Persistent fever in a child with eosinophilia and systemic symptoms: a case report

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Hong Kong Med J 2022;28:400–2
https://doi.org/10.12809/hkmj208607

Case

In October 2019, an 8-year-old girl with Diamond–Blackfan anaemia on long-term maintenance steroid therapy was admitted to a paediatric unit with meningitis. The meningitis was caused by extended spectrum beta-lactamase-producing *Klebsiella pneumonia* that was sensitive to meropenem but resistant to cephalosporin and penicillin group of antibiotics. She was treated with intravenous meropenem and her fever subsided.

On day 21 of meropenem treatment the patient's fever recurred with temperature of 39.7°C and associated abdominal pain, diarrhoea, and rash (Fig 1). Physical examination revealed a generalised blanchable erythematous maculopapular rash over her face, torso, and limbs with no mucosal involvement or lymphadenopathy (Fig 2). She was tachycardic at 150 beats per minute but her blood pressure was normal. She was given fluid boluses and managed in the paediatric intensive care unit with a noradrenaline infusion (0.05 μg/kg/min), prednisolone (increased to 20 mg daily), and the addition of vancomycin.

Autoimmune disease and infection workup including serology for Epstein–Barr virus, cytomegalovirus, and human herpesvirus 6 and stool culture for ova, cysts, and parasites examination were all negative. The patient's C-reactive protein level was 166.43 mg/L (normal range <10 mg/L) and procalcitonin was 3.63 ng/mL (normal range

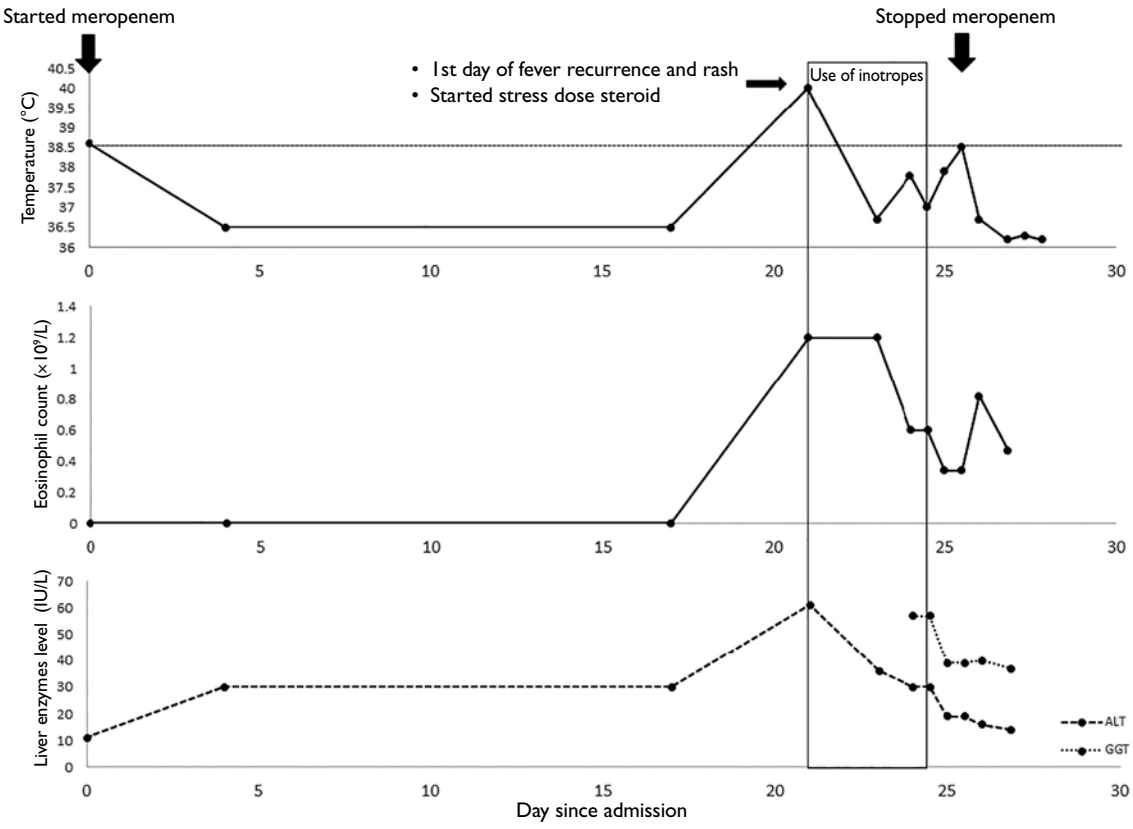

FIG 1. Temporal relationship of antibiotic use and clinical parameters
Abbreviations: ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase

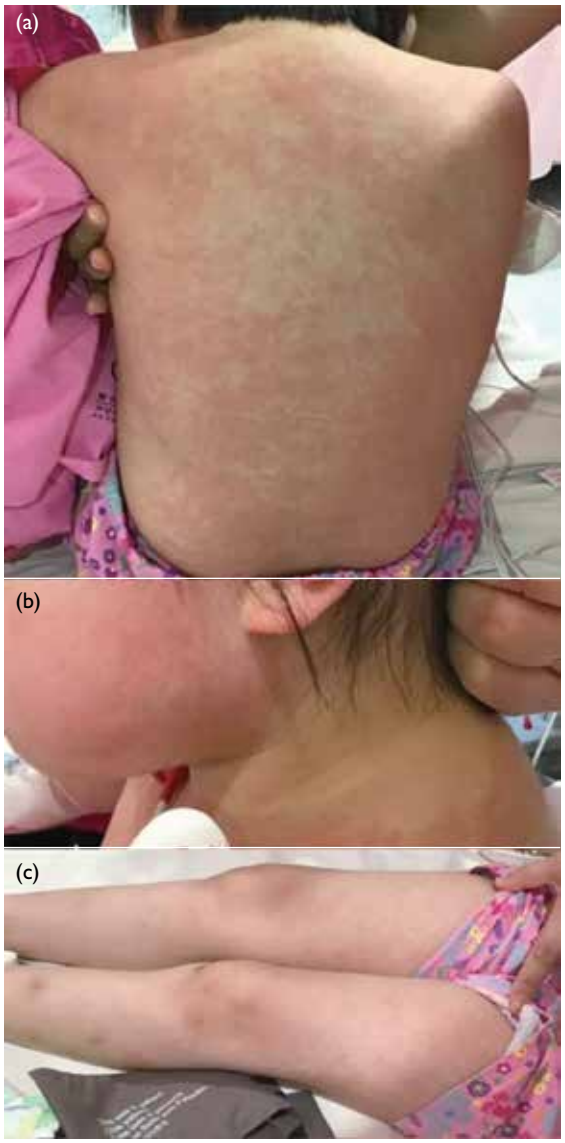

FIG 2. An 8-year-old girl with meropenem-associated drug reaction with eosinophilia and systemic symptoms. Clinical photographs show rash over (a) torso, (b) face, and (c) limbs

<0.5 ng/mL). There was evolving eosinophilia since fever recurrence. The absolute eosinophil count was elevated to 1.2×10^9/L (18.9% of total white cell count) on the first day of fever recurrence with a peak of 1.4×10^9/L (35.4% of total white cell count). Gamma-glutamyl transferase level was elevated (57 IU/L). Skin biopsy showed non-specific perivascular lymphocyte infiltration with no eosinophils. There was no erythema multiforme-like pattern, spongiosis, interface change or vasculitis and staining showed no fungus.

Meropenem-associated drug reaction with eosinophilia and systemic symptoms (DRESS) was suspected in view of her fever, rash, persistent eosinophilia, and deranged liver function alongside prolonged meropenem use and a negative infection workup. Meropenem was therefore stopped, and her fever subsided after 6 hours. She was also weaned off inotrope support. She remained hemodynamically stable and the rash did not worsen and gradually subsided in 48 hours. She was discharged from the paediatric intensive care unit 2 days later. There was no residual rash and eosinophil count had normalised 2 weeks after onset of DRESS symptoms.

Discussion

Children with fever and rashes pose challenges in diagnosis and management. Differential diagnoses must consider "drug versus bug" scenarios.[1] Drug reaction with eosinophilia and systemic symptoms is a rare reaction to certain medications and involves a widespread skin rash, fever, swollen lymph nodes, and characteristic blood abnormalities including eosinophilia, thrombocytopenia and atypical lymphocytosis.[2] Drug reaction with eosinophilia and systemic symptoms is classified as a form of severe cutaneous adverse reaction that usually develops within 6 weeks of initiation of the suspected drug.[3] It may be associated with hepatitis, carditis, interstitial nephritis or interstitial pneumonitis and is potentially life-threatening with a reported mortality rate up to 10%.[2] The estimated incidence of DRESS is 1 in 1000 to 1 in 10000 drug exposures and is more commonly observed in adults than children.[4]

The RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) developed a scoring system in 2007 to classify patients as having no, possible, probable, or definite DRESS based on clinical features and laboratory findings.[5] Our patient had a score of 3 and was classified as possible DRESS, with extreme eosinophilia, rash with >50% body surface area involvement and negative microbiological investigations. One point was deducted from the score for "rash resolution more than 15 days". Her aminotransferase and bilirubin level remained normal throughout although gamma-glutamyl transferase was elevated. Skin biopsy revealed perivascular lymphocytosis, a commonly observed feature among patients with DRESS.[5] Skin biopsy is indicated as one of the parameters in RegiSCAR if facilities are available.

Carbapenems, as members of the beta-lactam antibiotics, are reported to pose a low risk of allergic reaction or DRESS. The incidence of rash, pruritis and urticaria after use of carbapenem has been reported to be only 0.3 to 3.7%, with rash reported in only 1.4% of patients treated with meropenem.[6] Early suspicion of DRESS is crucial as discontinuation of the culprit drug can prevent development of potentially life-threatening complications. This case illustrates that all sepsis symptomatology subsided in a febrile patient with rash and eosinophilia, not by adding more drugs but by considering the possibility

of severe cutaneous adverse reactions and removing the culprit drug.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have no conflicts of interest to disclose.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki and a parent provided informed consent for all treatments and procedures. Consent was obtained from the patient and her parents for publication.

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