Possible Drug-induced Sweet's Syndrome due to Trimethoprim-sulphamethoxazole

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Sir,
Sweet's syndrome or acute febrile neutrophilic dermatosis, (SS) is characterized by sudden onset of painful erythematous plaques associated with fever, elevated neutrophil count and a diffuse neutrophilic infiltrate in the upper dermis (1). It is nowadays subdivided into five categories (2): classic/idiopathic, inflammatory, paraneoplastic, pregnancy-associated, and a recently described drug-induced form (3). The last is quite rare, representing less than 5% of all cases of SS (4)

We describe here a 40-year-old woman who experienced acute neutrophilic dermatosis after systemic treatment with trimethoprim-sulphamethoxazole (TMPS). Rapid resolution was observed after drug discontinuation and treatment with systemic corticosteroids. According to the modified Naranjo criteria for drug-induced SS (5), we considered the possible imputability of TMPS.

CASE REPORT

A 40-year-old, otherwise healthy, Caucasian woman was referred to our department for an oedematous and pustular eruption of the nose with a rapid extension to the upper trunk, the limbs and the oral mucosa. TMPS was initiated for vaginitis 6 days prior to the eruption. At presentation, physical examination revealed scattered erythematous patches, pustules and blisters localized on the scalp, the upper back (Fig. 1), the chest, the limbs and the palms. Oral erosions, cheilitis and bilateral conjunctivitis with lower palpebral oedema were also noted. She had fever (38.6°C) and presented a dry cough. The rest of the examination was unremarkable, in particular no lymph nodes, liver or spleen enlargement were palpated, and there was no sign of remaining vaginitis.

Laboratory tests disclosed an elevated white blood cell count with a notable increase in polymorphonuclear cells (18.8×10^{-3}/mm^3; upper normal limit 7.0×10^{-3}), an inflammatory syndrome with elevation of the erythrocyte sedimentation rate (83 mm/h), C reactive protein (67 mg/l, normal < 5), and alpha-2 globulin (9.3 g/l, normal < 8). Blood cultures and cutaneous swabs were negative for bacteria. Urine culture was contaminated by vaginal flora. Microscopic examination of the cutaneous lesions revealed a prominent neutrophilic infiltrate of the dermis without vasculitis consistent with SS. Chest X-ray was normal. Dramatic improvement was observed after TMPS withdrawal and initiation of an oral corticosteroid therapy (prednisone, 1 mg/kg/24 h). Corticosteroids were tapered over a 5-week period. Fever resolved within 48 h, while cutaneous lesions and inflammatory syndrome cleared within the first week. No relapse was noted and no neoplasia or inflammatory disease was diagnosed after 2.5 years of follow-up.

DISCUSSION

We report here the third case of drug-induced SS by TMPS (3, 6). The first case of drug-induced SS was reported in 1986 by Su & Liu (6) in a woman who was given TMPS also for vaginitis. In our case, rechallenge was not performed because of the extension of the lesions, the mucosal lesions and general signs. As stated by Thompson & Montarella (5) in their recent comprehensive review of drug-induced SS, Walker & Cohen's criteria do lack several important elements, such as establishment of previous conclusive literature, alternative causes for the reaction and similar reactions to the same or a similar drug. Therefore, we used the expanded Naranjo scale for drug-induced SS used by Thompson & Montarella (5), which incorporates some of the criteria established by Walker & Cohen (3) and Su & Liu (6), even though this scale has never been validated for such purpose. The modified scale includes ten criteria: existence of previous conclusive reports; temporally related onset to drug administration; temporally related resolution of lesions after drug withdrawal or treatment with a specific antagonist; recurrence of lesions temporally related to drug re-administration; presence of alternative causes (other than drug) that could, on their own, have caused the reaction; appearance of lesions after placebo administration; drug detection in blood (or other fluids) in concentrations known to be toxic; role of drug dosage in the worsening or improvement of the reaction; personal history of previous exposure to the same or similar drugs followed with similar reaction; and confirmation of adverse event by any objective evidence. We obtained in the above case a score of 4 (possible). There were no signs of any inflammatory disease, neoplasia or pregnancy. Moreover, SS was not preceded by any upper respiratory or gastrointestinal infection. However, the potential role

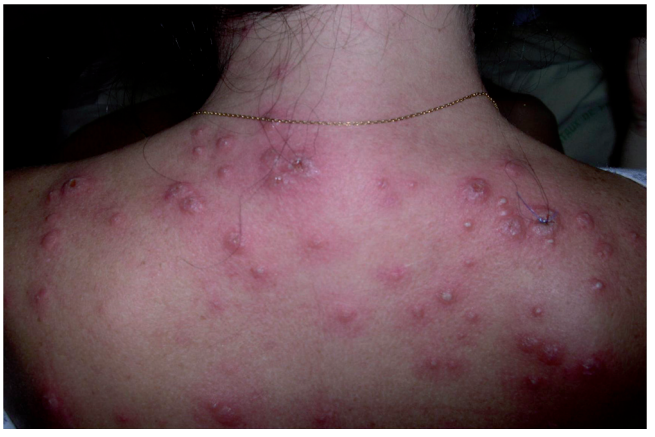

Fig. 1. Erythematous pustules and blisters on the upper back.

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of the vaginitis can be hypothesized. We considered it as unlikely for the following reasons: (*i*) at presentation, there was no local sign of infection of the genital tract, and (*ii*) a favourable course occurred under corticosteroid therapy without any associated antibiotherapy. Nonetheless, without any oral drug rechallenge, we cannot assess fully that the local infection did not take part in the occurrence of SS.

Drug-induced SS are rare and represent overall less than 5% of all cases (4). Approximately 50 cases have been reported, mostly as isolated clinical cases (Table I). In the first big series of SS patients (7), the authors did not find any link between drugs and neutrophilic dermatosis, except for one case induced after small-pox vaccination. Most of the published series of SS do not either seem to establish such a relationship (2, 8–10). Sitjas et al. (11) observed in a retrospective study of 30 patients with SS that 7 of them had received a new treatment before the rash occurred (non-specific anti-inflammatory drugs (NSAIDS), penicillin, carbamazepine). However, these drugs were often given for another confounding cause, especially an infection.

Table I. *Drugs reported as inducing Sweet's syndrome (5)*

Granulocytes growth factors
• G-CSF (granulocyte-colony stimulating factor)
• GM-CSF (granulocyte monocyte colony stimulating factor)
• All trans-retinoic acid
Vaccination
• Calmette-Guérin
• Influenza
• Streptococcus pneumoniae
• Small-pox
Antibiotics
• Clindamycin (14)
• Cyclines (minocycline, tetracycline and doxycycline)
• Quinolones: norfloxacin, ofloxacin
• Nitrofurantoin
• Streptogramin (quinupristin/dalfopristin)
• Trimethoprim-sulphamethoxazole
Antivirals
• Abacavir
• Acyclovir
Anti-tumoural biotherapies
• Proteasomes inhibitors (bortezomib)
• Tyrosine kinases inhibitors (imatinib)
Non-steroidal anti-inflammatory drugs
• Diclofenac
• Celecoxib, Rofecoxib
Psychotropes
• Amoxapine
• Clozapine
• Diazepam
• Lormetazepam
Miscellaneous
• Azathioprine
• Carbamazepine
• Furosemide
• Hydralazine
• Isotretinoin
• Lenalidomide
• Oral contraceptive levonorgestrel/ethynil oestradiol, gestodene/ethynil oestradiol
• Propylthiouracil

Delay is highly variable, ranging from several days to, exceptionally, 2 years (12), but mostly within 7 days (3, 4). Clinical presentation and histology are quite similar to the idiopathic form. Hyperleucocytosis could be less frequent during the drug-induced form (3, 13). Evolution is favourable after drug withdrawal. Fever vanishes within one to three days, eruption within 3–30 days under corticosteroid ointment and one week with oral corticosteroid therapy (4, 13). Relapses occur in case of drug re-introduction (13).

Physicians should look systematically for any newly introduced drug in case of acute neutrophilic dermatosis. A pre-existing underlying condition that may be associated with SS should not exclude such a possibility. However, in this situation, imputability criteria can be of great help for distinguishing such forms (5).

The authors declare no conflicts of interest.

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