

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): an atypical case during treatment with sulfasalazine

Sirs,

Serious adverse events occur infrequently with sulfasalazine (SSZ), a drug commonly used in the treatment of rheumatoid arthritis and inflammatory bowel diseases (1). We report an atypical case of SSZ-associated Drug Reaction with Eosinophilia and Systemic Symptoms, *i.e.* DRESS.

A 45-year-old Caucasian man complained of fatigue, abdominal discomfort, a rash over his right thigh, and fever (38.2°C) sixteen days after SSZ (500 mg twice daily) was initiated for a flare-up of seronegative spondyloarthritis. Dose had been stable, he denied alcohol consumption and was not taking over-the-counter and recreational medications or herbal remedies. There was no personal or family history of allergy or liver and skin disorders; he had type II diabetes, gastro-esophageal reflux, seronegative spondyloarthritis and bronchial asthma managed with metformin, omeprazole, repaglinide, and on-demand salbutamol and non-steroidal anti-inflammatory drugs. Six months prior, an abdominal sonogram showed fatty liver infiltration; liver and kidney function tests were normal at that time. The patient was fully alert and oriented; physical examination showed aphtous ulcers in the mouth, several cervical, axillary and inguinal non-tender lymph nodes, a few vesicles and pustules over his right thigh, mild scleral jaundice and no flapping tremor or any other stigmata of chronic liver disease. The rest of the examination was unremarkable. Blood tests disclosed anaemia, low white blood cells (WBCs), the presence of enlarged lymphocytes with blast-like features *i.e.* abundant cytoplasm, vacuoles and indentations of the cell membrane on peripheral blood smear, and elevated bilirubin and aminotransferases (Table I); eosinophils were 799 cells/mm³ (normal range 0-540 cells/mm³), C-reactive protein (CRP) was 38 mg/L (normal range 1-3 mg/L) and renal function tests were normal. Serological screening for viral hepatitis (hepatitis A, B, C, E and G virus; cytomegalovirus; herpes simplex; and Epstein-Barr virus) was negative and HBV-DNA and HCV-RNA were not detected in the peripheral blood. Search for autoimmune liver and kidney disorders was negative as were results of iron, copper, ceruloplasmin metabolism and α 1-antitrypsin concentrations. The patient refused a liver and bone marrow biopsy.

We suspected a systemic adverse effect of SSZ which was discontinued with ensuing symptomatic and biochemical improvement (Table I). The patient recovered rapidly and was discharged on the 10th day

Table I. Time course of laboratory tests.

	Range	Day - 180	Day 1	Day 2	Day 3	Day 5	Day 8	Day 10	Month 3
AST (U/L)	10-36	28	760	521	334	120	55	31	15
ALT (U/L)	10-36	34	581	448	297	187	48	28	25
Bilirubin (mg/dl)	0.6-1	0.7	4.2	3.5	2.3	1.6	0.9	1.1	0.7
Hb (g/dL)	12.5-15	14.5	10.1	9.9	10.2	10.3	10.8	12.1	12.6
WBCs (cells/mm ³)	4.0-7.0	6.5	2.8	2.9	3.2	3.5	3.8	6.4	5.9
Activated lymphocytes (% total lymphocytes)		NA	36	38	29	31	21	13	0
Eosinophils (cells/mm ³)	0-540	75	799	650	420	310	330	295	103
CRP (mg/L)	1-3	NA	38	NA	NA	30	NA	22	2.8

AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hb: haemoglobin; WBCs: white blood cells; CRP: C-reactive protein; NA: not available. Activated lymphocytes are enlarged lymphocytes with blast-like features *i.e.* abundant cytoplasm, vacuoles and indentations of the cell membrane seen on blood smear. Day 1 is the day of admission (see text for details).

with normal blood levels of enzymes and bilirubin, haemoglobin (Hb) was 12 mg/dl and WBCs 6.4×10^3 cells/mm³ with no atypical lymphocytes on peripheral blood smear. Oral aphtous ulcers and the skin rash disappeared after one month. A re-challenge test with SSZ was not done for safety reasons. At follow-up three months later, he remained asymptomatic with stable liver function tests and blood counts, and no evidence of active rash.

According to the Naranjo probability scale (2), SSZ was the probable cause of DRESS in this patient, a systemic disorder characterised by cutaneous and mucosal eruption, systemic symptoms, eosinophilia, atypical lymphocytosis, and internal organ involvement with lymphadenopathy, hepatitis, interstitial nephritis, pneumonitis or carditis, that was first described with phenytoin in 1950 (3, 4). The most frequently involved internal organ is the liver, followed by the kidney and lung (3, 4).

DRESS should be listed among the great mimickers in clinical medicine as it can present with many different symptoms, with fever and skin eruptions being the most common. A diffuse maculopapular and erythematous rash often associated with facial oedema is present in more than 70% of patients (3, 4). Furthermore, a wide spectrum of other cutaneous manifestations that range from erythema multiforme to exfoliative dermatitis, acute generalised exanthematous pustular dermatitis-like eruption, erythroderma, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been described (3, 4).

Our patient had a localised rash which is not the usual skin manifestation in the course of the syndrome, however this does not rule out by itself the diagnosis since our case fulfilled the diagnostic criteria of the syndrome despite the presence of atypical features for classic DRESS such as the presence of a localised rather than diffuse rash, slightly increased eosinophils, and the very short time to complete recovery. This is an important teaching point implicating that a severe and diffuse involvement of the skin is not strictly required to clinically rec-

ognise DRESS which lends support to the paradox that patients could be diagnosed with a definite DRESS even if they do not have a skin rash. Of concern, our patient had aphtous ulcers in the mouth which did reflect in our opinion the systemic involvement of the mucocutaneous tissues.

The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) has produced diagnostic criteria and a scoring system to provide a better definition and assist in the diagnosis of DRESS (5). RegiSCAR inclusion criteria require at least three of the followings: hospitalisation, reaction suspected to be drug-related, acute skin rash, fever at least 38°C, enlarged lymph nodes at two sites, involvement of at least one internal organ, blood count abnormalities such as low platelets, raised eosinophils, or abnormal lymphocyte count (5). The RegiSCAR scoring system grades DRESS cases as no, possible, probable, or definite with scores of 5 or more being classified as definite DRESS syndrome. Our case scored 6 points and was therefore classified as definite DRESS syndrome.

This rare idiosyncratic reaction is most often associated with aromatic anticonvulsants (*i.e.*, phenobarbital, phenytoin, primidone and carbamazepine) and allopurinol, with an estimated incidence of 1:1000 to 1:10 000 exposures to these drugs (3, 4). About 50 drugs are potential triggers of DRESS, with few cases described among users of SSZ (reviewed in 6). The incidence of DRESS caused by SSZ or other sulfonamides is however unknown. DRESS has a delayed onset, *i.e.* 2 to 8 weeks, after initiation of the causative drug and a timely diagnosis remains critical because the disorder usually improves after the offending drug is discontinued (3, 4). Treatment is supportive in almost all cases, complete recovery may require a prolonged time, the risk of recurrences remains high for several weeks or months even after initial improvement, and symptoms may recur upon re-challenge as soon as within one day of exposure (3, 4). Corticosteroids are given to patients with more severe presentation even though the

evidence for their efficacy is lacking and symptoms may worsen on tapering doses (3, 4). Autoimmunity could develop after recovery (3, 4).

Predictive factors for a serious course of DRESS are unknown and whether the type of causative drug may influence the ultimate outcome is also unclear. Previous studies have shown the death rate could be higher among patients with allopurinol-associated DRESS compared to DRESS cases caused by other drugs (7). Independent of the triggers, DRESS can progress to multiorgan failure and death, which is usually caused by fulminant liver failure, in up to 10% of patients (3, 4). DRESS-associated hepatitis can recur in the transplanted liver (8).

The pathogenesis is not understood. Mechanisms may include detoxification defects and reactive metabolite formation, slow acetylation, hypersensitivity, and reactivation of human herpes viruses (HHV), including Epstein-Barr virus, cytomegalovirus and HHV-6 and -7, or paramyxoviruses (3, 4). The detection of HHV-6 reactivation has been proposed as a diagnostic marker for DRESS but this needs to be further investigated (9). In our patient, serological screening for Epstein-Barr virus, cytomegalovirus, and herpes simplex was nega-

tive; we did not check for HHV-6. Genetic factors are also important as the risk seems to be greatly increased among individuals with a first-degree relative who did experience the syndrome (3, 4).

We should be aware of the potential risk of this severe systemic reaction when patients are started on SSZ. A close follow-up for early signs of DRESS is required particularly during the first weeks of therapy.

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