

Case report

Meropenem-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in a patient with known type IV penicillin hypersensitivity

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SUMMARY

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered variants of a disease continuum that results in a life-threatening exfoliative mucocutaneous disease. These are categorised as type IV cell-mediated delayed hypersensitivity reactions, and antibiotics are often implicated as a cause. Penicillins and other beta-lactam antibiotics are known to cause both immediate and delayed hypersensitivity reactions. While immediate IgE-mediated cross-reactivity between penicillins and carbapenems is well studied, less information on the risk of type IV delayed cell-mediated cross-reactivity between the two is available. We present a case of meropenem-induced SJS in a patient with documented history of SJS from amoxicillin. There are few cases of cross-reactivity with carbapenems reported in the literature, but based on the potential for life-threatening reaction, it is likely prudent to avoid the use of any beta-lactams in a patient with a history of SJS, TEN or any other severe cutaneous adverse reactions to another beta-lactam antibiotic.

BACKGROUND

Allergic reactions to antimicrobials are considered type B adverse drug reactions—pharmacologically unpredictable, non-dose dependent and often immune mediated (though aspects of this definition have changed over time with further mechanistic understanding). Type B reactions are further divided into types I through IV in the Gell and Coombs classification system. Type I, or IgE-mediated, reactions are well appreciated, with now predictable rates of cross-reactivity between certain antimicrobial classes.¹ Patients with reported type I penicillin allergy have an ~2% risk of IgE-mediated cross-reactivity to cephalosporins, <1% to carbapenems and 0% to monobactams.² Data on beta-lactam cross-reactivity for type II (cytotoxic), type III (immune complex) and type IV (cell mediated) reactions are less robust. Included within type IV are the severe cutaneous adverse reactions (SCARs), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS/TEN overlap, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP).³ Understanding of the risk of cross-reactivity in a patient with a history of a SCAR caused by a beta-lactam is critical in order to minimise the risk of a potentially life-threatening reaction.

CASE PRESENTATION

A 67-year-old Caucasian woman with a history of diabetes, hypertension and cerebrovascular accident was admitted to the hospital due to fever (102°F), diffuse abdominal pain and dark-coloured urine for 3 days. Pyelonephritis was diagnosed based on leucocytosis, pyuria and CT findings. Meropenem and vancomycin were empirically administered while evaluation as to a source of infection was underway, and vancomycin was discontinued shortly thereafter. A susceptible *Klebsiella pneumoniae* grew from the urine.

During infusion of the seventh dose of meropenem on day 3, the patient developed erythematous rash starting on the torso and spreading to the face and extremities, with oedema around the skin folds of her face, and all extremities. Simultaneously, she reported severe itching, nausea and vomiting. Leucocyte count rose to 25.7×10⁹/L and temperature to 103.7°F. Diphenhydramine was given and meropenem infusion was stopped. Levofloxacin was given for the remainder of the treatment course for pyelonephritis.

Over the course of the next several days vesicles and bullae developed on the lower extremities, and diffuse erythematous maculopapular rash on the torso persisted (figure 1). Mucosal involvement was noted on maxillary gingiva under her dentures and on the hard palate (figure 2). It was estimated that 10% of her body surface area was affected and her SCORTEN score (SCORE of Toxic Epidermal Necrosis) was calculated at 3 with an estimated mortality of 35.5%.⁴ Erythema was induced by firm downward pressure on the inner left thigh at a relatively uninvolved skin segment, using a gloved finger. After a lag time of 10 min, the biopsy was taken to include the border of the erythematous and non-erythematous skin. Skin biopsy showed full thickness necrosis of epidermis and dermal inflammation, consistent with SJS/TEN (figure 3). Over the course of the week, the patient continued to be febrile and leucocyte count trended up to 30.2×10⁹/L with neutrophil predominance. Her liver enzymes, and renal functions remained at baseline and no ophthalmological manifestations or lymphadenopathy were observed. Perturbations in lymphocyte, eosinophil and platelet counts were absent. The patient received maintenance fluids to equilibrate the loss from the denuded skin, was treated with oral prednisone and topical tacrolimus.



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Figure 1 Non-blanching erythema, skin sloughing and raised lesions in the patient's left leg.

She required transfer to the intensive care unit due to desquamation of ~10% body surface area (BSA).^{5 6}

INVESTIGATIONS

1. Leucocyte count: $19.8 \times 10^9/L$ on admission $\rightarrow 30.2 \times 10^9/L$ on day 7 $\rightarrow 9.6 \times 10^9/L$ on discharge.
2. Urine analysis: leucocyte esterase $500/\mu L$, marked bacteria, 26–50 white cells/hpf, marked proteinuria.
3. CT abdomen on admission showed cortical enhancement of the left kidney, with perinephric fat stranding with no hydronephrosis.
4. Skin biopsy (left thigh): full thickness necrosis of epidermis and dermal inflammation confirming the biopsy was compatible with SJS (figure 3).

DIFFERENTIAL DIAGNOSIS

The clinical features of this case were consistent with a SCAR, which includes SJS, TEN, SJS/TEN overlap, DRESS and AGEP. The lack of organ involvement, lymphadenopathy, thrombocytopenia and eosinophilia effectively excluded DRESS as a possibility. There were, however, aspects of both SJS/TEN and AGEP noted in this patient. While the clinical findings of vesicles, bullae, Nikolsky sign and desquamation were consistent with a disorder along the SJS–TENS spectrum, the rapid onset was more consistent with the usual



Figure 2 Patient's oral cavity showing mucosal erosions on the palate.

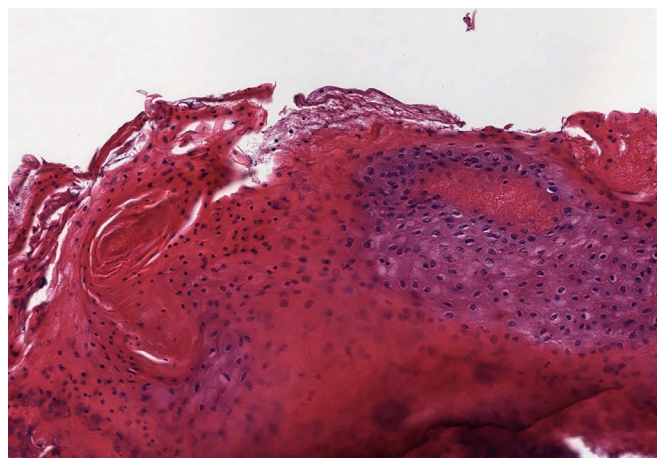


Figure 3 Skin biopsy showing full thickness epidermal necrosis, dermal inflammation and basal separation.

time course of AGEP. However, the time to onset of SJS–TENS spectrum symptoms here may have been decreased in the setting of beta-lactam prior sensitisation. This patient did have features that could have suggested a diagnosis of AGEP; some areas appeared pustular before coalescing, and there was notable neutrophilia and facial oedema with worsening in facial folds. However, histopathological findings in AGEP are non-specific and desquamation should be superficial only, unlike what was seen in this case. Additionally, mucosal involvement is less commonly seen in AGEP. Overall, the clinical features and full thickness epidermal necrosis aligned with diagnostic criteria for SJS–TENS spectrum.

OUTCOME AND FOLLOW-UP

Patient was discharged after a prolonged hospital course of 28 days. At time of discharge, the rash was limited to ~2% BSA on the thighs (figure 4) and leucocyte count had normalised to $9.6 \times 10^9/L$, and patient has been afebrile for 8 days.

DISCUSSION

SJS, SJS/TEN overlap and TEN, all type IV hypersensitivity SCARs, are life-threatening exfoliative mucocutaneous diseases occurring along a continuum. They are distinguished based on the percentage



Figure 4 Patient's left leg showing scabbing and healing of bullae and rash.

of BSA with epidermal separation (<10% SJS; >30% TEN; 10%–30% SJS/TEN overlap). The incidence of SJS/TEN is 1–6 cases per million person-years. Clinical presentation can include fever, cutaneous oedema, cutaneous and mucosal erosions, epidermolysis and bleeding from areas of skin desquamation. Although very rare these conditions may be fatal or severely disabling.⁷ The mortality from SJS/TEN is 10% overall and can be predicted using the SCORTEN score (score of 1%–3.2% mortality; score 5–7%–90% mortality). Mortality is mostly secondary to sepsis, acute respiratory distress syndrome and multiorgan failure.⁴

Pathogenesis of SJS/TEN is due to T-cell-mediated cytotoxic reaction against keratinocytes leading to apoptosis; the key histological finding is widely dispersed necrotic keratinocytes or full thickness necrosis of the epidermis. Other less common findings are lymphohistiocytic infiltration of the upper dermis and eosinophils in the epidermis. A skin biopsy is required to confirm the diagnosis, but clinical features in the presence of a triggering agent are highly suggestive. The mainstay of management is stopping the offending agent and providing supportive care with fluids replacement, wound care and a sterile environment.⁷ Adjunctive therapies such as corticosteroids, intravenous Igs, and immunosuppressants have been used but not definitively proven to be beneficial; this remains an area requiring further research as current practice varies.^{3,8}

Medications were implicated as a cause in 75% of cases using the algorithm of drug causality of epidermal necrolysis classification⁹; the major drug classes implicated are antibiotics and anticonvulsants. Drug manufacturer's package inserts for meropenem,¹⁰ doripenem¹¹ and imipenem–cilastatin all list SJS and TEN as possible adverse drug reactions identified in postmarketing analysis,¹² but there are few cases in the literature reporting carbapenem-induced SCARs. Two instances of TEN due to imipenem–cilastatin and one due to meropenem are reported in one case series,¹³ and one carbapenem causing a SCAR reported in another.³ Other reports show a recurrence of SJS or TEN in patients known to have similar reaction to another beta-lactam antibiotic (ampicillin and ertapenem; cefotaxime and meropenem).^{14,15} Additionally, there are reports of absence of cross-reactivity clinically between penicillin and carbapenem³; amoxicillin and carbapenem,¹⁶ and of low rates of penicillin–carbapenem type IV cross-reactivity via skin testing (4/73 in Schiavino *et al*¹⁷ and 0/204 in Romano *et al*¹⁸).

While carbapenems have been used to either replace an initial offending beta-lactam antibiotic,³ or for infectious complications of SJS/TEN,¹⁹ it is generally accepted that anyone with a type II, III or IV hypersensitivity reaction should never be retested, rechallenged or desensitised.²⁰ Furthermore, a thorough allergy history to classify the type of reaction is critical in all patients reporting an allergy. This can help determine when an antibiotic can be safely administered based on history of a mild, non-allergic or remote IgE-mediated allergy alone, versus times it may be appropriate to initiate skin testing, or when to avoid any further testing or challenge.²¹

Learning points

- ▶ Carbapenems and penicillins share a common beta-lactam ring, that can cause type I (immediate) hypersensitivity cross-reaction as well as type IV (delayed) hypersensitivity.
- ▶ Type IV hypersensitivity reactions like Stevens-Johnson syndrome or TEN are absolute contraindications for the use of the same class of antibiotic.
- ▶ It is important take a thorough allergy history and document the type of reaction of all the reported allergic medications.

This case report highlights the need to avoid all beta-lactam ring containing antibiotics in a patient with documented history of a severe T-cell-mediated hypersensitivity reaction like SJS/TEN to any beta-lactam containing antibiotic.

Contributors MS: wrote the manuscript and did the literature search for this case, he was also the intern taking care of the patient. CN: helped in writing the case and acquiring pathology images. PB: was the senior resident on the team and guided the whole project. SAS: mentor and expert from infectious disease for the case, she helped revised the manuscript, added additional literature references and corrected multiple drafts of the manuscript.

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