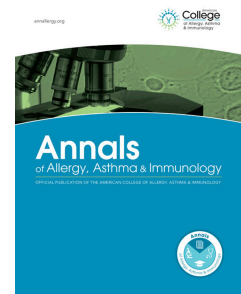


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Alex Wonnapharhown, MD, Tarah Talakoub, DO, Joseph Yusin, MD, Thomas Yusin, BS, Sherwin Hariri, MD



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Recurrent Immediate Hypersensitivity Reaction to Radiocontrast Media Despite Premedication
Found to Be IgE-mediated

Alex Wonnapharhown, MD¹, Tarah Talakoub, DO², Joseph Yusin, MD², Thomas Yusin, BS³,
Sherwin Hariri, MD⁴

¹Cedars-Sinai Medical Center, Department of Medicine

²Veterans Affairs Greater Los Angeles Healthcare System, Department of Allergy and
Immunology

³Tulane Medical School

⁴Cedars-Sinai Medical Center

Corresponding author: Alex Wonnapharhown, MD

Cedars-Sinai Medical Center

8700 Beverly Blvd., Department of Internal Medicine Suite 5512, Los Angeles, CA 90048

Phone: (310) 423-5161

Fax: (310) 423-0436

Email: Alex.Wonnapharhown@cshs.org

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Approximately 75 million computed tomography (CT) scans are performed with radiocontrast media (RCM) annually¹ and IgE-mediated immediate hypersensitivity reactions to nonionic RCM have been reported in 0.7 to 3% of patients². Pretreatment with prednisone and diphenhydramine has significantly reduced immediate generalized reactions to RCM³. Recently, studies suggest that skin testing can support the diagnosis of an IgE-mediated reaction to RCM and can also help guide selection of an alternative RCM if subsequent RCM exposure is anticipated^{1,2}. Furthermore, a desensitization protocol has also shown promise in preventing recurrent breakthrough reactions⁴.

A 73-year-old Caucasian woman with asthma and a bicuspid aortic valve status post replacement was diagnosed with severe prosthetic stenosis and transcatheter aortic valve replacement was recommended. However, several years prior to presentation, she had developed dyspnea and urticaria during her first cardiac angiogram, which was treated with steroids. During a second cardiac angiogram, she received the Greenberger premedication protocol and still developed urticaria and angioedema within minutes after exposure, which was also treated with steroids. She then underwent a CT angiogram after being premedicated with the Greenberger protocol, cetirizine, fexofenadine, ranitidine, and montelukast, and still developed facial angioedema and urticaria 12 hours after the procedure, which was treated with methylprednisolone and diphenhydramine. The patient denied any previous contrast exposure prior to these episodes. Due to the need for cardiac intervention with repeat RCM one year after her last reaction, the patient underwent a skin testing protocol⁵ with iodixanol, resulting in negative skin prick tests, but positive intradermal tests [Table 1]. An IgE-mediated immediate hypersensitivity reaction to RCM was deduced and the patient underwent a modified premedication regimen, in addition to a desensitization protocol⁴ prior to her cardiac

intervention, which was successful in preventing angioedema and urticaria, and the patient only experienced mild pruritus that resolved within 24 hours.

Symptoms of immediate hypersensitivity reactions to RCM are rare and resemble anaphylaxis. Immediate reactions are rare and fatal hypersensitivity reactions have been reported in 1 to 3 persons per 100,000 administrations of RCM⁶. 70% of symptoms occur within 5 minutes after administration of RCM⁷ and up to 30% of patients who experienced immediate hypersensitivity to RCM did not have previous exposure to RCM⁶.

The pathophysiology of immediate reactions to contrast media includes cellular membrane interaction, complement system activation, bradykinin formation, and an IgE-mediated mechanism. Studies support that hypersensitivity reactions to contrast media involve mast cell activation, in addition to increased plasma histamine and tryptase levels. Basophil activation tests can also be positive in patients with hypersensitivity to RCM. Furthermore, significantly higher levels of IgE against ionic radiocontrast medias ioxaglate and ioxitalamate have been seen in patients with a history of reactivity to ioxaglate compared to that seen in control patients⁶.

Predicting future reactions to RCM is difficult. Up to 88% of patients with a prior allergic-like reaction to RCM do not experience a repeat reaction when subsequently premedicated with corticosteroids. Of those who do experience breakthrough reactions, 67% of patients with a moderate or severe previous reaction experienced repeated moderate or severe breakthrough reactions despite premedication with corticosteroids to low-osmolality contrast medium. Rates of reaction do not appear to significantly differ in relation to the type of low-osmolality contrast medium used. Risk factors associated with breakthrough reactions include a history of severe allergy to any trigger, allergies to four or more allergens, history of any drug

allergy, and chronic corticosteroid use⁸. Successful premedication options include corticosteroids, H1-antihistamines, and H2-antihistamines⁶, however cases of severe anaphylactic reactions can still occur despite pretreatment with antihistamines and corticosteroids⁷.

Additional diagnostic work-up can be done to support the diagnosis of an immediate hypersensitivity reaction to RCM. Elevated serum tryptase obtained 1 to 4 hours after the beginning of symptoms supports an IgE-mediated hypersensitivity reaction and the median serum tryptase in IgE-mediated reactions is 45 ng/mL⁵. Skin testing with a panel of 10 RCM (including iodixanol, ioversol, iopromide, iomeprol, iohexol, iopamidol, iobitridol, ioxaglate, ioxithalamate, and amidotrizoate) 1 to 6 months after the initial event has been shown to have up to a 94.2% negative predictive value for immediate hypersensitivity reactions². The specific RCM panel chosen for skin testing should be comprehensive enough to optimize the likelihood of finding the culprit RCM, evaluate for cross-reactivity, and identify an alternative option. Skin testing to RCM involves first performing skin prick testing to undiluted RCM, with a wheal of ≥ 3 millimeters after 20 minutes regarded as positive. If skin prick testing is negative, then intradermal skin testing to 1:10 dilution (to reduce irritation) of RCM is performed, with a wheal increase of ≥ 3 millimeters after 20 minutes regarded as positive^{5,9}. In Kwon 2019, intradermal testing was done without initial skin prick testing, due to reported low positive rates of skin prick testing¹. The high percentage of patients tolerating skin test-negative RCM supports the high sensitivity of intradermal skin testing in patients with suspected RCM allergy¹⁰ and multiple studies have supported that skin testing results can help guide the safe selection of a skin test-negative RCM alternative in patients who need future repeat RCM administration^{1,10}.

With close to 75 million yearly exposures to RCM, allergists face a growing need for an

70 efficient RCM immediate reaction evaluation protocol. IgE-mediated immediate reactions to
71 RCM are rare, associated with various atopic risk factors, manifest with symptoms of
72 anaphylaxis, and are associated with positive skin testing and elevated tryptase level.
73 Pretreatment regimens with prednisone and antihistamines have been successful in preventing
74 the majority of adverse outcomes, however cases of severe anaphylactic reactions still occur
75 despite pretreatment. As in the case presented and literature review, patients with positive skin
76 testing consistent with an IgE-mediated reaction to RCM may benefit from a modified
77 pretreatment protocol with additional antihistamines and higher dose steroids followed by
78 desensitization. Furthermore, patients may also benefit from skin testing to additional RCM to
79 guide alternative RCM choices. However, the current difficulty of obtaining needed materials
80 may limit the feasibility of extensive RCM skin testing. Future studies should aim to elucidate a
81 more standardized pretreatment and desensitization protocol for severe RCM immediate
82 reactions.

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Table 1: Results of skin prick and intradermal testing to iodixanal

Prick Testing #1: undiluted contrast dye	Prick Testing #2: undiluted contrast dye	Intradermal #1: Diluted with sterile water 1:10	Intradermal #2: Diluted with sterile water 1:10
Negative Control: 0mm	Negative Control: 0mm	Negative Control: 0mm	Negative Control: 0mm
Positive Control: 7mm +Erythema	Positive Control: 8mm +Erythema	Positive Control: 5mm No erythema	Positive Control: 5mm No erythema
Contrast Dye: Negative	Contrast Dye: Negative	Contrast Dye (1:10): 9mm +Erythema	Contrast Dye (1:10): 11mm +Erythema