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SHORT COMMUNICATION

A Case of Drug Reaction with Eosinophilia and Systemic Symptoms Induced by Ethambutol with Early Features Resembling Stevens-Johnson Syndrome

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Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, are severe cutaneous adverse reactions (SCARs), which can be fatal if not treated promptly. These 2 entities have phenotypically and pathophysiologically distinct features (1). However, there are clinical similarities between them, which can cause confusion in diagnosis, leading to delays in proper management. We report here a case of ethambutol-induced DRESS with early features resembling SJS.

CASE REPORT

A 68-year-old woman was admitted to our emergency department with maculopapular rashes on her trunk and extremities and painful erosions on her oral mucosa (Fig. 1a). On physical examination, prominent targetoid lesions were observed, with blisters and positive Nikolsky's sign (Fig. 1b). The patient had a high fever (39.6ºC) and acute conjunctivitis. Laboratory tests showed the following: C-reactive protein (CRP) 12.9 mg/dl (normal 0–0.5 mg/dl); leukocytes 3,810/mm^3 (4,000–10,000/mm^3); eosinophils 220/mm3 (< 500/mm^3); aspartate aminotransferase (AST) 35 IU/l (0–40 IU/l); alanine aminotransferase (ALT) 12 IU/l (0–40 IU/l); and serum creatinine 0.7 mg/dl (0.7–1.4 mg/dl). Culture and serological tests were negative for bacteria, HIV, and hepatitis A, B and C virus.

Her medication history revealed that she had started anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol and levofloxacin) for tuberculous pericarditis 7 weeks earlier. As a diagnosis of SJS was suspected, anti-tuberculous medications were discontinued and systemic corticosteroid was started (methylprednisolone 1 mg/kg/day). Her skin rash and oral mucosal lesions subsequently improved gradually. By hospital day 9, her fever had resolved and CRP decreased to 3.5 mg/dl, therefore the dose of methylprednisolone was tapered down to 0.5 mg/kg/day. However, on hospital day 11, she suddenly began to deteriorate, with maculopapular eruptions combined with painful cervical lymphadenopathy. Notably, her cutaneous manifestations at this time were quite different in nature from the initial findings that had suggested SJS, such as targetoid lesion or blister formation. Laboratory tests revealed leukocytosis (13,020/mm^3) with hypereosinophilia (2,734/mm^3), atypical lymphocytosis (10%; normal < 1%), elevated ALT (63 IU/l), and acute renal dysfunction (serum creatinine 4.7 mg/dl). Immunoglobulin M against cytomegalovirus and Epstein-Barr virus tested on hospital day 12 were negative. Five days later, AST/ALT increased to 95/118 IU/l and serum creatinine peaked at 5.4 mg/dl. The total score on the RegiSCAR scoring system was 9, suggesting definite DRESS (1 point each for enlarged lymph nodes, atypical lymphocytes, rash extent > 50%, skin rash suggesting DRESS, evaluation of other potential causes; 2 points each for eosinophilia (≥ 1,500/mm^3), liver/kidney involvement) (2).

Renal biopsy was performed and diffuse eosinophilic infiltrations were observed in the renal interstitium (Fig. 2). For treatment, 3 courses of haemodialysis and high-dose systemic corticosteroid re-administration were required. The patient began to recover and was discharged after one month of hospitalization. For complete resolution, low-dose oral corticosteroid treatment was continued for an additional month.

Four months later, drug patch tests and lymphocyte transformation tests (LTT) were performed to determine the agent responsible. Patch tests were performed at 10% in petrolatum with isoniazid, rifampicin, ethambutol, and levofloxacin; and demonstrated a grade 2 positive reaction to ethambutol at 48 h. LTT was performed as described previously (3). The LTT yielded a positive result to ethambutol only, with stimulation index of > 2.5 (Fig. S1; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1600). In conclusion, ethambutol was identified as the culprit agent in our case.

DISCUSSION

SCARs include various syndromes, such as SJS/TEN and DRESS. Although they are under the same denomination, SJS/TEN and DRESS are thought to be distinct entities (1). Pathophysiologically, SJS/TEN is caused by drug-specific expansion of $CD8^+$ T lymphocytes and subsequent activation of the caspase cascade via perforin/granzyme or Fas-Fas ligand pathways. This reaction induces keratinocyte necrosis, thus causing widespread epidermal detachment (4). DRESS is considered a systemic reaction due to a complex interplay among drug-specific

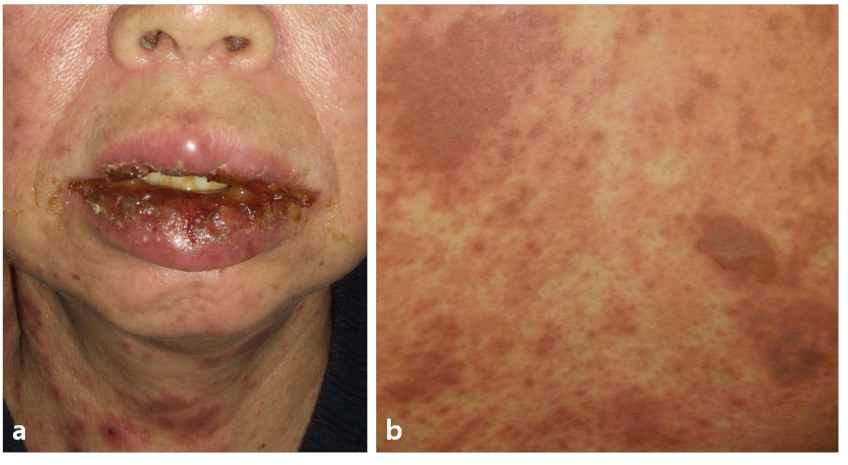

Fig. 1. Physical findings on admission. (a) Oral mucosal lesions. (b) Blistering lesions on the back.

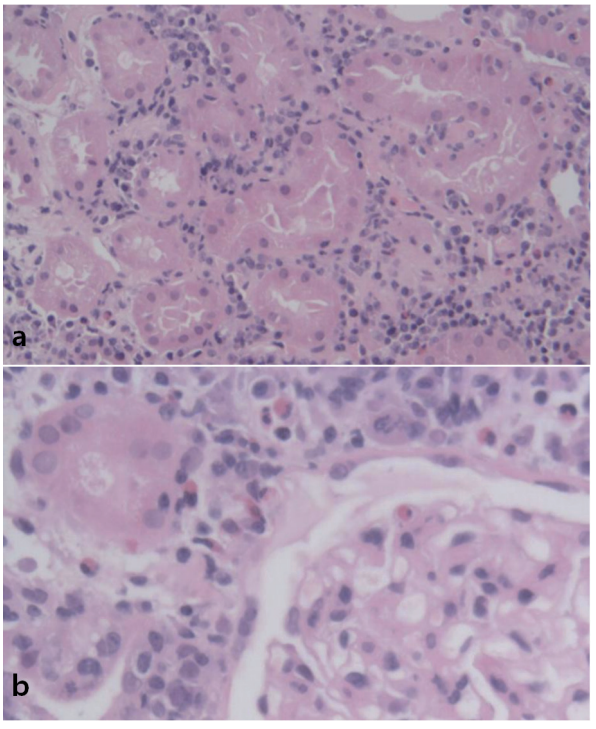

Fig. 2. Renal biopsy showing tubulitis and interstitial infiltrate of lymphocytes and eosinophils, compatible with acute tubulointerstitial nephritis (haematoxylin and eosin stain: (a) × 100, (b) × 200).

T-cell activation, HHV-6 reactivation, and antiviral immune responses (5). The differences between DRESS and SJS/TEN are further supported by genetic studies that show different HLA associations for each entity (1).

However, similarities between the 2 syndromes are not uncommonly present, since the diagnostic criteria for DRESS is not based on specific skin manifestations. These similarities may have caused confusion in the classification of adverse skin reactions, as noted by Wolf et al. (6). Conversely, cases of SJS/TEN can also have systemic manifestations that fit into the definition of DRESS (7). This has led to some reports on overlapping cases of SJS/TEN and DRESS (8–10). Some authors have even proposed that there may be an overlapping subtype of DRESS (11). In a retrospective study on SCARs overlap, 2 of 106 confirmed SJS/TEN and DRESS cases were found to be SJS/TEN-DRESS overlap (12). The patient described herein initially presented with features of SJS, but subsequently developed typical features of DRESS, meeting the criteria of definite DRESS by the RegiSCAR scoring system on day 11. With all this clinical information, it remains difficult to determine whether the present case is a SJS-DRESS overlap or DRESS from the beginning that developed a delayed flare-up with systemic involvement after steroid tapering. However, it is clinically meaningful to recognize that there are some cases of SCARs that have mixed features.

The direct oral challenge test is the gold standard for investigation of the causal relationship of drug hypersensitivity reactions, but it is contraindicated in severe cases. Patch tests and LTTs were carried out and proved useful in the confirmation of the culprit drug in our case. Previous studies have reported that positivity of patch test was 32.1% and sensitivity and specificity of LTT were 60–70% and 85–93%, respectively, in patients with DRESS (3, 13). Our case supports the role of safer diagnostic tools, such as patch test and LTT, for the diagnosis of severe drug hypersensitivity.

In conclusion, we report here a case of ethambutol-induced DRESS initially presenting with features of SJS, in which the culprit drug was confirmed by patch test and LTT.

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