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Case Report

BASOPHIL ACTIVATION IN THE DIAGNOSIS OF LIFE-THREATENING HYPERSENSITIVITY REACTION TO IODINATED CONTRAST MEDIA: A CASE REPORT

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ABSTRACT

Hypersensitivity to iodinated radiologic contrast media occurs in 1-3% of patients. A complete allergological work-up requires the identification of the pathogenic mechanism as well as the identification of safe alternatives. The current diagnostic approach relies upon skin tests, since no other in vitro test is standardized. However skin tests do not have an absolute predictive value, cannot be executed immediately and may expose the patients to the risk of severe reactions. Recently the flow-cytometric evaluation of activated basophils, also known as basophil activation test (BAT) has been introduced.

Our case report of a 28-year old female who experienced an anaphylactic shock immediately after administration of iomeprol supports the role of BAT in the diagnosis and management of hypersensitivity reactions to contrast media. The possibility of shortening the diagnostic work-up without endangering the health of patients represents the main advantage of this test.

Key words: Basophil activation, RCM, anaphylaxis, tryptase, mast cells

INTRODUCTION

Hypersensitivity to iodinated radiologic contrast media (RCM) can result in severe, life-threatening reactions. Generally, as the allergological work-up frequently remains negative, these reactions are mostly considered non- allergic. Therefore the osmotic effect of RCM on basophils and/or mast cells is

frequently thought to be the trigger of the histamine release by these cells. However also the new non- ionic, low osmolar RCM are responsible for hypersensitivity reactions in 1-3% of exposed patients (1). Actually, today diagnosis of IgE mediated RCM allergy is generally established by skin tests (STs) (1), as there are no standardised specific (s)IgE tests available. However, diagnosis of RCM allergy is easily overlooked as the predictive value of the STs is not absolute (1). Recently, a novel in vitro test has entered the field of allergy diagnosis, particularly of drug hypersensitivity (2). The principles and applications of this technique that relies upon in vitro activation of basophils (basophil activation test, BAT) are detailed elsewhere (2). Briefly, activation of basophils is quantified flow cytometrically using specific monoclonal antibodies against surface markers such as CD63 or CD203c that are barely expressed on resting cells (2).

CASE REPORT

We report a case of a 28-year old female, who experienced an anaphylactic shock (generalised urticaria, angioedema, dizziness, severe hypotension with immeasurable blood pressure during the first 30 minutes, and loss of consciousness) immediately after administration of iomeprol (Iomeron®) for cardiac computed tomography. The patient was treated with intravenous epinephrine (total dose 3 mg) and methylprednisolone (125 mg) and intramuscular promethazine (25 mg), after which she fully recovered.

Revision of the radiological record disclosed she was also exposed to latex and chlorhexidin. STs, according to the recommendations of the European Network on Drug Allergy (ENDA) (1), and a BAT (2), for the potential causative agent iomeprol (Iomeron®) and for iobitridol (Xenetix®), iohexol (Omnipaque®), and iopromide (Ultravist®) were performed.

Furthermore for BAT experiments 5 healthy volunteers were enrolled.

The protocol of BAT is detailed elsewhere (2). Briefly, 100 μ L aliquots of endotoxin-free heparinised whole blood were stimulated with dilution buffer as a negative control, anti-IgE (10 μ g/mL; Pharmingen, BD Biosciences, San Jose,

California, USA) as a positive control and serial dilutions (stimulation concentration 10, 100 and 1000 μ g/mL) of the aforementioned iodinated contrast media. Basophils were gated as low side scatter (SSC)/IgE⁺ cells. Upregulation of CD63 and CD203c were measured as activation markers (see figure 1).

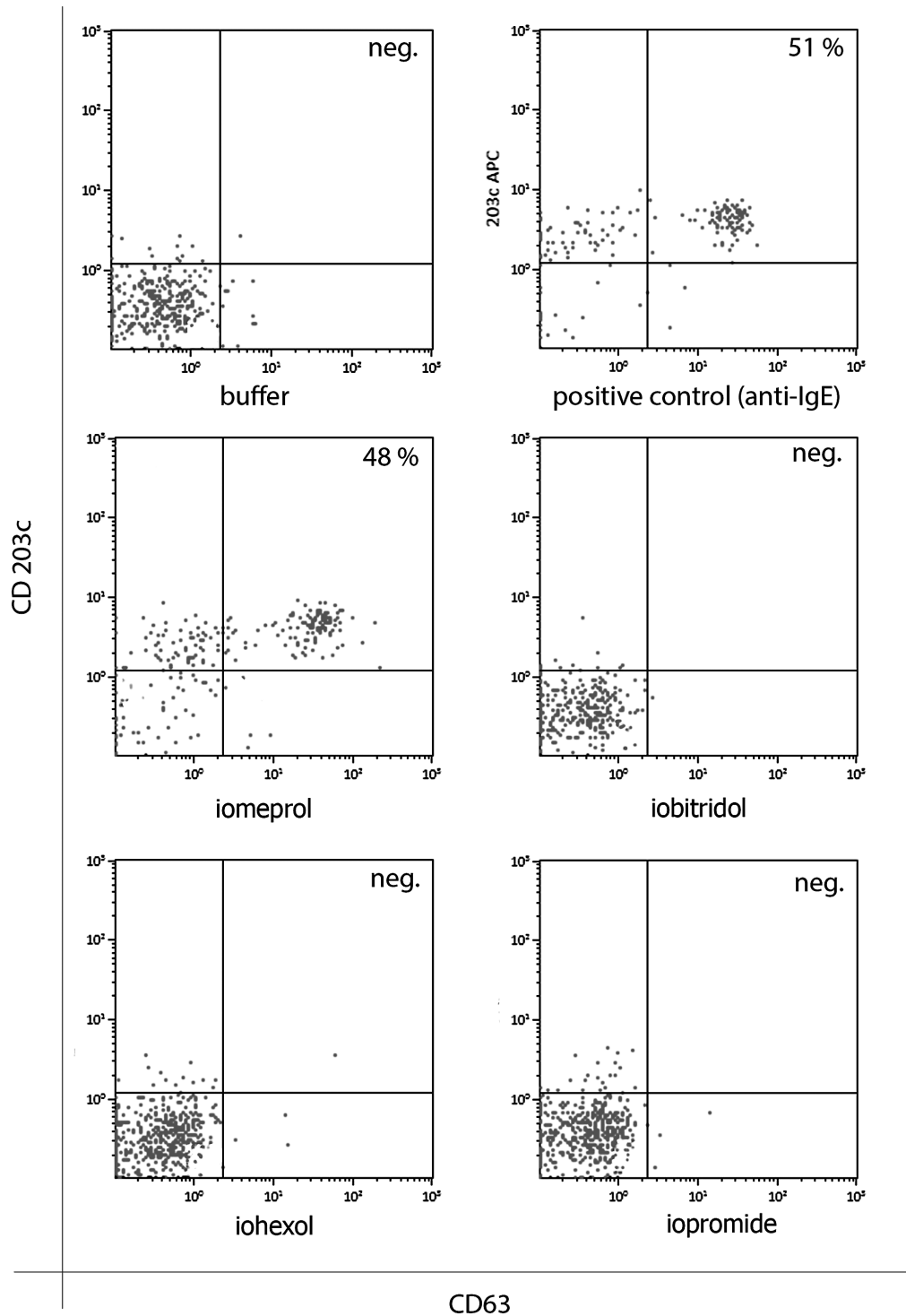


Figure 1: BAT with iomeprol, iobitridol, iohexol and iopromide.

The figure shows the upregulation of CD63 (x-axis) and CD203c (y-axis) on basophils after stimulation with buffer (negative control), anti-IgE (positive control) and the different iodinated contrast media.

Table 1: Results of sIgE and STs

sIgE (kUa/L)		ST (wheal/flare in mm)	
Latex	< 0.10	0/0	
Chlorhexidin	< 0.10	0/0	
		Dilutions	
		1:10	Pure
Iomeprol	NA	9/30	–
Iobitridol	NA	0/0	0/0
Iohexol	NA	5/25	–
Iopromide	NA	0/0	0/0

NA = not available.

Allergologic evaluation included STs and sIgE for latex and chlorhexidin.

Baseline and acute serum tryptase were detected with a fluorescence immunoassay (FEIA ImmunoCAP, Thermo Fisher, Brussels).

Serum tryptase, a biomarker for mast cell activation, raised to 35.9 ng/mL (normal value < 11.4 ng/mL) during the reaction, whereas the baseline value was 6.9 ng/mL. Table 1 summarises the results of STs and specific IgE (sIgE) assays (when available). Figure 1 shows the upregulation of CD63 and CD203c in BAT experiments. Iomeprol induced a dose-dependent CD63 and CD203c upregulation (1000 µg/mL stimulation concentration), whereas no activation was detected after stimulation with iobitridol, iohexol and iopromide (all 1000 µg/mL).

Expression of CD63 and CD203c on basophils from 5 healthy control individuals remained unchanged

DISCUSSION

This case shows several particularities. First, it highlights that even a non-ionic monomer RCM can still trigger life-threatening immune-mediated anaphylaxis. Diagnostic work-up strongly suggests an IgE-mediated hypersensitivity for iomeprol (Iomeron®). Second, it emphasises that the diagnosis of allergy to RCM cannot be considered as complete when it fails to address the issue of cross-reactivity and to identify a safe alternative for the future, as our patient demonstrated also a positive ST to iohexol (Omnipaque®). Alternatively, as observed in the series by Pinnobphun et al (3), BAT might disclose positive results that goes unnoticed in STs. In this series, intradermal tests were positive in only 15 out of 36 (42%) patients with an immediate hypersensitivity reaction to RCM, whereas BAT was helpful for the diagnosis in half of the patients with negative intradermal test, who were all exposed

to iopromide. This could reflect different responses to RCM by basophils and mast cells and endorses the complementarity of both techniques, as already described for hypersensitivity reactions to other medications (4).

An advantage of the BAT is that it allows multiple simultaneous evaluations without the risk of endangering the health of the patient. Indeed STs with drugs can be associated with a potential risk of severe and even fatal anaphylaxis (5). Furthermore, since drugs can trigger basophils by either IgE-dependent or IgE-independent mechanisms, the BAT results are helpful in the diagnosis of adverse drug reactions as the presence of sIgE is not a *conditio sine qua non* for a positive result.

Moreover STs might yield false negative results when executed immediately after the acute event, due, in part, to the interference of antireactive medications (i.e. antihistamines). As these medications do not seem to interfere with the BAT, it appears that it can be performed almost immediately (Ebo D, unpublished data) after the acute reaction, although it is currently recommended to postpone it up to 4 weeks after the acute event.

Finally, it demonstrates the importance of acute and baseline tryptase quantifications, as these are useful when activation of mast cells is suspected and allow discrimination with mastocytosis which is a well-known risk factor for non-allergic hypersensitivity reactions to RCM.

CONCLUSION

This case-report supports the complementary role of BAT in the diagnosis and management of hypersensitivity to RCM. In particular it allows to shorten the diagnostic work-up without endangering the health of patients.

CONFLICT OF INTEREST: None declared.

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