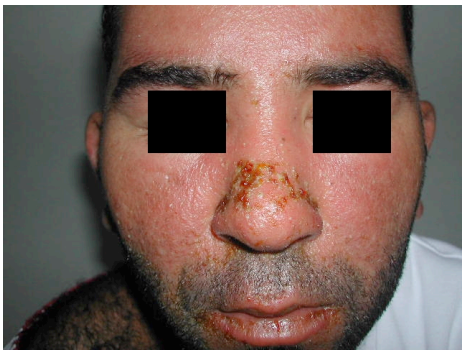

Figure 1: Maculopapular Erythematous and Pustular lesions and marked facial Edema

Firm, 2 to 4 cm size, lymph nodes were present in the cervical, axillary and inguinal regions. The neurological, cardiac, pulmonary and abdominal examinations were normal. White blood cell count was 22.2 × 10^9/L with 53% lymphocytes, 26.3% neutrophils, 12.9% eosinophils, 7.6% monocytes and 0.2% basophils. The platelet count, hemoglobin level, erythrocyte sedimentation rate and C reactive protein level were normal. Alanine aminotransferase level was 694 U/L (normal < 37 U/L), aspartate aminotransferase level was 423 U/L (normal < 35 U/L), prothrombin time was 86%, bilirubin, alkaline phosphatase and cholesterol levels were normal. Lactate deshydrogenase level was 1506 U/L (normal 100 to 190 U/L). Creatine kinase, creatinine, sodium, potassium, calcium levels and serum protein electrophoresis were normal. Blood and stool cultures were negative. Serologic tests for hepatitis viruses (A, B and C), HIV, EBV, CMV, parvovirus B19, *brucella* and *Toxoplasma gondii* were negative. Indirect immunofluorescence assay showed a positive anti-HHV-6 IgM and IgG, supporting a recent HHV-6 infection. Lymph-node biopsy revealed para-cortical histiocytosis and reactive plasmocytosis with no sign of malignancy. Skin biopsy showed diffuse spongiosis of the epidermis with numerous apoptotic bodies and peri-vascular inflammatory infiltrate in the dermis. These findings are commonly described in DRESS syndrome.

Sulfasalazine was discontinued and therapy with dexamethasone 4 mg twice daily was started. Within 6 days, apyrexia was obtained and skin lesions resolved with desquamation 3 days after. Aminotransferases, lactate dehydrogenase levels and eosinophile count became normal 22 days after. Steroid dose was reduced gradually since the second week and discontinued after 4 weeks. Ten months later, the clinical outcome was favorable and anti-inflammatory drugs, including indomethacine and paracetamol were continued as long-term treatment for ankylosing spondylitis.

DISCUSSION

The etiopathogeny of DRESS syndrome remains unclear. Recent studies have provided evidences suggesting that HHV-6 is implicated in the pathogenesis of the DRESS syndrome [7]. It is similar to the rush induced by administration of ampicillin during *Epstein-Barr virus* infection and also similar to the increased frequency of drug eruptions in individuals infected with human immunodeficiency virus [2, 3, 8].

There were reasonable doubts about the role of HHV-6 in DRESS syndrome. Indeed, HHV-6 activity may be considered as an epiphenomenona and a result of the DRESS syndrome. This is supported by the high seroprevalence of HHV-6 infection in adults (more than 95%), its latency (which may complicate result interpretation of diagnostic assays) [9], the presence of HHV-6 IgM in approximately 5% of healthy adults [9] and a proven HHV-6 reactivation in 54% to 65% of critically sick patients, without apparent effect on these patient morbidity neither mortality [8]. Recently, Kano and *al*. [7], demonstrated that HHV-6 reactivation was observed in DRESS syndrome and not in other severe adverse drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. This provides evidence to indicate that HHV-6 is implicated in the pathogenesis of the DRESS syndrome. Hashimoto and *al*. [2] suggest that DRESS syndrome include two clinical parts : the first is due to drug reaction and the second to HHV-6 reactivation. The latter explains the slow resolution and relapses observed in the DRESS syndrome. In our patient and in few others reported cases [6, 10, 11], the presence of IgM antibodies suggests a primary infection. However, a reactivation cannot be excluded in this situation [10].

Other virus have been recently associated with DRESS syndrome including cytomegalovirus and *Epstein-Barr virus* [8]. Therefore, looking for such viral infection should be considered.

The management of DRESS syndrome consists of the discontinuation of the causative drug for

lifelong. The use of systemic corticosteroids remains controversial [1]. Beyond the risk of septic complications and relapses after arrest, their use may lead to activation of HHV-6 or other viruses. In spite of this, corticotherapy have been used successfully in cases of DRESS syndrome with confirmed HHV-6 infection similar to our case [5, 12]. One explanation of this finding might be that the corticosteroid suppresses an excessive immune response to the causative drug. The failure of corticosteroids, specially after arrest, have been reported, with development of acute renal and cardiac failure, fulminant type1 diabetes mellitus and encephalitis [2].

A success of intravenous immunoglobulin containing high HHV-6 IgG titers have been reported in few cases [7]. This result should be confirmed by others studies.

The use of antiviral drug such as ganciclovir and valaganciclovir may be effective [5, 10]. We think that their association with corticosteroids should be considered in the management of DRESS syndrome even before performing the diagnosis of HHV-6 infection.

In conclusion, further studies are necessary to clarify the exact role of HHV-6 as well as other viruses, in the pathogenesis of DRESS syndrome. The interruption of the incriminated drug is the only undisputed way in its management.

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