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Case Series

The Value of Low Dose Provocation Test in the Diagnosis of Non-Immediate Iodinate Contrast Media Hypersensitivity

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Abstract

Background: Iodinated contrast media enhance the visibility of vascular structures and organs during radiographic procedures. Although generally considered safe, it is the third leading cause of cutaneous drug reactions. Iodinated contrast media is one of the most frequently used drugs in diagnostic medicine, but non-immediate hypersensitivity reactions are believed to be underreported because of delayed onset, which makes recognising and diagnosing these reactions challenging. For this reason, it is important to raise awareness about non-immediate hypersensitivity reactions to iodinated contrast media in the medical society.

Case Reports: We present two case reports of non-immediate hypersensitivity reaction to iodinated contrast media after the first exposure. *Patient I* reacted to iohexol and iopromide with fixed drug eruption. *Patient II* reacted to iodixanol with a maculopapular rash on the chest and abdomen, Quincke's oedema in her face and neck. Both patients had negative skin testing (prick, intradermal and patch test), but drug provocation test confirmed the allergy to iodixanol for *Patient II*. *Patient I* underwent premedication before re-exposure to iodinated contrast media, but it was unsuccessful. Histological examination of eruptions of both patients showed dermatitis, usual for drug hypersensitivity.

Conclusion: In this article, we demonstrate the importance of drug provocative test as well as limitations of skins tests and premedication.

INTRODUCTION

In Lithuania more than 100 000 computer tomography (CT) scans are performed each year, half of them with iodinated contrast media (ICM). ICM enhance the visibility of vascular structures and organs during radiographic procedures. Although generally considered safe, it can still cause immediate (occur <1 h after injection) and non-immediate (>1h after injection) hypersensitivity reactions (NIHR). Acute-onset reactions appear after 0,4% of all exposures. Non-immediate hypersensitivity reactions nowadays are believed to be even more common (affect about 2-5% of patients receiving an ICM) but underreported, because of delayed onset and challenging diagnostics [1-3]. We present two clinical cases of non-immediate hypersensitivity reactions to iodinated contrast media.

Patient I

A 37-year-old man underwent computer tomography (CT) with iohexol (Omnipaque 647 mg/ml, 100 ml) for confirmation of sarcoidosis diagnosis. Two days later, erythema fix occurred on the waist and persisted for 3 days (Figure 1). Sarcoidosis diagnosis was confirmed and a year later a CT scan with iopromide (Ultravist 632 mg/ml, 100 ml) was performed for sarcoidosis follow-up. After two days erythema fix occurred on the waist and lasted for 3 days (Figure 2). One-month later patient reached out to an allergologist and patch test (PT), prick test and intradermal tests (IDT) with diatrizoate, iohexol, iopromide, iopamidol, iodixanol were performed. Prick tests (1:1 dilution) and intradermal tests (1:10 dilution) were negative after 15 min, patch test (1:1 dilution) was negative after 48, 72 and 96 hours. The patient declined to perform a drug provocation test. One year later it was time for the next CT scan with ICM for sarcoidosis follow-up. Because of positive clinical history, it was decided to premedicate the patient with 32 mg of Methylprednisolone and 1 mg of Clemastine per os 12 and 2 hours before the CT scan with iopromide (Ultravist 632 mg/ml, 100 ml). Premedication was unsuccessful and the patient experienced erythema fix on the waist 2 days after procedure again. This time skin rash lasted for 2 weeks and biopsy was performed. The affected skin showed lymphocyte and neutrophil infiltration of the epidermis, perivascular and interstitial derma as well as spongiosis with neutrophils, single necrotic keratinocytes, vacuolar alteration of the basal layer in the epidermis and oedema of the papillary derma. Histological examination of skin eruption was compatible with drug induced dermatitis and non-immediate hypersensitivity reaction to iopromide was confirmed (Figure 3).

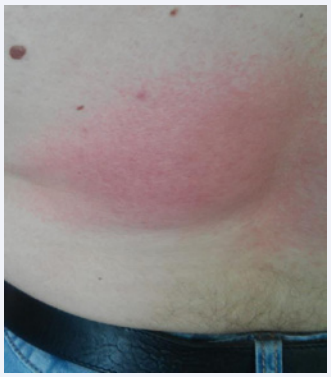

Figure 1 Erythema fixes on the waist.

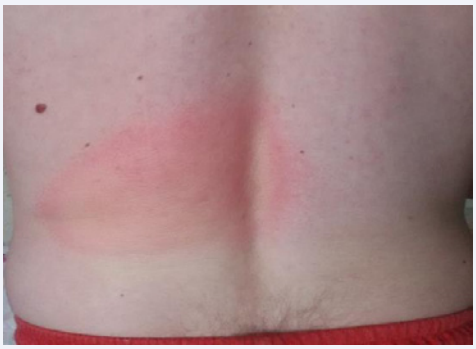

Figure 2 Erythema fix on the waist.

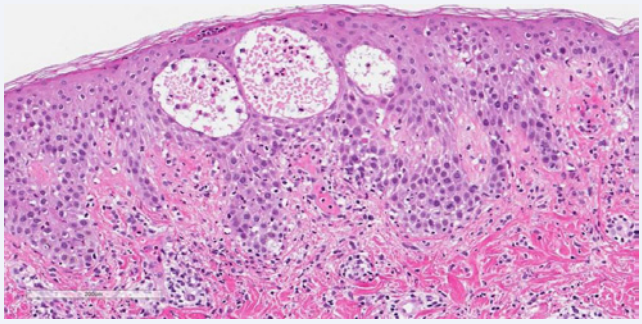

Figure 3 Biopsy of erythema fix.

Patient II

67-year-old woman underwent a CT scan with iodixanol (Visipaque 550 mg/ml, 100 ml). After a day she experienced maculopapular rash on the chest and abdomen, Quincke's oedema in her face and neck. It resolved in a few days after the treatment with antihistaminic drugs. Five years later, CT scan with ICM had to be performed because of suspected pheochromocytoma. The patient underwent an allergological examination before the CT to determine a safe contrast agent. Prick (undiluted), intradermal tests (1:10 dilution) and patch test (undiluted) were performed with diatrizoate, iohexol, iopromide, iopamidol, iodixanol. All tests were negative for immediate and non-immedaite reactions. In Allergology and Clinical Immunology Day-clinic intravenous drug provocation test with iodixanol was performed with an inicial concentration of 1 ml, followed by injection of 20 ml after 30 minutes. The cumulative dose was 21ml of iodixanol. The test was negative for immediate reactions. After 24 hours, the non-immediate hypersensitivity reaction was confirmed (the patient experienced erythematous maculopapular rash on the abdomen) (Figure 4). Biopsy report of the rash showed perivascular infiltration of mononuclear cells and eosinophils in the dermis and confirmed drug involved reaction. A month later, intravenous drug provocation test was performed with iopromide (Ultravist 632 mg/ml, injection of 1 ml and 20 ml after 30 minutes, cumulative dose – 21ml). The test was negative for immediate and delayed hypersensitivity reactions. It was advised that a CT scan with iopromide is safe and can be performed if needed.

DISCUSSION

Iodinated contrast media is one of the most frequently used agents in diagnostic medicine and the third leading cause of cutaneous drug reactions [2,4]. A most common nonimmediate hypersensitivity reaction is maculopapular rash, followed by delayed urticaria and angioedema. Less common manifestations are fixed drug eruption, Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized pustulosis, vasculitis [5]. Both our patients experienced reactions after their first exposure to ICM, which can be explained with previous sensitisation by structurally related molecules [5] or, alternatively, with the p-i concept (pharmacologic interaction of drugs with immune receptors), which is explained by direct stimulation of T cells by diagnostic agents through a human leukocyte antigene restricted pattern.

The onset of NIHR is usually after a patient is discharged from a hospital and in the absence of a medical professional. Therefore, clinical history is challenging, and reaction can be incorrectly attributed to other factors. Diagnosing and recording even mild reactions is important as it prevents them from repeating when a patient needs ICM imaging in the future [6]. NIHRs are diagnosed using intradermal tests (at 1:10 dilution) and a patch test (with undiluted ICM) within 2-6 months after the exposure [5]. Skin prick test with undiluted ICM is also recommended before performing intradermal tests to avoid severe immediate anaphylactoid reaction [7]. If the intradermal test is negative with 1:10 dilution, it can be repeated with

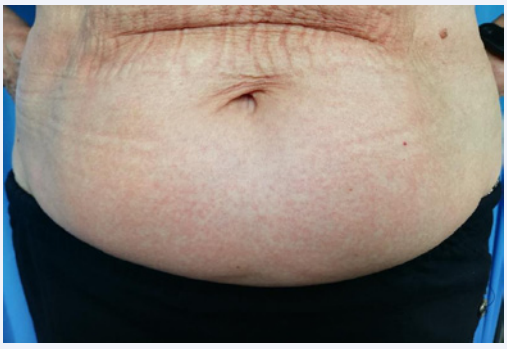

Figure 4 Maculopapular rash on the abdomen.

undiluted ICM (grade of recommendation, C), we performed all tests with the same diagnostic schedule, but we did not repeat the test for any of our patients. Negative predictive value of skin tests is about 86,1%. Therefore, a negative test result does not rule out the hypersensitivity to ICM completely. Fortunately, patients with false negative skin test usually experience a mild or moderate reaction after the re-exposition [8]. The sensitivity of intradermal tests is higher than the patch test for NIHR. It is also recommended to perform skin tests with an as wide battery of ICMs as possible to identify possible cross-reactivity, which in NIHR is especially common between iodixanol, iohexol, iopentol, ioversol, and iomeprol [5,9]. Our *Patient I* experienced cross-reactivity between iohexol and iopramide, although skin tests were negative for both contrast agents. Studies show that cross-reactivity in skin testing of ICM occur in up to 50% of skin tests [10].

A provocative drug test is considered to be a gold standard for the diagnosis of drug hypersensitivity reactions, although it is neither the part of routine allergological workup yet nor standardised or validated [11]. Because of its risk of hypersensitivity reactions, DPT should be performed only in experienced and well-equipped institutions. Studies of NIHRs show that 32,3-41,7% of patients with negative skin tests have positive DPT [12,13]. Both our patients had negative skin tests, but hypersensitivity to ICM was confirmed with DPT for *Patient II* and with following diagnostic computed tomography with full dose of ICM for *Patient I*. DPT is suitable to confirm a negative skin test result as well as to search for an alternative ICM in skin-test positive patients [2].

In order to avoid cross-reactivity or if it is impossible to choose another ICM, premedication can be applied, although it is not always successful in NIHR [8, 14]. There are different protocols for premedication, but, in general, it is recommended to start premedication no later than 6 hours before exposure to ICM. We unsuccessfully premedicated *Patient I* with 32 mg of Methylprednisolone and 1 mg of Clemastine per os 12 and 2 hours before injecting ICM, based on recommendations of European Society of Urogenital Radiology [15]. The most commonly used regime for premedication is prednisone 50 mg per os or intravenous methylprednisolone 40 mg administered 13, 7, and 1 hour before the exposure to ICM [5]. In Romano et al., case report a more aggressive but successful protocol with daily intake of methylprednisolone and cyclosporine for 1 week before and 2 weeks after iodinated contrast media administration was demonstrated [16]. Further studies are necessary to establish an optimal regime of premedication to avoid NIHR to ICM.

Immediately after the reaction, skin biopsy and some in-vitro tests can be performed. Biopsies provide information about the underlying pathophysiological process and can show a variety of inflammatory disease patterns in the skin, but no pattern is specific to a drug eruption. On the other hand, some features (like eosinophilia) can support a diagnosis of drug eruption in the unclear cases [5,7,17]. Histological findings of other studies are in concordance with our results. Fixed drug eruption usually presents with epidermal spongiosis and necrosis, hydropic degeneration of the basal layer, lymphocyte infiltration of dermis and epidermis. Findings of vacuolar interface dermatitis, perivascular infiltration of lymphocytes and eosinophils supports the diagnosis of maculopapular drug eruption but is nonspecific to it [7,17].

Lymphocyte transformation test (LTT) is the main in-vitro test for a non-immediate drug hypersensitivity, which measures the proliferation of T cells after recognition of the specific drug. It is an equivalent to the patch test, which detects T-cell mediated drug hypersensitivity reactions in-vivo [18]. LTT sensitivity in NIHR is not yet clear and ranges from 13 to 75% in different studies [2,19,20]. In our cases, it was not performed due to its low sensitivity and high-cost value. This and other in-vitro tests (like coculture of dendritic cells and lymphocytes) are promising because they are not harmful to a patient, but further research is needed to implicate them to routine diagnosis [18].

We demonstrate a rare clinical presentation of erythema fix as a non-immediate hypersensitivity to ICM with a provocation test confirmed cross-reactivity between iohexol and iopramide. Both our cases showed non-immediate reactions to iodinate contrast media that were not observed directly after infusion. Based on our experience, a prolonged observation after drug injection or contacting the patients of the following day could be suggested. e showed the importance of low dose drug provocation test for confirmation of non-immediate iodinate drug hypersensitivity. The limitations of skins tests and non-utility of premedication in the case of non-immediate reactions, especially in the case of erythema fix, were also discussed.

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