Severe Cutaneous Adverse Reactions Following Intravenous Contrast: A Report of 2 Cases

Dear Editor,

With the advent of computer tomography (CT) imaging and cardiac catheterisation procedures, radiologic investigations employing the use of iodinated contrast media have experienced rapid growth in the last 20 years, with increasing numbers of patients receiving contrast.[1]

Most contrast-related adverse events (AE) are mild, including nausea, vomiting and urticaria. However, some are severe, resulting in renal impairment, shock and cardiac arrest. Of the severe cutaneous AEs, there are immediate reactions such as anaphylaxis, as well as delayed reactions such as maculopapular exanthems, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The use of high-osmolar contrast media (HOCM), which was prevalent from 1985 onwards, gave way to the safer low-osmolar contrast media (LOCM) in the early 1990s. This has led to a fall in the incidence of AEs attributed to contrast media from 6% to 8% to 0.2% to 0.7% as described by Cochran et al[2] in 2001.

Nevertheless, severe and delayed dermatologic manifestations can still result from contrasted scans. We report 2 patients who suffered from SJS/TEN overlap after receiving iodinated contrast.

Case 1

A 61-year-old Malay female was admitted for an acute ST-elevation myocardial infarction (STEMI). Her past medical history was significant for hypertension, hyperlipidaemia, type 2 diabetes mellitus complicated by end-stage renal failure and ischaemic heart disease. She underwent coronary artery bypass graft surgery (CABG), which was complicated by pericardial tamponade, sternal wound dehiscence and multiple hospital-acquired infections (HAIs). She also had a history of urticaria secondary to amlodipine 2 years ago; this suspected drug allergy was not formally evaluated.

During her inpatient stay, she received a total of 3 CT scans with intravenous contrast (Omnipaque) administration.

The first scan performed on 12 November 2013 was uneventful. Two weeks later, a second scan was performed. Two weeks thereafter, she complained of generalised pruritus. An inpatient dermatology referral was then made by the primary team. The initial assessment was widespread xerotic eczema. Moisturisers and topical corticosteroids were prescribed.

Over the next 5 days, from 13 to 17 December 2013, a dusky reticulate erythema assumed prominence over her dry scaly erythematous plaques, and it rapidly spread over her face, trunk, and limbs. Nikolsky's sign was positive in lesional and perilesional skin. Body surface area (BSA) involvement was 5% sparing the mucosal surfaces. At this juncture, SCORTEN was 1 in view of her age.

A skin biopsy revealed almost a complete separation of necrotic epidermis from the underlying dermis, associated with perivascular and interstitial lymphocytic infiltrate and scattered apoptotic bodies.

Three new medications (cefazolin, linagliptin and metoclopramide) had been started 3 weeks prior to the onset of her symptoms, Cefazolin was given from 29 October to 18 November 2013; metochlorpromide and linagliptin were each given as single doses on 22 November. They were deemed possible inciting agents of a suspected severe cutaneous drug reaction and were discontinued. She was started on oral prednisolone at 0.5 mg/kg/day on 18 December.

On the same day, she underwent a third CT scan with intravenous contrast in an attempt to investigate the source of persistent sepsis.

The next day after the third episode of contrast administration, the patient reported skin pain and painful swallowing. Clinical examination revealed increased skin denudation and erosions over the upper back, face, trunk and limbs. Detached BSA was 16%. There was conjunctival injection and haemorrhagic crusting of her lips (Figs. 1 and 2). Her diagnosis was revised to SJS/TEN overlap and intravenous immunoglobulin (IVIG) infusion was commenced at 1 g/kg/day for 2 days. Intravenous contrast was implicated as the most likely culprit agent.

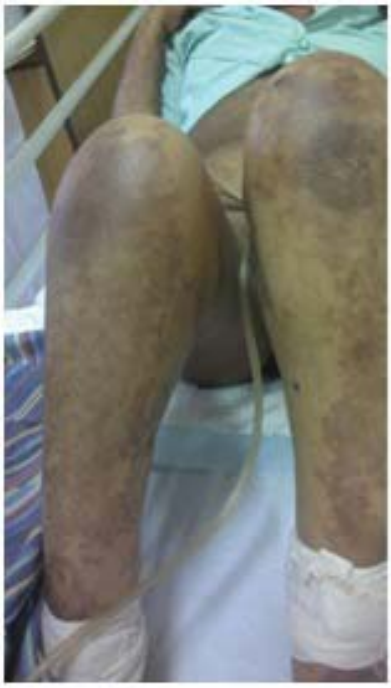

Fig 1. An increasingly dusky reticulate erythema seen over the extensor surfaces of the lower limbs.

Fig 2. Skin denudation and erosions over the upper chest and face.

She did not have clinical evidence to suggest other organ involvement. Transminases were normal with an alanine aminotransferase (ALT) of 29 U/L and an aspartate transaminase (AST) of 6 U/L. Eosinophils were elevated at 1.49 x 10^9/L. Her creatinine was elevated at 466 umol/L consistent with her background of end-stage renal failure.

After 1 day of IVIG, she succumbed to severe sepsis without re-epithelialisation.

Case 2

A 60-year-old Malay male with end-stage renal failure from poorly controlled hypertension had an ascending aortic aneurysm requiring yearly CT aortograms for the past 4 years prior to presentation. He had no previous history of drug allergies.

He was admitted on 29 November 2013, after receiving intravenous contrast (Iopaque) during a routine imaging scan 3 days earlier. This was his fourth CT aortogram. There was no exposure to new medications.

He complained of a 2-day history of fever, painful lips, multiple episodes of diarrhoea, and increasingly painful skin.

Clinical examination revealed dusky erythematous patches over the arms, neck, upper back, thighs and calves. There were multiple flaccid bullae seen over the upper outer arms and thighs. Nikolsky's sign was positive with exquisite cutaneous tenderness. Detached BSA was 11%. Haemorrhagic crusts were seen on the lips. SCORTEN was 4 in view of the patient's age, urea of 37 mmol/L, bicarbonate of 37 mEq/L and BSA.

A diagnosis of SJS/TEN overlap was made and he was commenced on intravenous immunoglobulin at 1 g/kg/day for 3 days. Skin biopsy revealed a completely necrotic epidermis lifted off the dermis, with mild oedema and a sparse lymphocytic.

There was no clinical evidence of other organ involvement. Transminases were normal with an ALT of 48 U/L and AST of 41 U/L. Eosinophils were 0.61 x 10^9/L. His creatinine was elevated at 1251 umol/L consistent with his background of end-stage renal failure.

Though the detached BSA eventually extended to 18%, he recovered with complete re-epithelialisation by day 12 of admission and was discharged.

Discussion

The use of contrast media has become increasingly commonplace with radiological procedures used for both

diagnostic and therapeutic purposes. In the last 20 years, the use of CT scans has increased by 8 times.[3] It is important that physicians remain cognisant of the inherent risks of contrast media.

Immediate reactions include anaphylactoid reactions which occur unpredictably and independently of the dose or concentration of the agent without an identifiable antigen-antibody response.[4,5] Common risk factors for these reactions include patients who have had a previous anaphylactoid event to contrast media, atopic individuals with multiple allergies, and asthmatics.[5] Physicians are most watchful for these immediate contrast-related reactions; the inciting agent is usually appropriately identified and intervention is administered. On the other hand, delayed allergic-like events are defined by the The American College of Radiology as those that occur between 3 hours to days after administration of contrast.[6] Severe cutaneous adverse reactions (SCARs) such as DRESS, SJS and TEN fall under this category of reactions.[7]

The longer latency period for the development of SCARS[8,9] translates to a lower likelihood that the managing physician connects the adverse cutaneous reaction to contrast administration. In fact, by this time, many physicians may not even consider contrast as a possible inciting agent. New drugs may have been administered in the intervening time frame which complicates an aetiological search. Complex medical patients with a septic picture may even be subjected to further contrasted scans. This was evident in our first case, where repeated contrasted scans were done, resulting in worsening of her skin condition.

Interestingly, there are striking similarities in both our patients who suffered from a SJS/TEN overlap following the use of contrast media. Both were of Malay ethnicity and suffered from end-stage renal disease. The contrast medium used in both cases was iohexol, a LOCM with an osmolality of 322 mOsm/kg.

Pre-existing renal disease is an established risk factor for physiological chemotoxic reactions to contrast media due to specific physicochemical effects of the contrast agent which leads to renal-specific effects such renovascular constriction, decreased blood flow, and alteration in glomerular permeability.[4] However, it is unclear if this is associated with an increased risk of cutaneous adverse effects. We postulate that in our 2 cases, the delayed renal clearance of the contrasted medium might have played a role in the development and severity of the SCARs. The elimination half-life of iodinated contrast increases progressively with renal impairment, and it is with dialysis that the contrast is removed. Approximately 58% of a 50 mL dose administered will be removed after a single dialysis session.[10]

It is also known that genetic factors influence an individual's susceptibility to develop SCARs. There is a strong association of allopurinol-related SCARs with the *HLA-B*5801* allele[11] in Han Chinese populations as well as carbamazepine-induced SJS with the *HLA-B*1502* allele that are found in Indians.[12] Similarly, it is possible that ethnic and thus, genetic factors play a role in the development of SCARs with contrast media as both of these patients were of Malay ethnicity. Further studies are needed to elucidate the possibility of pharmacogenetic influence on the development of SCARs with contrast media.

Conclusion

Whilst delayed and severe cutaneous reactions such as SJS and TEN due to LOCM may be uncommon, they do indeed occur. A high index of suspicion is required to accurately identify and cease the culprit agent, and thereby reduce morbidity and mortality.

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