

SHORT COMMUNICATION

Acute Generalized Exanthematous Pustulosis Induced by Paroxetine in an Adolescent Girl

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Acute generalized exanthematous pustulosis (AGEP) is a rare severe cutaneous reaction pattern, which, in the majority of cases, occurs in adults (males and females are equally affected). AGEP has rarely been described in the paediatric population (1, 2). Viral illnesses, vaccinations (e.g. anti-pneumococcal vaccine) and drugs (up to 90% of cases) have been implicated in the pathogenesis of AGEP (1, 2). Among drugs, the more commonly identified culprit agents are antibiotics (beta-lactams, macrolides, quinolones, pristinamycin, anti-infective sulphonamides), antimycotics (terbinafine, ketoconazole), calcium channel blockers (diltiazem), analgesics, antipyretics (paracetamol) and antimalarials (1). To date, however, the precise pathophysiological mechanism has not yet been identified and no report of AGEP caused by paroxetine, an antidepressant, has previously appeared in the English literature.

CASE REPORT

A 16-year-old girl with anorexia nervosa, with no personal or familial history of psoriasis, was referred to our Pediatric Department for a generalized pruritic pustular eruption. Twelve days after starting treatment with oral paroxetine (20 mg daily) the patient noticed erythematous papules and pustules on her neck and face, which had spread to the extremities and trunk over 3 days (Fig. 1a, b). Physical examination revealed bilateral symmetrical erythematous confluent patches on her arms, legs, abdomen, and back, studded with numerous scattered non-follicular pustules. The patient was afebrile with no lesions of the scalp; there was no mucous membrane involvement.

Laboratory examination revealed neutrophilic leukocytosis, while C-reactive protein levels were within the normal range.

Biopsy and histology revealed spongiform pustulation, subcorneal pustules and perivascular and diffuse dermal infiltrate of lymphocytes and eosinophils; mild dermal oedema was also noted (Fig. 1c, d). No micro-organism was identified in pustule cultures.

The AGEP validation score of the European Severe Cutaneous Adverse Reactions study group was used as diagnostic tool: in our patient the score was 10 (cut-off for definitive diagnosis = 8).



Fig. 1. (a) Acute generalized exanthematous pustulosis in a 14-year-old girl. (b) Rash on the right arm. (c) Spongiform pustulation, subcorneal pustules and diffuse dermal infiltrate of lymphocytes and eosinophils; mild dermal oedema. Hematoxylin-eosin (H&E); $\times 40$. (d) Histological detail in sections from a lesion. (H&E); $\times 100$.

Detailed pharmacokinetic and pharmacogenetic analyses were carried out. Paroxetine plasma concentrations resulted within the normal range (46 ng/ml, with normal reference values ranging from 30 to 120 ng/ml (3)). Normal pattern of paroxetine metabolism was confirmed by the pyrosequencing analysis displaying no allelic variants in the CYP2D6 gene (4).

Epicutaneous patch-testing and drug re-challenge were not performed due to the risk of triggering an even more serious and potentially life-threatening AGEP.

Other possible differential diagnoses of pustular eruptions, such as bacterial folliculitis, pustular psoriasis, subcorneal pustular dermatosis, immunoglobulin A (IgA) pemphigus, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, viral infections or vaccinations, were promptly excluded by anamnesis, dermatological evaluation and serological tests for the common viral agents.

Considering the clinical and histopathological features, and given the temporal association with paroxetine administration, in the absence of other triggering factors, a diagnosis of AGEP attributable to paroxetine was made. Paroxetine was immediately discontinued and the patient was treated with oral steroids (prednisone 50 mg daily); cutaneous eruptions progressively improved and resolved by 2 weeks.

DISCUSSION

AGEP is primarily an adverse reaction to drugs. Although many medications have been hypothesized as causative agents, a strong association is documented for only a few drugs; *in primis* pristinamycin, aminopenicillins, terbinafine, diltiazem and (hydroxy) chloroquine (5).

In adults, cases of AGEP caused by central nervous system-active medications (olanzapine, sertraline, carbamazepine) have been reported, although rarely (6–8). To our knowledge this is the first case of AGEP induced in a paediatric patient by paroxetine, which is one of the most widely prescribed antidepressants, due to its better established safety profile compared with other antidepressants.

The pathophysiology of AGEP is not fully understood. An altered immunological response to small molecules with up-regulated drug-specific T-cell proliferation and interleukin (IL)-8/CXCL8 production has been suggested (9). Alternatively, a type IV hypersensitivity reaction, with excessive production of antigen-antibody complexes and massive neutrophil chemotaxis, may be the underlying pathogenic mechanism (1). In order to explore the possibility that our patient may have developed AGEP due to higher than expected paroxetine exposure, we performed detailed pharmacokinetic and pharmacogenetic evaluations. Intriguingly, in our patient, the pharmacokinetic and pharmacogenetic assays did not display paroxetine plasma concentration above

limits nor genetically-based reduced drug clearance, allowing us to exclude the above-mentioned pathogenic hypothesis. To date, however, genetic predisposition to AGEP has not been completely assessed.

Certain class I HLA and class II HLA alleles have recently been found to be the genetic determinants triggering drug hypersensitivities in severe cutaneous reactions, such as bullous fixed drug eruptions, drug-induced hypersensitivity syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis (10). Notably, HLA-B*51, DR*11, DQ*3 have been linked to the genetic predisposition to AGEP (10); however, the possibility that as-yet unidentified specific HLA alleles may predispose to the development of drug-induced skin reaction in patients treated with selective serotonin reuptake inhibitors represents an intriguing hypothesis that requires further study.

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