Leflunomide-induced DRESS syndrome

Giulia Spallone1
Alessandro Di Stefani2
Loredana Sarmati3
Pasquale Sordillo3
Luca Bianchi1

1 Department of Dermatology, “Tor Vergata”
University of Rome, Rome, Italy
2 Division of Dermatology, “Complesso Integrato Columbus”, Catholic University of the Sacred Heart, Rome, Italy
3 Department of Infective Diseases, “Tor Vergata”
University of Rome, Rome, Italy

Address for correspondence:
Giulia Spallone
Policlinico Tor Vergata
Rome, Italy
E-mail: giuliaspallone@hotmail.it

Summary
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is characterized by fever, rash, eosinophilia and organ damage that develops 2-6 weeks after the initiation of a medication. Reversion of systemic manifestations is very slow, ranging between 1 and 6 months. It is burdened of a 10% mortality rate (1). Although initially referred to aromatic antiepileptic drugs or as drug-induced pseudolymphoma, it is now observed with other drugs and estimated to occur in at least 1 per 1500 new users of phenytoin or carbamazepine.

We report a case of DRESS syndrome in a 53-year-old woman that developed after the introduction of leflunomide used to treat rheumatoid arthritis. Steroids are the mainstays of treatment for moderate to severe cases of DRESS syndrome. Initiation of steroids for the treatment of DRESS syndrome can require multidisciplinary collaboration for optimal management in particular in patients affected by pre-existing inflammatory condition.

Case report
A 53-year-old woman affected by rheumatoid arthritis developed high fever (39°C) and a pruriginous erythematous maculopapular cutaneous eruption on whole body (Figure 1a) 5 weeks after starting leflunomide (20 mg/day). Patient denied assumption of any drug other than leflunomide. Clinical examination revealed enlarged cervical and sub occipital lymph nodes. Laboratory tests showed eosinophilia (0.44 x 10³/μL; 7.8%), low lymphocyte count (0.89 mla/μL; 15.8%) and raised aspartate aminotransferase (101.00 U/L), alanine aminotransferase (176.00 U/L), alkaline phosphatase (611 U/L), gamma-glutamyltransferase (430.00 U/L), bilirubin (direct: 3.88 mg/dl; total: 4.70 mg/dl) and lipase (1088.00 U/L). Blood and throat cultures were negative. Hepatitis A, B, C virus, Epstein-Barr virus, Morbillivirus, HSV types 6, 7, 8, Human Immunodeficiency Virus, Cytomegalovirus, Weil-Felix and Widal-Wright test were negative, as well as anticyclic citrullinated peptide antibodies were present and rheumatoid factor was elevated. Abdomen ultrasonography revealed cholelithiasis. CT chest was negative.

Cutaneous biopsy evidenced mild spongiosis and exocytosis, basal vacuolization, scattered necrotic keratinocytes and dermal lymphocytic inflammatory infiltrate with interstitial eosinophils (Figure 1b).
DRESS syndrome

Discussion

To meet the definition of DRESS, patients must have three of the four main RegiSCAR criteria: an acute rash, fever above 38°C, lymphadenopathy at two sites, involvement of at least one internal organ, and abnormalities in lymphocyte and eosinophil counts. Additional criteria include hospitalization and that the reaction is suspected to be drug-related (2-4). Nine cases of leflunomide-induced DRESS syndrome are reported (5, 6). Bocquet proposed the term “drug rash” with Eosinophilia and Systemic Symptoms (DRESS) to simplify the nomenclature of drug-hypersensitivity syndromes (1). More recently, a Japanese consensus revised a set of 7 criteria (7).

Systemic involvement includes hepatitis, interstitial nephritis or pneumonitis. Hepatitis is the most common presentation, as congruent with our case. Hypereosinophilia probably accounts for multiorgan involvement that differentiates this hypersensitivity syndrome from other cutaneous drug eruptions. Proposed etiopathogenetic mechanisms include genetic deficiency resulting in accumulation of toxic drug metabolites, virus-drug interactions, and drug-specific T cell-mediated reactions (8). DRESS syndrome usually arises within 1-8 weeks after drug therapy. In our case, fever and rash developed 5 weeks after taking leflunomide, an oral disease-modifying antirheumatic drug for rheumatoid and psoriatic arthritis. Skin rash, subacute lupus erythematosus, lichenoid or blistering eruption, ulcerative dermatitis, vasculitis, are possible cutaneous reactions to leflunomide.

Due to its multitude of clinical features, DRESS syndrome mimics a number of serious systemic disorders. Differential diagnosis include septicemia, autoimmune diseases, including vasculitides, tick-borne diseases, and other conditions like viral hepatitis. Scarlet fever should also be ruled out. Existence of herpes viruses, particularly type 6, is suggestive of diagnosis and may be a cofactor in the pathogenesis.

In our case, infectious diseases were ruled out through viral and bacterial examinations, and connective tissue disorders were excluded through negative anti dsDNA and ANA profiles. Furthermore, no history of animal/insect bites was detected. The first modality to treat DRESS syndrome is discontinuing the causative drug. In our case, leflunomide was abruptly discontinued, systemic corticosteroids were prescribed and clinical and laboratory parameters gradually returned to normal values.

Patients with DRESS, although optimum therapy remains controversial and a standardized treatment has not been assessed, are usually treated with systemic corticosteroids. In individual cases, treatments with systemic corticosteroids and intravenous immunoglobulins are reported to be effective; however, no controlled trials are published. In conclusion, we report a case of DRESS induced by leflunomide for rheumatoid arthritis.

As dermatologists, we may be either the prescribers of leflunomide for psoriatic arthritis, or the consultants for the diagnosis of the cutaneous counterpart of this severe syndrome. Prompt recognition and withdrawal of the causative drug are essential to avoid a potential severe outcome.

References

3. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck...