Stevens-Johnson syndrome-toxic epidermal necrolysis: a fatal cutaneous adverse reaction to oral acyclovir

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DESCRIPTION
An otherwise healthy 26-year-old man presented to the emergency department with fever and generalised rash for the preceding 2 days. He had been prescribed a 7-day course of tablet acyclovir 400 mg (three times per day) for treatment of herpes labialis infection by his local physician. He commenced to take the medication the following day (day 1). A day later (day 2), he developed fever, malaise, stinging eyes, pain on swallowing and tender skin lesions, which appeared first on the face and spread rapidly to involve the back, trunk and extremities. Subsequently, areas of skin peeling with painful erosion of mucous membrane were noted. He had no known drug allergy, nor was he taking any other drugs (conventional or complementary medicine) apart from acyclovir, which was immediately stopped. On admission (day 5), cutaneous examination revealed dusky-red purpuric macules (many surmounted by vesicles) of various sizes with a tendency to coalesce, involving approximately 25% of body surface area (figure 1B). Multiple flaccid blisters with positive Asboe-Hansen sign were noted in over the trunk. Positive pseudo-Nikolsky sign was elicited, revealing large areas of raw and bleeding dermis beneath. Mucous membrane involvement, which had preceded the skin eruption, was characterised by painful erosion, haemorrhagic crusting of the lips, oral cavity and mucopurulent conjunctival discharge (figure 1A). Multinucleate giant cells were not visualised on Tzanck smear of blister. Laboratory investigations were notable for raised creatinine, transaminases, leucocytosis and thrombocytopenia. Based on severity of illness score for toxic epidermal necrolysis (score=3), the mortality risk was estimated to be 35.8%.

Causality assessment was ‘probable’ according to Naranjo Probability Scale (score=6) and ‘probable/likely’ as per the WHO-Uppsala Monitoring Centre criteria. Based on clinical features and temporal association with the drug, a diagnosis of acyclovir-induced Stevens-Johnson syndrome (SJS) was established.

The culprit and all other non-essential drugs were promptly discontinued. He was started on oral cyclosporine (5 mg/kg) along with adequate supportive care. In spite of vigorous management, his condition progressively worsened (complicated by acute kidney injury, acute respiratory distress syndrome and deteriorating Glasgow Coma Score). He eventually succumbed to the ongoing disease process on day 11.

Acyclovir is a synthetic guanosine analogue which is widely prescribed for herpes simplex and varicella zoster virus infections. It is a potent and highly selective inhibitor of viral DNA polymerase with little side effects on the host. Adverse events like injection site inflammation, phlebitis, bullous reaction, acute renal failure and neurotoxicity have been reported with intravenous acyclovir therapy.3 We hereby report a fatal case of SJS and toxic epidermal necrolysis (SJS/TEN), developing in a young adult who was prescribed oral acyclovir.

SJS/TEN represents a rare, potentially life-threatening, immune-complex-mediated cutaneous adverse drug reaction characterised by extensive epidermal detachment, erosion of mucosa and severe constitutional symptoms with 10%–30% body surface area detachment.5 The present understanding of epidermal necrolysis

Figure 1 (A) Mucopurulent conjunctival discharge, erosions with haemorrhagic crusting involving lips, oral and nasal mucosa, with areas of detached necrotic epidermis over face; (B) Multiple dusky-red purpuric macules surmounted with blisters over the trunk and extremities.

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suggests it is an immune-driven pathway mediated by granulysin released by drug-specific cytotoxic CD8 T-cells and natural killer cells.\(^3\) Although any drug can cause SJS/TEN, the usual culprit agents are aromatic anticonvulsants, allopurinol, non-steroidal anti-inflammatory drugs, sulfonamide antibiotics and nevirapine.\(^1\) Review of literature highlighted two previous reports (none of which had a fatal outcome, unlike the present case) that incriminated acyclovir as a culprit agent in SJS/TEN.\(^4\)\(^5\)

We highlight an adverse cutaneous drug reaction to a commonly prescribed drug, acyclovir; thereby adding to the expanding list of implicated drugs for SJS/TEN.

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**Patient’s perspective**

They tried a lot to save my son. They stood by me when I was helpless. They are the real heroes. They did their best. It was my fate that I lost my son. God bless them. - Father of the patient

**Learning points**

- Acyclovir is a potent and highly selective inhibitor of viral DNA polymerase with little side effects on the host. Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS/TEN) overlap represents an extremely rare adverse effect of this widely prescribed drug.

- Physicians should be acquainted with the scoring system, severity of illness score for toxic epidermal necrolysis, as it serves as a useful predictor of mortality for SJS/TEN patients at the time of admission. This will aid clinicians in risk–benefit analysis and better utilisation of limited resources especially in resource-poor settings.