



## Letter

## Optimal management of DRESS syndrome in course of infectious endocarditis

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a life-threatening adverse reaction characterized by a delayed onset after therapy initiation (usually 2–4 weeks), eosinophilic organ damage, and a paradoxical worsening of symptoms after discontinuation of the causative drug. DRESS syndrome pathogenesis implies different potential mechanisms, including detoxification defects leading to drug metabolite formation, slow acetylation processes, and reactivation of human herpes viruses.<sup>1</sup>

Immediate administration of corticosteroids and immunosuppressant agents is the treatment of choice in view of a mortality rate of up to 10%.<sup>1</sup> However, high-dose corticosteroid therapy may represent a therapeutic dilemma in a course of chronic infections.

Here, we report a case of bacterial endocarditis complicated by vancomycin-induced DRESS syndrome; based on the pathogenetic mechanisms of this hypersensitivity reaction, steroid-sparing agents were chosen to avoid a progression of the ongoing infection.

A 75-year-old man was referred for a 2 months' history of low-grade fever that appeared after surgical aortic valve replacement. Repeated blood cultures were negative. A transesophageal echocardiography disclosed a mobile vegetation at the prosthetic aortic valve, and empiric antibiotic treatment was started with intravenous gentamicin (1 mg/kg three times/day for 14 days), vancomycin (1g twice/day), and oral rifampicin (300 mg twice/day). Fever disappeared, and inflammatory markers significantly decreased by the first week of therapy. However, after 27 days of antibiotic treatment the patient developed high spiking fever, and inflammatory markers raised again. Vancomycin and rifampicin were replaced by intravenous daptomycin (6 mg/kg/day) and ceftriaxone (2 gr/day) but he remained febrile; moreover, 2 days after the introduction of the new antibiotics, a severe erythematous macular rash rapidly appeared on the trunk and face without mucosal involvement. All of the ongoing therapies were withdrawn. Laboratory tests showed an increasing peripheral blood eosinophilia (PBE), atypical lymphocytes, and a progressive deterioration of liver and renal function. In particular, the blood cell count showed  $0.6 \times 10^9$  eosinophils/L; 6.2% of total leukocytes with a normal peripheral blood-smear evaluation; alanine- and aspartate-aminotransferase, alkaline-phosphatase and gamma-glutamyltransferase were 264 U/L (normal, 6–55), 45 (5–41), 247 (56–199), and 150 (11–50), respectively. Erythrocyte sedimentation rate was 24 mm/hour (0–15), C-reactive protein was 60 mg/L (0–6), lactate dehydrogenase was 262 U/L (125–220), and serum creatinine was 1.31 mg/dL (0.5–1.25). Blood cultures were persistently negative. A second transesophageal echocardiography demonstrated a partial reduction of the endocarditic vegetation. Finally, a DRESS syndrome was suspected and confirmed by using the RegisSCAR scoring system<sup>2</sup>; in particular, a score of 7 classified our patient as definitely having

DRESS, and intravenous methylprednisolone 0.5 mg/kg/day (20 mg twice/day) was promptly started together with oral H1 and H2 receptor antagonists (hydroxyzine 25 mg and ranitidine 75 mg twice/day). Despite these treatments, PBE and liver enzymes continued to rise. Autoimmune serologic studies and serum IgE levels were normal. Serology for herpes viruses was consistent with a reactivation of Epstein-Barr virus, whereas cytomegalovirus and HHV-6 DNA were negative.

Because of the ongoing endocarditis, we hesitated to increase the corticosteroid dosage, and we decided to use high-dose intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for 5 consecutive days; we also associated a detoxifying intravenous treatment with N-acetylcysteine (50 mg/kg three times/day for 12 days) and an anti-leukotriene agent (montelukast 10 mg/day). Furthermore, to eradicate the aortic valve infection, we reintroduced gentamicin for 1 more week as the less probable culprit drug involved in the hypersensitivity reaction. On the fifth day of IVIG treatment, fever disappeared and C-reactive protein returned within the normal limits; liver function deteriorated, and PBE rose (up to  $3.2 \times 10^9$  eosinophils/L; 21% of total leukocytes) for 1 more week and then decreased together with the resolution of the cutaneous eruption (Fig 1). A third echocardiography performed at day 49 showed a complete resolution of the endocarditis. The patient was discharged on maintenance therapy with oral methylprednisolone (10 mg twice/day gradually tapered off), montelukast (10 mg/day), hydroxyzine (25 mg/day), and ranitidine (75 mg/day) for 2 months.

At DRESS syndrome onset and 3 months later, basophil activation test and lymphocyte transformation test (performed as previously described)<sup>3</sup> gave negative responses to the suspected antibiotics. Three months after DRESS syndrome onset, when the patient was 15 days free from steroid and antihistamine therapy, patch tests (performed with all the cited antibiotics diluted in petroleum jelly as previously described)<sup>4</sup> gave a positive result at 48 and 72 hours for vancomycin (erythema at 1% dilution), thus supporting a causal role of this drug. Negative patch tests were obtained at days 2, 3, and 7 on an age-matched not allergic male used as negative control. Finally, HLA phenotyping was positive for HLA-B\*1503, a finding never described before in association with vancomycin-induced DRESS syndrome.

Inpatient vancomycin use is increasing and appears as an emerging cause of this hypersensitivity reaction.<sup>5</sup> However, the reported case points out another important topic: prolonged antibiotic therapies for chronic infections may increase the risk of hypersensitivity to antimicrobial drugs. In this sense, efforts are urged to design a comprehensive therapeutic approach, efficacious in dampening the immunological response without exacerbating the ongoing infection. Here, we were able to minimize the corticosteroid dosage to 0.5 mg/kg/day methylprednisolone by using

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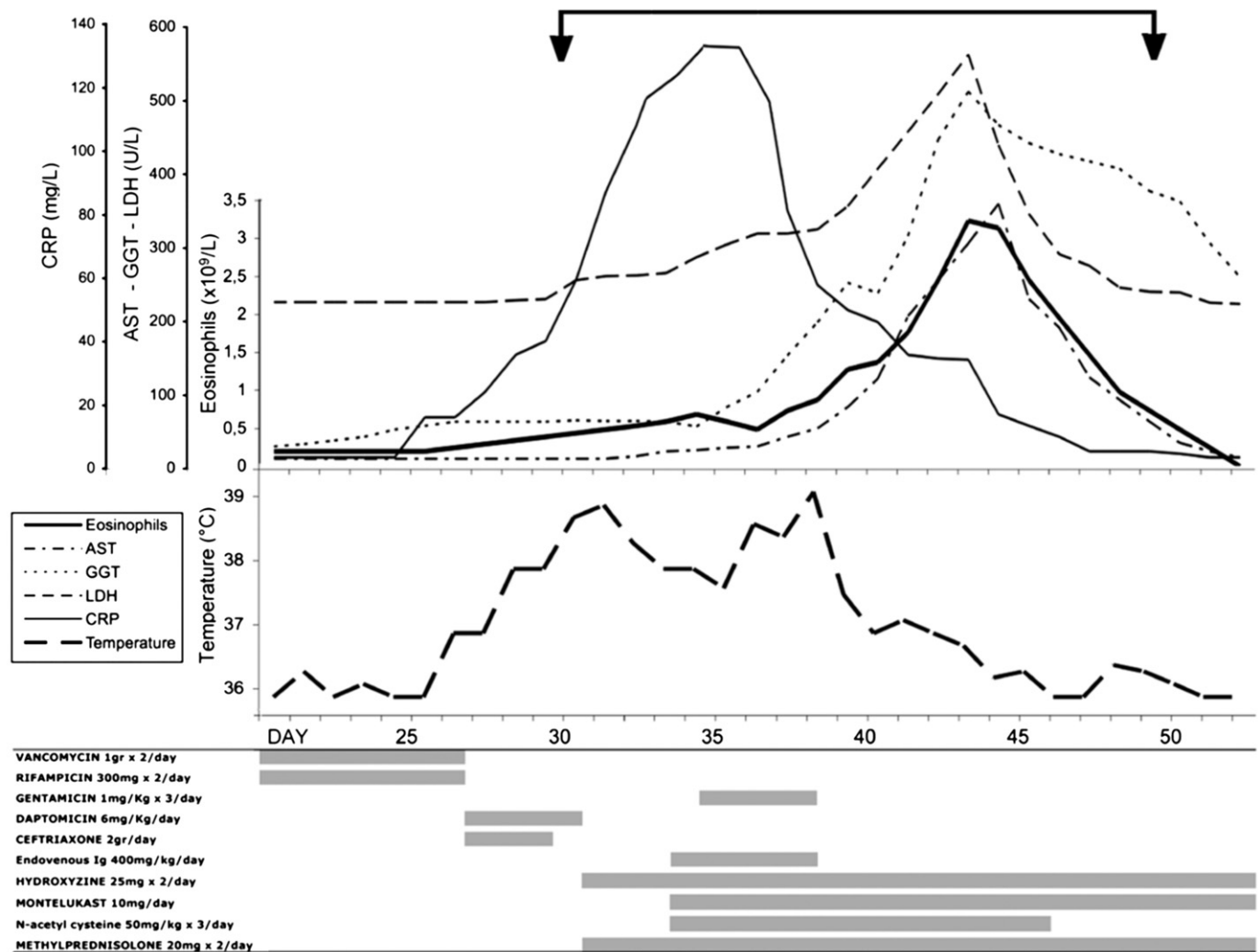


**Figure 1.** Graph illustrating the eosinophil, aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), lactate dehydrogenase (LDH), C-reactive protein (CRP), and temperature trend over the acute course of DRESS syndrome in relation to the different treatments (gray bars at the bottom); arrows indicate the onset and resolution of the erythematous rash.

steroid-sparing agents according to the known pathogenetic features of DRESS syndrome.

By using high-dose IVIG therapy, we aimed at achieving a substantial anti-inflammatory effect, a compensation for the decreased immunoglobulin concentration observed in the early phase of DRESS syndrome, and a protective effect against herpes viruses reactivation.<sup>6</sup> Whether IVIG treatment contributed as well to the resolution of bacterial endocarditis remains an interesting matter of speculation. N-acetylcysteine was introduced based on well-known antioxidant properties; in particular, by increasing glutathione synthesis and neutralizing free radicals it has been demonstrated to prevent acetaminophen overdose-induced hepatotoxicity.<sup>7</sup> Thus, in consideration of the detoxification defects and slow acetylation mechanisms implicated in the pathogenesis of DRESS syndrome, N-acetylcysteine was considered a potentially effective candidate for hepatic protection against drug-induced toxicity. Montelukast was chosen because leukotriene receptor-1 antagonists have been shown to decrease PBE in different pathological conditions by reducing the production of eosinophil survival-cytokines.<sup>8</sup>

In conclusion, by combining different treatments, we reduced DRESS syndrome activity without worsening the endocardial infection. To our knowledge, this therapeutic strategy has never been described before; however, further experiences are needed to validate our approach and to design a comprehensive management for life-threatening hypersensitivity reactions in the course of infectious diseases.

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