Delayed Cutaneous Reactions to Iodinated Contrast

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PRACTICE **POINTS**

- Delayed cutaneous reactions to iodinated contrast (IC) are common, but patients frequently are misdiagnosed and inadvertently readministered the offending agent.
- The most common IC-induced delayed reactions are self-limited exanthematous eruptions that develop within 1 week of exposure.
- Risk factors for delayed reactions to IC include atopy, contrast exposure during high pollen season, use of the agent iodixanol, a history of other cutaneous drug eruptions, elevated serum creatinine levels, and treatment with recombinant interleukin 2.
- Dermatologists can help prevent recurrent reactions in patients who require repeated exposure to IC by recommending gadolinium-based contrast agents and/or premedication.

Iodinated contrast (IC) often is overlooked as a cause of delayed drug reactions. As a result, patients may continue to be readministered these agents, experiencing preventable morbidity. We report an illustrative case of a delayed cutaneous reaction to IC and review the literature on the epidemiology and management of this underrecognized phenomenon.

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Case Report

A 67-year-old woman with a history of allergic rhinitis presented in the spring with a pruritic eruption of 2 days' duration that began on the abdomen and spread to the chest, back, and bilateral arms. Six days prior to the onset of the symptoms she underwent computed tomography (CT) of the abdomen and pelvis to evaluate abdominal pain and peripheral eosinophilia. Two iodinated contrast (IC) agents were used: intravenous iohexol and oral diatrizoate meglumine–diatrizoate sodium. The eruption was not preceded by fever, malaise, sore throat, rhinorrhea, cough, arthralgia, headache, diarrhea, or new medication or supplement use. The patient denied any history of drug allergy or cutaneous eruptions. Her current medications, which she had been taking long-term, were aspirin, lisinopril, diltiazem, levothyroxine, esomeprazole, paroxetine, gabapentin, and diphenhydramine.

Physical examination was notable for erythematous, blanchable, nontender macules coalescing into patches on the trunk and bilateral arms (Figure). There was slight erythema on the nasolabial folds and ears. The mucosal surfaces and distal legs were clear. The patient was afebrile. Her white blood cell count was 12.5×10^9/L with 32.3% eosinophils (baseline: white blood cell count, 14.8×10^9/L; 22% eosinophils)(reference range, 4.8–10.8×10^9/L; 1%–4% eosinophils). Her comprehensive metabolic panel was within reference range. The human immunodeficiency virus 1/2 antibody immunoassay was nonreactive.

The patient was diagnosed with an exanthematous eruption caused by IC and was treated with oral hydroxyzine and triamcinolone acetonide cream 0.1%. The eruption resolved within 2 weeks without recurrence at 3-month follow-up.

Comment

Delayed cutaneous eruptions caused by IC are underrecognized in medicine and are infrequently described

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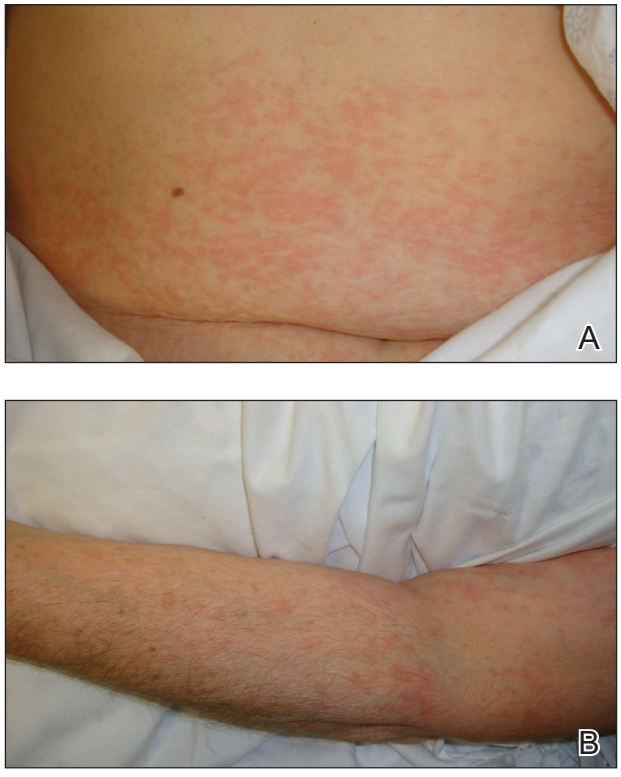

Erythematous, blanchable, nontender macules coalescing into patches on the abdomen (A) and left arm (B).

in the dermatology literature.[1] Unlike urticaria and other well-known immediate reactions to IC, delayed reactions develop when patients are less likely to be under medical supervision.[2] Moreover, only 12% to 33% of patients with delayed reactions to IC seek medical attention.[3-6] As a result, these delayed reactions often are attributed to other causes.[1] Patients may then be unknowingly reexposed to the offending contrast agent and experience recurrent eruptions, such as in one fatal case of toxic epidermal necrolysis (TEN).[7-11] Given the role of dermatologists in the diagnosis and prevention of cutaneous drug reactions, it is important to be mindful of delayed cutaneous eruptions caused by IC.

Clinical Presentation of Delayed Reactions—Most delayed cutaneous reactions to IC present as exanthematous eruptions in the week following a contrast-enhanced CT scan or coronary angiogram.[2,12] The reactions tend to resolve within 2 weeks of onset, and the treatment is largely supportive with antihistamines and/or corticosteroids for the associated pruritus.[2,5,6] In a study of 98 patients with a history of delayed reactions to IC, delayed-onset urticaria and angioedema also have been reported with incidence rates of 19% and 24%, respectively.[2] Other reactions are less common. In the same study, 7% of patients developed palpable purpura; acute generalized exanthematous pustulosis; bullous, flexural, or psoriasislike exanthema; exfoliative eruptions; or purpura and a maculopapular eruption combined with eosinophilia.[2] There also have been reports of IC-induced erythema multiforme,[3] fixed drug eruptions,[10,11] symmetrical drug-related intertriginous and flexural exanthema,[13] cutaneous vasculitis,[14] drug reactions with eosinophilia and systemic symptoms,[15] Stevens-Johnson syndrome/TEN,[7,8,16,17] and iododerma.[18]

IC Agents—Virtually all delayed cutaneous reactions to IC reportedly are due to intravascular rather than oral agents,[1,2,19] with the exception of iododerma[18] and 1 reported case of TEN.[17] Intravenous iohexol was most likely the offending drug in our case. In a prospective cohort study of 539 patients undergoing CT scans, the absolute risk for developing a delayed cutaneous reaction (defined as rash, itching, or skin redness or swelling) to intravascular iohexol was 9.4%.[20] Randomized, double-blind studies have found that the risk for delayed cutaneous eruptions is similar among various types of IC, except for iodixanol, which confers a higher risk.[5,6,21]

Risk Factors—Interestingly, analyses have shown that delayed reactions to IC are more common in atopic patients and during high pollen season.[22] Our patient displayed these risk factors, as she had allergic rhinitis and presented for evaluation in late spring when local pollen counts were high. Additionally, patients who develop delayed reactions to IC are notably more likely than controls to have a history of other cutaneous drug reactions, serum creatinine levels greater than 2.0 mg/dL (reference range, 0.6–1.2 mg/dL),[3] or history of treatment with recombinant interleukin 2.[19]

Patients with a history of delayed reactions to IC are not at increased risk for immediate reactions and vice versa.[2,3] This finding is consistent with the evidence that delayed and immediate reactions to IC are mechanistically unrelated.[23] Additionally, seafood allergy is not a risk factor for either immediate or delayed reactions to IC, despite a common misconception among physicians and patients because seafood is iodinated.[24,25]

Reexposure to IC—Patients who have had delayed cutaneous reactions to IC are at risk for similar eruptions upon reexposure. Although the reactions are believed to be cell mediated, skin testing with IC is not sensitive enough to reliably identify tolerable alternatives.[12] Consequently, gadolinium-based agents have been recommended in patients with a history of reactions to IC if additional contrast-enhanced studies are needed.[13,26] Iodinated and gadolinium-based contrast agents do not cross-react, and gadolinium is compatible with studies other than magnetic resonance imaging.[1,27]

Premedication—Despite the absence of cross-reactivity, the American College of Radiology considers patients with hypersensitivity reactions to IC to be at increased risk for reactions to gadolinium but does not make specific recommendations regarding premedication given the dearth of data.[1] As a result, premedication may be considered prior to gadolinium administration

depending on the severity of the delayed reaction to IC. Additionally, premedication may be beneficial in cases in which gadolinium is contraindicated and IC must be reused. In a retrospective study, all patients with suspected delayed reactions to IC tolerated IC or gadolinium contrast when pretreated with corticosteroids with or without antihistamines.[28] Regimens with corticosteroids and either cyclosporine or intravenous immunoglobulin also have prevented the recurrence of IC-induced exanthematous eruptions and Stevens-Johnson syndrome.[29,30] Despite these reports, delayed cutaneous reactions to IC have recurred in other patients receiving corticosteroids, antihistamines, and/or cyclosporine for premedication or concurrent treatment of an underlying condition.[16,29-31]

Conclusion

It is important for dermatologists to recognize IC as a cause of delayed drug reactions. Current awareness is limited, and as a result, patients often are reexposed to the offending contrast agents unsuspectingly. In addition to diagnosing these eruptions, dermatologists may help prevent their recurrence if future contrast-enhanced studies are required by recommending gadolinium-based agents and/or premedication.

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