

CASE REPORT

CASO CLINICO

Sulphasalazine-induced DRESS: a case report

DRESS da sulfasalazina: un caso clinico

M. ISPANO, L. CAMOZZI, R. ANSALONI, S. MOSCA, A. CIOFFI*, S. CANTONI

Azienda Ospedaliera "Ospedale Niguarda Ca' Granda", Milano; * Cattedra di Allergologia e Immunologia Clinica, Università "Federico II" di Napoli

Key words

DRESS • Eosinophilia • Sulphasalazine

Parole chiave

DRESS • Eosinofilia • Sulfasalazina

Summary

Drug Hypersensitivity Syndrome, also known as Drug Rash with Eosinophilia and Systemic Symptoms, is a potentially life-threatening drug-related syndrome characterized by fever, skin rash and systemic involvement. Prompt diagnosis is vital, in order to identify and immediately withdraw the offending drug. The present report describes a case of sulphasalazine – induced Drug Rash with Eosinophilia and Systemic Symptoms occurring in a 33-yr old caucasian man.

Riassunto

La Drug Rash with Eosinophilia and Systemic Symptoms è una sindrome correlata all'assunzione di farmaci, potenzialmente fatale, caratterizzata da febbre, eruzione esantematica e coinvolgimento sistemico. Una diagnosi tempestiva è di vitale importanza per permettere l'identificazione del farmaco responsabile e la sua immediata sospensione. In questo articolo è descritto un caso di Drug Rash with Eosinophilia and Systemic Symptoms correlato all'assunzione di sulfasalazina.

Introduction

Drug Hypersensitivity Syndrome (DHS), also known as *Drug Rash with Eosinophilia and Systemic Symptoms* (DRESS), is a severe, idiosyncratic systemic reaction defined by the clinical triad of fever, skin rash and systemic involvement (e.g. reactive hyperplasia of lymphoid tissues, hepatitis, myocarditis, nephritis or pneumonitis), which may develop 1 to 8 weeks after exposure to several drugs¹. Allopurinol, anticonvulsants (particularly carbamazepine, phenobarbitone and phenytoin) and sulphonamides are among the most frequent causative agents¹⁻³. Fever is a common early feature, usually preceeding a widespread and long-lasting papulopustular or erythematous skin eruption, which often progresses to exfoliative dermatitis. The severity of skin lesions does not correlate with the extent of systemic involvement, which may range from minimal to life-threatening¹. Eosinophilia and atypical lymphocytosis are common, occurring in up to 30% of cases.

DRESS mortality is estimated at around 8%². Consequently, in patients presenting with fever and skin rash, developing within few weeks from the beginning of a new drug treatment, blood tests to demonstrate eosinophilia and alterations secondary to end

organ involvement should be performed as soon as possible.

We report a case of sulphasalazine – induced DRESS in a 33-year-old white male presenting with fever, maculopapular rash, acute hepatitis, and haematological abnormalities.

Sulphasalazine is a compound consisting of sulphapyridine and 5-aminosalicylic acid⁴. The drug is administered orally in several inflammatory diseases, including rheumatoid arthritis, seronegative arthritis and inflammatory bowel disease.

Case report

A 33-yr-old caucasian man, immigrant from Turkey, was admitted to the Emergency Department with a 2 day history of sudden onset, generalized erythematous rash, fever (38.5 °C) and rhinopharyngitis. The patient reported a ten year history of rheumatoid arthritis; no medical record of previous treatment for this condition was available. Two months before admission the patient was seen at our hospital for an episode of anterior uveitis, and a diagnosis of HLA-B27+ seronegative spondyloarthropathy was made. Sulphasalazine 500 mg/day and prednisone 25 mg/day were

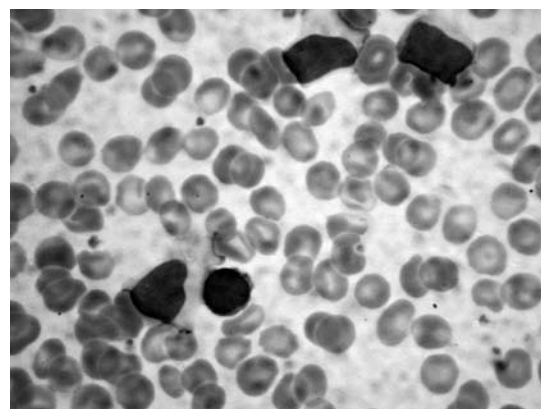
prescribed, which the patient had started three weeks prior to development of the skin rash. Both drugs were discontinued by the patient: prednisone approximately 10 days before admission for unspecified reasons and sulphasalazine 2 days before admission when skin rash developed.

On admission physical examination revealed extensive maculopapular skin rash, painful multiple bilateral cervical lymph nodes, rhinopharyngitis and hepatosplenomegaly. Blood test revealed leukocytosis ($16.5 \times 10^9/L$) and abnormal liver function tests. Chest X-ray was normal. He was treated with methylprednisolone 100 mg i.v. prior to be transferred to the ward.

The following day white cell count increased to $28.9 \times 10^9/L$ and differential count revealed lymphocytosis ($16.2 \times 10^9/L$), monocytosis ($3.2 \times 10^9/L$) and a neutrophil count to the upper limit of normal ($9.2 \times 10^9/L$). Eosinophils were within normal limits. Blood tests revealed a mild elevation of the erythrocyte sedimentation rate (13 mm/hr), increased C reactive protein (2.94 mg/dl; normal range 0-0.5 mg/dl), increased alanine aminotransferase (184 U/L; normal range 3-45 U/L), aspartate aminotransferase (64 U/L; normal range 0-40 U/L), total bilirubin (1.67 mg/dl; normal range 0.25-1 mg/dl), alkaline phosphatase (369 U/L; normal range 50-250 U/L) and gamma-glutamyltranspeptidase (107 U/L; normal range 2-50 U/L). Serum levels of C3 and C4 were normal. Serology was not diagnostic for acute cytomegalovirus or Epstein Barr virus infection. Activated lymphocytes and monocytes were seen on peripheral blood smear; phenotypic analysis of peripheral blood mononuclear cells did not disclose evidence of monoclonality. Ultrasound abdominal examination confirmed hepatosplenomegaly, without lymphadenopathy.

Since the clinical picture was highly suggestive of a viral infection, on admission only supportive therapy was instituted and glucocorticoids were discontinued. However, over the following two days the clinical picture progressed: lymphadenopathy extended to axillar and inguinal nodes, the rash became exfoliative and extended to approximately 70% of body surface area, multiple oral ulcerations developed and fever reached $40^\circ C$. On day 6, blood count revealed an eosinophil count of $2.8 \times 10^9/L$ (normal range $0.00-0.45 \times 10^9/L$). A fine needle biopsy of two lymph nodes (retronuchal and inguinal) showed a picture of reactive hyperplasia; in situ hybridization for Epstein Barr virus was negative. A skin biopsy revealed a remarkable perivascular infiltrate of lymphocytes and eosinophils (Fig. 1). An adverse reaction to sulphasalazine was suspected and therapy with i.v. prednisolone (60 mg/day) was instituted with prompt improvement of the clinical picture: fever resolved on the third day of treatment; the rash resolved and blood leukocytosis, including hypereosinophilia, returned to

Fig. 1. Peripheral blood smear: presence of atypical mononucleosis-like lymphocytes compared with a single non activated lymphocyte.

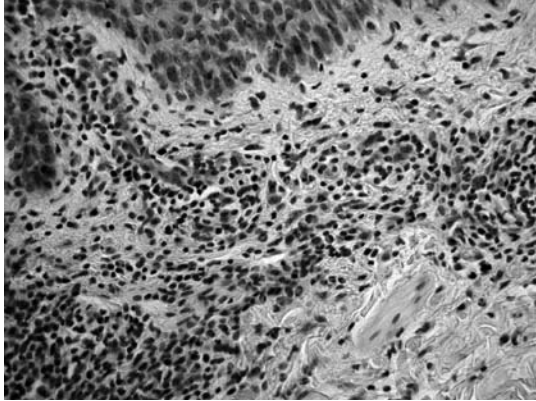


normal within one week. Liver function tests returned to normal values within 4 weeks.

Discussion

Hypersensitivity drug reactions can mimic several disorders and may present with involvement of various organ systems. Skin involvement is a common presentation of drug reaction: urticaria, measles-like rash, exfoliative dermatitis, nodules and purpura are frequently observed. Typically, an erythematous, maculopapular rash appears within one to three weeks after drug exposure, originates on the trunk, and eventually spreads to the limbs. Beside cutaneous involvement, hypersensitivity drug reactions may present with a non specific systemic inflammatory response, including fever, fatigue, nausea, vomiting and diarrhea. These signs and symptoms are rarely attributed to adverse drug reactions and often delay the diagnosis. The clinical picture of DRESS, for example, is not so distinctive to make possible a diagnosis at first glance. Clinical findings as skin rash, fever, lymphadenopathy and rhinopharyngitis orientate the diagnosis toward a viral infection, such as EBV or cytomegalovirus infection. To further complicate the picture, antibiotics such as ampicillin may cause an erythematous rash when administered to patients with EBV infection. DRESS is rarely caused by antibiotics and occurs 3 weeks to 3 months after the exposure to the offending drugs, while ampicillin-related rash in EBV infection generally occurs 2-10 days after ingestion of the drug. In our patient the negative serology and in situ hybridization on lymph node biopsy excluded an acute EBV infection. Interestingly, however, a link between DRESS and viral infections is strongly suggested by recent studies indicating a sequential

Fig. 2. Skin, punch biopsy. H&E stain. Inflammatory infiltrate made up of lymphocytes and macrophages mingled with many eosinophils. Mild exocytosis of lymphocytes. Note the absence of Civatte bodies. The finding is consistent with drug reaction.



reactivation of latent herpesviruses (such as EBV), occurring before and during the course of DRESS, as responsible of the syndrome itself⁵.

In our patient, differential diagnosis on admission included EBV infection, cutaneous lymphoma, vasculitis and adverse drug reaction. However, the

negative serology and in situ hybridization on lymph node biopsy excluded acute EBV infection. Lymphoma was unlikely given the result of skin biopsy and phenotypical characterization of the peripheral blood lymphocytes which excluded the presence of a monoclonal cell population. Skin biopsy ruled out the possibility of cutaneous vasculitis. Therefore, our final diagnosis in this patient was of sulphasalazine-induced DRESS presenting as maculopapular rash, liver involvement and haematological abnormalities. It is worth to emphasize that, in the clinical course of our patient, eosinophilia was not detected in the early phase of the reaction, possibly because high dose methylprednisolone had been administered prior to patient's transfer to the ward. The pharmacological effect of methylprednisolone may explain the early findings of the differential blood count: neutrophilia and normal eosinophil count. It is conceivable that the appearance of eosinophilia in this patient was delayed by steroid treatment.

Although sulphasalazine hypersensitivity is relatively rare^{6,7}, recognition of skin rash with fever and lymphadenopathy in our patient as signs of an adverse drug reaction allowed prompt discontinuation of sulphasalazine and treatment with corticosteroids that prevented further progression of DRESS and led to resolution of symptoms within two weeks.

References

- ¹ Sullivan JR, Shear NH. *The drug hypersensitivity syndrome: What is the pathogenesis?* Arch Dermatol 2001;137:357-64.
- ² Wolkenstein P, Revuz J. *Drug-induced severe skin reactions. Incidence, management and prevention.* Drug Safety 1995;13:56-68.
- ³ Brooks H, Taylor HG, Nichol FE. *The three week sulphasalazine syndrome.* Clinical Rheumatology 1992;11:566-8.
- ⁴ Watkinson G. *Sulphasalazine: a review of 40 years' experience.* Drugs 1986;32:1-11.
- ⁵ Shiohara T, Inaoka M, Kano Y. *Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses.* Allergol Int 2006;55:1-8.
- ⁶ Bocquet H, Bagot M, Roujeau JC. *Drug-induced pseudo-lymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS).* Semin Cut Med Surg 1996;15:250-6.
- ⁷ Mihas A, Goldenberg D, Slaughter R. *Sulphasalazine toxic reactions. Hepatitis, fever and skin rash with hypocomplementemia and immune complexes.* JAMA 1978;239:2590-1.