Delayed Hypersensitivity Reaction to Iron Salts: From Diagnosis to Desensitization

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0789

Key words: Iron Deficiency Anemia. Delayed hypersensitivity. Desensitization. Lymphocyte Transformation Test. Diagnosis.

Palabras claves: Anemia Ferropénica. Hipersensibilidad retardada. Desensibilización. Test de Transformación Linfocitaria. Diagnóstico.

Iron deficiency anemia (IDA) is a global public health problem, because of its relation to common instances of malnutrition, multiple medical conditions and also because of the severely compromised quality of life of those who suffer its symptoms [1]. IDA is highly prevalent in women in the reproductive age reaching up to 32.8% worldwide [2].

Iron treatment is considered a safe procedure, but adverse events could develop, although the former seldomly occur. However, cases of severe allergic reactions have occurred following iron administration [1-3], which 25% of them are known to result from iron hypersensitivity and it is estimated that 1 in every 5 million doses of intravenous iron administered produce allergic reactions, most of them immediate, with a mortality rate in the United States of 3 death per year [1].

A 48-year-old woman with a personal history of surgical intervention (gastric by-pass) for morbid obesity developed IDA with hemoglobin levels of 8.1 g/dl, transferrin saturation of 4.3%, ferritin of 12.62 ng/ml, blood iron levels of 16 ug/dl trace elements (minerals and vitamins) deficiency associated to malnutrition syndrome. She was referred from the Endocrinology and Nutrition department. The endocrinologist initially treated the IDA with oral therapy, which was not well tolerated by the patient, who presented immediate vomiting.

doi: 10.18176/jiaci.0789

The digestive symptoms and the lack of iron absorption due the bypass were the reasons to switch to an intravenous formulation.

With the first infusion of intravenous iron carboxymaltose (IC) she developed fever and asthenia after 24 hours of the administration. The symptoms subsided in 4 days without any medication.

The patient was referred to our Allergy Department. Skin prick test (SPT) with IC was performed 8 months after the reaction with immediate and delayed reading (96 hours) with negative results. Intradermal test was not done because of the high risk of skin residual lesions. The referring physicians confirmed that IC was the mandatory treatment due the instance of malnutrition and intolerance to oral iron therapy. We assessed the management risks and informed consents were signed. Based on risk stratification a drug provocation challenge (DPC) with IC was performed, no immediate reactions were reported. After 3 days the patient developed fever, nausea, diarrhea and myalgia. Oral prednisone (30 mg), cetirizine (10 mg) and paracetamol (1000 mg) were prescribed with symptoms resolution after 24 hours. Administration with IC was contraindicated in our patient. Due to the worsening of the IDA and the need of iron therapy we decided to seek an alternative with iron sucrose (IS). SPT with IS was performed with immediate and delayed reading with negative results. DPC with IS was performed and after 4 hours of the administration the patient presented fever and generalized arthralgias.

In an attempt to determine the underlying mechanism of this reaction, we performed a lymphocyte transformation test (LTT) 2 months after the reaction with IC and IS. Peripheral blood mononuclear cells were isolated from whole blood using LymphoPrepTM gradient centrifugation. 200 µl of cell suspensions (10^6 cells/ml) in AIM V Medium were added to

doi: 10.18176/jiaci.0789

each culture-plate well and were stimulated with 20 µg/µl, 2 µg/µl, 0.2 µg/µl, 0.02 µg/µl and 0.002 µg/µl of IC and IS. Dynabeads CD3/CD28 (1 µl/well) was used as positive control, and the negative control comprised the cells without any stimulation. Cultures were performed in triplicate and incubated for 4 days at 37°C in an atmosphere of 5% CO2/95% air. On day 4, the culture plates were centrifuged and 100 µl of each well was replaced by fresh AIM-V medium containing 10 µCi of 3H-thymidine (3H). On day 6 cells were harvested with a vacuum manifold and the radioactivity incorporation into DNA was measured using a liquid scintillation counter. The result is expressed as stimulation index (SI), which is the relationship between the mean of triplicate d.p.m. of the drug-stimulated cultures and the mean of triplicate d.p.m. of the negative controls.

Generally a value of SI between 2 and 3 is recognized as weakly positive response. SI≥3 was considered as positive response in our evaluation. [4-6]. Our patient had a positive reading at a concentration of 0.02 µg/µl and 0.002 µg/µl of IS and 20 µg/µl, 2 µg/µl, 0.2 µg/µl of IC. LTT with IS and IC in 3 different healthy controls showed no proliferative responses (Figure 1). Since the patient was in need of intravenous iron treatment a rapid drug desensitization [7] was performed with no breakthrough nor delayed reactions (See suplemmentary table).

Most of the reported hypersensitivity reactions (HSR) known with iron salts are immediate, 1 of 200000 patients who were treated with high-molecular-weight iron dextran presented anaphylaxis. Many of the patients with a HSR to an iron salt preparation tolerated a different preparation with a re-challenge. Delayed reactions are rare, only 11 cases were reported [8]. Tolerance to alternative iron formulation was achieved by re-challenge in 2 of these patients. These are descriptive cases, without allergy workup. Our patient presented a delayed reaction

doi: 10.18176/jiaci.0789

to IC. Skin tests with late reading were negative and diagnosis was confirmed with a drug provocation test (DPT). The patient presented another delayed reaction with re-challenge with IS. In cases of confirmed HSR, and need of treatment, desensitization (DS) is an effective and secure alternative for treatment administration. Our patient tolerated DS to IS with no breakthrough nor late reactions. LTT is currently the most used test for the diagnosis of T cell-mediated hypersensitivity, especially in B-lactam and anticonvulsants DHRs [4]. To our knowledge LTT has not been used in the diagnosis of HSR to iron salts. We demonstrate here that LTT could be a useful tool to elucidate the delayed hypersensitivity mechanism to iron salts. Nevertheless, further research is needed to evaluate the role of LTT in the diagnosis of delayed HSR to iron salts.

To our knowledge, this is the first case of type IV HSR to iron carboxymaltose and iron sucrose, confirmed with positive DPT and LTT, with successful desensitization. This case illustrates LLT as a promising new tool for the diagnosis of T cell-mediated drug HSR to iron preparations.

Funding

No funding has been required for the present study.

Conflict of interest

The authors certify that any of them have any conflict of interests.

doi: 10.18176/jiaci.0789

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Figure 1. Cell stimulation index according to drug concentration.

A. Lymphocyte transformation test results for Iron Sucrose. B. Lymphocyte transformation test results for Iron Carboxymaltose. The test is considered positive when the SI is greater than 3 and, controls showed no proliferative responses in LTT with the drug.