Severe form of Dress Syndrome treated with bolus corticotherapy

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Abstract

Drug hypersensitivity syndrome or DRESS is a drug reaction with eosinophilia and systemic symptoms. The prescription of systemic corticosteroids has been proposed in case of visceral involvement with the possibility of corticosteroid bolus in the presence of severe signs of DRESS. We report the case of a patient who developed DRESS syndrome two months after taking Mesalazine and fifteen days after taking Sulfasalazine with moderate hepatic impairment which progressed to severe hepatic cytolysis despite the discontinuation of the incriminating treatment and the introduction of low-dose corticosteroid therapy. The administration of bolus corticosteroids for three days followed by oral corticosteroids allowed the control and the clinical and biological improvement of the disease.

Keywords: Toxidermy, Mesalazine, sulfasalazine, hepatic cytolysis, corticosteroid bolus.

Introduction

Drug hypersensitivity syndrome or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is a severe toxidermia triggered by an immunological reaction to certain drugs[1]. It is characterized by a skin rash, visceral involvement visceral involvement and hematological abnormalities[2]. The systemic involvement can progress to multi-visceral failure, which is life-threatening and constitutes the severity of the syndrome[3]. Early diagnosis, discontinuation of the responsible treatment and initiation of systemic corticosteroid therapy are the mainstays of DRESS syndrome treatment[4]. Clinical worsening despite discontinuation of the offending drug and use of low-dose corticosteroids are considered characteristic of DRESS syndrome. High-dose corticosteroid therapy or even bolus corticosteroids have been proposed as alternatives[4,5]. We report on a case study of DRESS Syndrome, which shows some of the evolutionary and therapeutic particularities.

Patient and observation

A 35-year-old man who had been followed for 3 months for hemorrhagic rectocolite and psychosis was hospitalized for a generalized and pruritic rash associated with fever, which occurred two months after taking mesalazine and fifteen days after taking sulfasalazine.

The clinical examination revealed a maculopapular exanthema spread over the whole body, facial edema, cheilitis, painful and mobile cervical, supraclavicular and axillary adenopathies of variable size (1-2 cm in diameter), all evolving in a context of apyrexia and altered general condition (Figure 1). The biological work-up showed a hyperleukocytosis at 28 440 elements/mm3, a hypereosinophilia at 1 991 elements/mm3, a lymphocytosis at 13 082 elements/mm3, an acute hepatic cytolysis ALAT= 159 UI/l (3 N), ASAT=481 UI/l (8N), a hyponatremia at 127 mEq/l (135-148), and a normal prothrombin rate. Liver ultrasound ruled out an obstructive origin. The virological work-up revealed a serology of Herpes simplex virus I and II (IgG positive and IgM negative). Hepatitis A, B and C, HIV, Epstein-Barr virus and cytomegalovirus serologies were negative. Bacteriological samples, blood cultures and ECBU were sterile. The Chest X-ray was without abnormalities. The skin biopsy showed an achanthosic papillomatous orthokeratotic epidermis, with an excoriation lesion containing subcorneal pustules under the cornea. The superficial dermis was the site of a lymphocytic infiltrate and a slight pigmentary incontinence associated with a vascular congestion that could be related to a toxidermia. The diagnosis of DRESS syndrome was established according to the validation criteria of the REGISCAR group. The pharmacological investigation incriminated

Mesalazine and Sulfasalazine in order of frequency with an imputability score of I3B4 for Mesalazine and Sulfasalazine. Mesalazine and Sulfasalazine were discontinued and systemic corticosteroids at a dose of 0.5 mg/kg/d combined with an antihistamine and an emollient were started. The evolution after three days of corticosteroid therapy was marked by an abrupt onset of fever at 39 degrees Celsius, subicterus, improvement of skin lesions and regression of facial edema and adenopathy.

The evolution of the biological workup was marked by the worsening of the hepatic cytolysis: ASAT: 4,177 IU/L (92.8N), ALAT: 3,676 IU/L (91.9N), GGT: 477 IU/L (8.5N), PAL: 2,194 IU/L (21.9N), disorders of hemostasis (Prothrombin rate: 36%, Fibrinogen: 1.44, Factor V: 50%), a decrease in platelets to 70,000 elements/mm3 with an infectious workup: ECBU, CRP, prolcitonin, Chest X-ray, which was without abnormalities. A bolus of methylprednisolone 60 mg per day for five days followed by oral corticosteroid therapy 1mg/kg/d was recommended with an improvement in the biological workup, namely normalization of the liver workup, hemostasis workup, and platelets, and persistence of neutrophil hypeleukosis.

Discussion

The particularity of our observation lies in the severe form of the DRESS syndrome due to because of an aggravation of the hepatic cytolysis with hepatocellular insufficiency under general corticosteroid therapy which improved with corticosteroid boluses. Drug hypersensitivity syndrome (DRESS) is a severe form of toxidermia that can be life-threatening[3]. Its severity lies in its systemic manifestations, which can evolve into multivisceral failure and be life-threatening. Its pathophysiology is now better understood, involving a predisposing immunogenetic background and a reactivation of herpes viruses dominated by the HHV-6 virus[2,3,6]. Its incidence is not well known and could occur in one case in 10,000 of exposure to drugs such as sulfonamides and antiepileptics with an estimated mortality of 10%[3,6]. The involvement of Mesalazine and Sulfasalazine in DRESS syndrome has been reported by several authors[2,7,8]. The clinical manifestations appear between two and eight weeks after the introduction of the responsible drug and more rapidly in case of reintroduction of the same drug[9]. In our patient, the symptoms appeared two months after taking mesalazine and fifteen days after taking sulfasalazine. The most common drugs involved are allopurinol, aromatic amine anticomitants lamotrigine, antibacterial sulfonamides, but also Mesalazine, Sulfasalazine Dapsone and minocycline[9,10]. According to the literature, patients with a history of allergy to antibacterial sulfonamid

Aucune source spécifiée dans le document actif.es have a six-fold higher risk of reactions to non-antibacterial sulfonamides (9.9%) than subjects without an allergic history (1.6%). Predisposition to allergic reactions seems to be the most favored theory by the same authors rather than a cross-reaction with sulfonamides[11]. Our patient had no history of drug allergy to antibacterial sulfonamides. Clinically, the initial presentation may mimic a viral infection with high fever, malaise malaise, painful polyadenopathy, maculopapular exanthema and facial edema. Skin involvement is constant in the majority of cases and the oral mucosa is affected in only about 10% of cases. The evolution is usually favorable if the drug is stopped early, but fatal evolution is possible in about 10% of cases[6,9]. In our patient, the symptoms had regressed rapidly with the cessation of treatment and the initiation of corticosteroid therapy. Biologically, hyperleukocytosis is frequent with eosinophilic polynucleosis and lymphocytosis which are often associated with hepatic cytolysis (80% of cases)[2]. In our patient, the hypereosinophilia improved after 3 days of general corticosteroid therapy with persistent neutrophilia that persisted beyond 1 month of corticosteroid therapy.

The involvement of reactivation of herpes viruses (HHV-6, HHV-7, EBV and CMV), against which the body mounts a strong immune response, has been reported in the pathophysiology of DRESS syndrome[9,12]. This viral reactivation for HHV6, 7 was not investigated because it was not available, but the investigation for the other viruses was negative. Pathologically, DRESS syndrome is characterized by a perivascular lymphocytic infiltrate, with the presence of eosinophilic polynuclei associated with scattered keratinocytic necrosis in the superficial dermis with epidermotropism[2,9]. The severity of DRESS

syndrome is related to multivisceral damage (renal failure, hepatic cytolysis, interstitial lung disease, myocarditis, pancreatitis, meningoencephalitis or macrophagic activation syndrome). According to the literature, deterioration of liver function associated with a drop in prothrombin levels suggests severe and sometimes fatal forms[2,3,13]. The therapeutic attitude depends on the visceral involvement and the clinico-biological evolution. The suspect drug must be stopped and contraindicated. Reporting of the incriminating drug to pharmacovigilance is mandatory[9,13]. In the presence of serious signs (transaminases greater than five times normal; pneumonia, cardiac and/or renal involvement and hemophagocytosis), treatment includes systemic corticosteroids equivalent to 1 mg/kg/day of prednisone with a multidisciplinary approach according to the therapeutic algorithm of the French Society of Dermatology[14]. It should be continued with a progressive decrease over several weeks or even months to control and avoid the risk of recurrence. Methylprednisolone 30 mg/kg intravenously for three days can be administered as an alternative to oral corticosteroids followed by oral corticosteroid therapy[5,14]. Confirmation of major viral reactivation suggests the addition of an antiviral (ganciclovir) or intravenous immunoglobulin to the general corticosteroid therapy according to some authors[2,3,8]. Our patient presented a worsening of the hepatic cytolysis with a decrease of the prothrombin level and of the coagulation factor V, a sub-icteric cholestasis, an elevation of the alkaline phosphatases and of the gamma-GT, three days after the introduction of the corticosteroid therapy at a low dose of 0.5 mg/kg/day. Local or systemic corticosteroid therapy controls the manifestations of inflammatory and autoimmune diseases[5]. The transient worsening of liver damage under low-dose corticosteroids had justified the administration of corticosteroid boluses relayed by oral corticosteroid therapy with a good evolution.

Conclusion

DRESS syndrome is a rare but serious toxidermia that can be life threatening. The diagnosis must be made early and the incriminating drug(s) must be stopped permanently. The treatment of severe DRESS is not well defined, as corticosteroids may not be effective, and the evolution towards a worsening of the disease with low doses of corticosteroids is always possible, as was the case in our observation. High-dose corticosteroid therapy or even bolus corticosteroids may be an alternative in the case of severe hepatic impairment.

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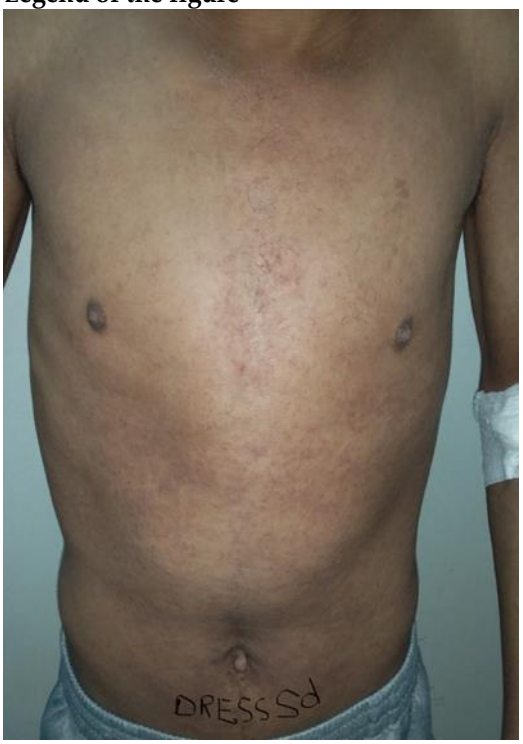

Figure 1: Maculopapular exanthema and scaling of the trunk and abdomen

References

[1] Benidamou "Salma, Krati" K. Nouveau cas de DRESS Syndrome chez une patiente suivie pour RCH et traitée par dérivés salicylés. HEGEL - HEpato-GastroEntérologie Libérale 2015.

[2] Bourguignon R, Piérard-Franchimont C, Paquet P, Piérard GE. SYNDROME DRESS À LA SULFASALAZINE. Rev Med Liege n.d.:6.

[3] Chebbi W, Souissi J, Chelli J, Larbi F, Zantour B, Sfar MH. DRESS syndrome: à propos de trois observations. Pan Afr Med J 2014;19.

[4] Moling O, Tappeiner L, Piccin A, Pagani E, Rossi P, Rimenti G, et al. Treatment of DIHS/DRESS syndrome with combined N-acetylcysteine, prednisone and valganciclovir – a hypothesis. Med Sci Monit 2012;18:CS57–62.

[5] Bayan C-AY, Lopez A, Fontecilla NM, Geskin LJ. Successful treatment of drug reaction with eosinophilia and systemic symptoms syndrome relapse with oral pulsed dexamethasone. JAAD Case Rep 2018;4:959–61.

[6] Aquino RTR de, Vergueiro CSV, Magliari MER, Freitas THP de. Sulfasalazine-induced DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). Sao Paulo Med J 2008;126:225–6.

[7] Ben salem C, Fathallah N, Slim R, Larif S, Zayani H, Ghariani N. Sulfasalazine-Induced Dress: A Report of Five Cases. Clin Ther 2017;39:e4.

[8] Shiohara T, Kano Y. Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. Expert Opin Drug Saf 2016:1–9.

[9] Tehrany DYA, Laffitte E, Grosgurin O. Syndrome DRESS (drug reaction with eosinophilia and systemic symptoms). Rev MÉDICALE SUISSE 2016:6.

[10] Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int 2019;68:301–8.

[11] Zawodniak A, Lochmatter P, Beeler A, Pichler WJ. Cross-Reactivity in Drug Hypersensitivity Reactions to Sulfasalazine and Sulfamethoxazole. Int Arch Allergy Immunol 2010;153:152–6.

[12] Descamps V, Ranger-Rogez S. DRESS syndrome. Joint Bone Spine 2014;81:15–21.

[13] Lebrun-Vignes B, Valeyrie-Allanore L. Toxidermies. Rev Médecine Interne 2015;36:256–70.

[14] Martínez-Cabriales SA, Rodríguez-Bolaños F, Shear NH. Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS): How Far Have We Come? Am J Clin Dermatol 2019;20:217–36.