Clinical Communications

Skin testing in gadolinium allergy: 2 case reports

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Clinical Implications

- We present 2 cases of anaphylaxis to gadobutrol. We propose an algorithm for investigating such reactions, indicating the importance of skin testing to confirm the diagnosis and identify safe alternatives.

TO THE EDITOR:

The use of gadolinium-based contrast agents (GBCAs) has increased over the last 20 years, but anaphylactic reactions are rare, ranging from 0.004% to 0.01%.[1] There were 614 reports of GBCA anaphylaxis to the Food and Drug Administration adverse reporting system between 1988 and 2012.[2] Deaths have been reported to gadobenate dimeglumine,[3] gadobutrol,[4] and gadoteridol.[5] We present 2 cases of anaphylaxis to gadobutrol and propose a management algorithm, indicating the importance of skin testing to confirm diagnosis and identify safe alternatives.

Case 1: A 65-year-old man presented with paroxysmal atrial flutter undergoing magnetic resonance imaging (MRI) angiography before ablation. Immediately after the second bolus of gadobutrol he developed tongue and facial angioedema. His pulse became weak and blood pressure unrecordable. He received 4 doses of intravenous (IV) epinephrine (0.1 mg), 2 intramuscular doses of epinephrine (0.5 mg), succinylated gelatine (500 mL), normal saline (1 L), and IV hydrocortisone (200 mg) and was admitted to intensive care. Tryptase levels measured at 1, 4, and 24 hours were 69.1, 48.7, and 16.5 ng/mL, respectively (normal, 2-14 ng/mL). Baseline tryptase level was 13.8 ng/mL. This was his first exposure to GBCA, he was nonatopic, and his medications included sotalol.

Skin tests were undertaken 3 months later to the MRI contrasts agent gadobutrol (Gadovist; Bayer plc, Berkshire, United Kingdom) and gadopentetate dimeglumine (Magnevist; Bayer plc). Skin prick test (SPT) results using the undiluted available MRI contrast agents were negative (gadobutrol 604 mg/mL and gadopentetate dimeglumine 469 mg/mL). However, intradermal test (IDT) results were strongly positive (20 mm wheal with pseudopodia and 30 mm flare) to gadobutrol at a dilution of 10^{-2} (Figure 1), confirming gadobutrol allergy. SPT and IDT results to gadopentetate dimeglumine were negative and this agent was suggested as an alternative GBCA for future use.

Case 2: A 47-year-old man with low-grade glioma required annual MRI head scans. IV gadobutrol was administered and the scan was completed without incident. Within a few minutes, his face became hot and flushed; he then developed widespread urticaria and returned to hospital and collapsed. He was treated with IV chlorphenamine and hydrocortisone. The first set of observations recorded after he had stabilized were normal. Serum tryptase level taken at 4 hours after the initial reaction was 9 ng/mL, with a baseline of 4 ng/mL.

SPT (undiluted concentration) results were negative but IDT (10^{-2} concentration) results were strongly positive to gadobutrol (wheal, 12 × 12 mm; flare, 35 × 45 mm), confirming allergy to gadobutrol. SPT and IDT results were negative to gadopentetate dimeglumine, and the patient tolerated a subsequent MRI head scan with gadopentetate dimeglumine.

SPT and IDT were undertaken on 10 healthy controls. Seven of the 10 had previous uneventful MRI, and 2 were atopic. SPT to gadobutrol 604 mg/mL and gadopentetate dimeglumine 469 mg/mL and IDT at 10^{-2} were all negative, confirming a nonirritant concentration.

DISCUSSION

These cases demonstrate IgE-mediated allergic reactions to gadobutrol confirmed by skin testing. Previous studies reported the incidence of immediate hypersensitivity reactions to GBCA,[3,4] but did not confirm with skin testing whether reactions were IgE-mediated. The main risk to patients is that of recurrence. Jung et al[4] reported 112 reactions in 102 patients, where 6 patients had a recurrent hypersensitivity reaction to GBCA and 2 patients had more than 2 reactions. In our patient

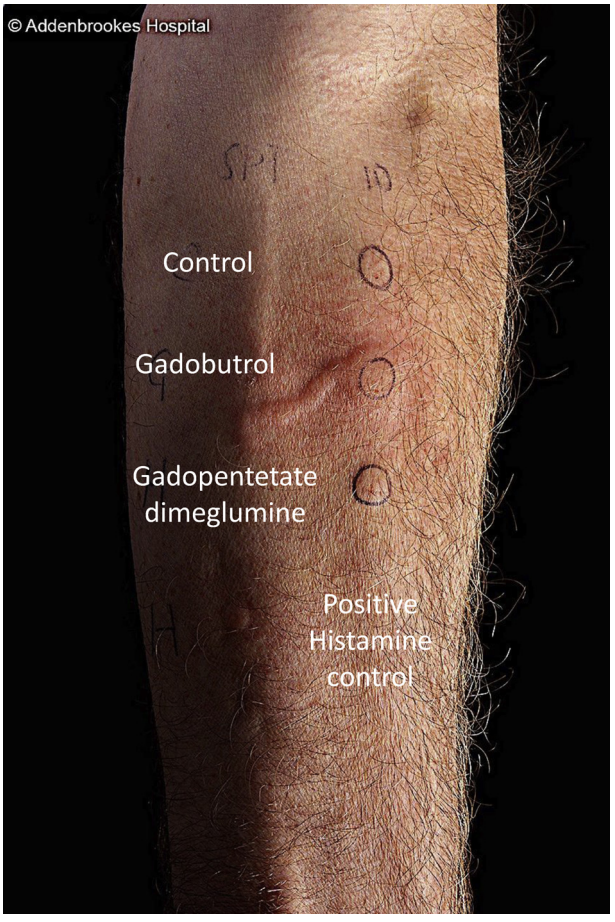

FIGURE 1. Positive IDT to gadobutrol, showing an extending wheal with widespread erythema.

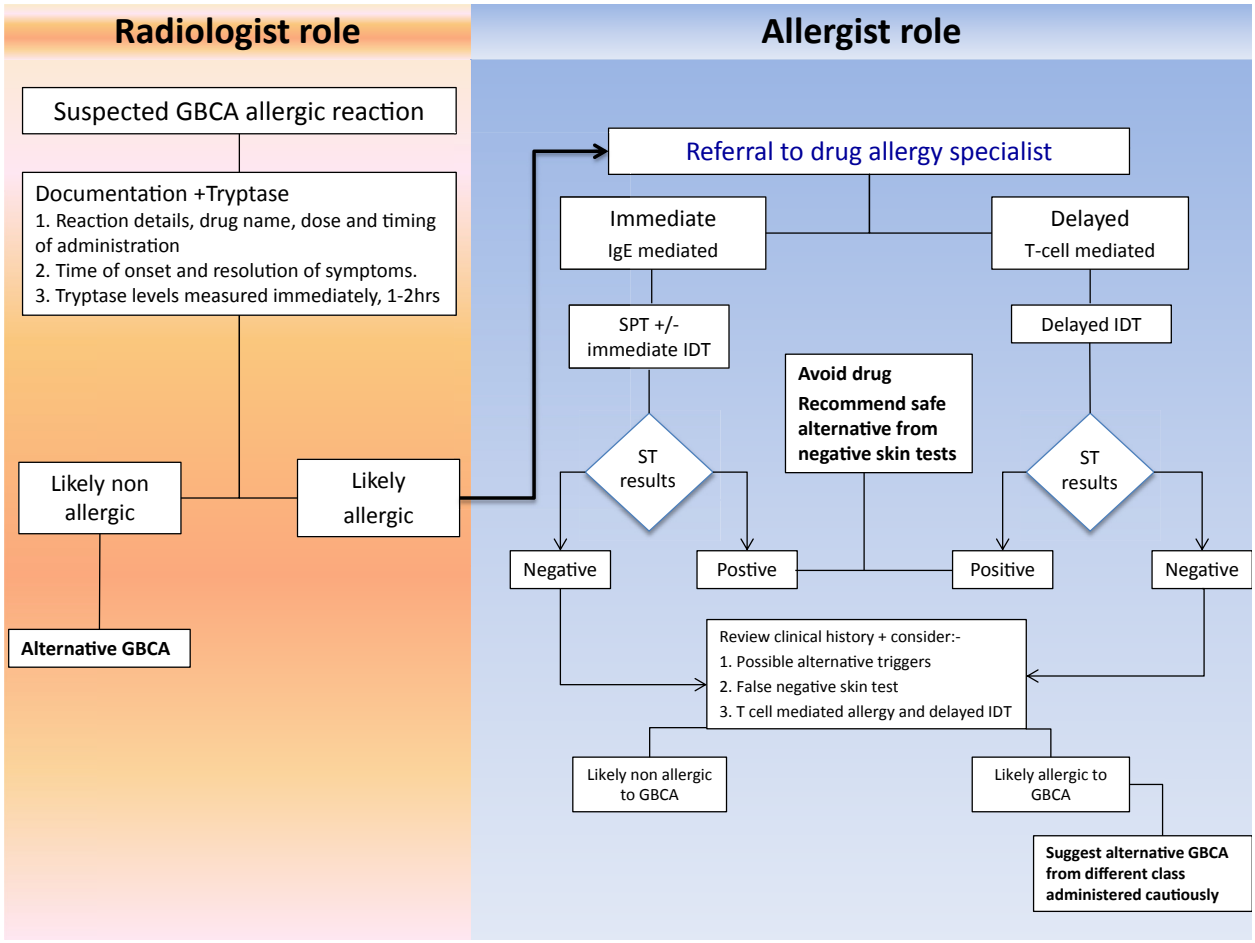

FIGURE 2. Algorithm for the investigation of suspected hypersensitivity reactions to GBCAs.

this was their first reaction and only case 2 had previous exposure to GBCA.

A recent death to gadoteridol had a similar history to case 1, with no documented previous exposure to GBCA and fatal anaphylaxis following the second bolus of gadoteridol.[5] Jung et al[4] reported atopy as a risk factor; however, this may be incorrect because chronic urticaria and drug allergy are not features of atopy. Our patients were nonatopic.

Case 2 tolerated gadopentetate dimeglumine following negative skin test results. A further study by Chiriac et al[6] demonstrated a good negative predictive value for GBCA skin test results. Of 27 patients studied, only 5 had positive skin test results and of these 1 tolerated a subsequent MRI contrast to which skin test results were negative.[6] More data, particularly on sensitivity, are required.

Gadobutrol (macrocyclic) differs structurally from gadopentetate dimeglumine (linear) and there is no evidence of cross-reactivity between the 2 agents (Figure E1). We were able to skin test only with gadobutrol and gadopentetate dimeglumine although in the future, skin tests should be considered to additional GBCAs to better define allergic cross-sensitization. Galera et al[1] described allergy in 2 patients and suggested lack of cross-reactivity between different classes of GBCAs.[1] His first patient developed anaphylaxis to gadoteridol; IDT results were positive to gadoteridol only, with negative test results to gadoterate, gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide. The second patient had anaphylaxis to gadobenate dimeglumine and was positive only to the index drug. This suggests lack of cross-reactivity between GBCAs; however, further research is required. Previous studies suggest that SPT to the neat solution is nonirritant.[1,6] Galera et al[1] reported that IDT at undiluted concentration was irritant, and suggested using a 10^{-1} concentration. Our study in normal controls confirmed that a 10^{-2} concentration is nonirritant for IDT.

We propose an algorithm for the management of patients developing an allergic reaction to GBCAs. The radiologist should document the type of GBCA, time of administration, nature, onset and resolution of symptoms, and emergency treatment administered (Figure 2).[7] Tryptase levels should be measured within 30 minutes of the reaction, 1 to 2 hours later (and when possible 24 hours later).[7,8] Both cases had a greater than 2-fold increase in tryptase level above baseline. Case 2 did not have serum tryptase level measured within 2 hours, when the level would likely have peaked. However, studies have shown that a tryptase level increase to more than 135% above baseline during a suspected immediate hypersensitivity reaction indicates mast cell degranulation even when below the 95 upper percentile, 11.4 ng/mL.[9] If GBCA allergy is suspected, referral to a drug allergy service for skin testing allows confirmation of the agent causing the reaction and identification of potential safe