Desensitization to pertuzumab with positive skin test in a mixed phenotype hypersensitivity reaction

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Pertuzumab is a humanised monoclonal antibody that binds to the dimerisation domain of human epidermal growth factor receptor 2 (HER2), inhibiting its heterodimerisation with other receptors of the HER family. Its use is approved in addition to trastuzumab and docetaxel in patients with metastatic breast cancer with positive HER2 receptors, improving survival. The most common adverse effects include grade III or IV febrile neutropenia and diarrhoea [1]. Hypersensitivity reactions to monoclonal antibodies are possible and recognising them is important for subsequent therapeutic management [2]. A case of a hypersensitivity reaction to pertuzumab has been described in the literature, demonstrating the importance of diagnosis and therapeutic management of these reactions [3], including desensitisation as a therapeutic tool[4]. We present a case of a hypersensitivity reaction to pertuzumab with a positive intradermal test and a successful 13-step desensitisation protocol.

A 56-year-old woman with a personal history of pollinosis, high blood pressure, was diagnosed with HER2-positive breast cancer. Treatment with trastuzumab-pertuzumab-docetaxel was started. Within 10–15 minutes after the first dose of pertuzumab after premedication with dexamethasone and ondansetron (part of the oncologist's protocol), she presented with chills, headache, and low-grade fever (37.5 °C). The infusion was stopped, paracetamol was administered, and the described condition disappeared in approximately 40 minutes. The infusion was continued at a slower rate, achieving the full dose, followed by docetaxel and trastuzumab without incident. At three weeks, five minutes after starting the infusion of the second dose of pertuzumab, she presented with a persistent cough, facial flushing, and headache. The infusion was suspended, and the patient was treated with paracetamol, dexamethasone, and dexchlorpheniramine, with symptoms subsiding in approximately 30 minutes, and the patient then tolerated trastuzumab and docetaxel again without incident. The tryptase curve was not measured in the two reactions.

Given that treatment with the pertuzumab-trastuzumab-docetaxel scheme improved her prognosis and survival, we performed an allergy study two weeks after the second reaction, at the time of consultation from oncology, with prick test evaluating pertuzumab at a concentration of 1.6 mg/ml and intradermal reaction at 0.016 mg/ml and 0.0016 mg/ml, showing positivity in the intradermal reaction at 0.016 mg/ml (Figure 1). The prick and intradermal skin tests with ondansetron and dexamethasone were negative. The decision was made to desensitise pertuzumab, designing a protocol of 13 steps and three bags (online supplementary table), with the last step administered

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at a rate of 120 ml/hr. Premedication was administered the night before with montelukast 10 mg, acetylsalicylic acid 500 mg, dexamethasone 20 mg and cetirizine 10 mg, and one hour before desensitisation, doses of 500 mg acetylsalicylic acid and 20 mg dexamethasone were repeated. Dexchlorpheniramine 5 mg, ranitidine 50 mg, paracetamol 1 g and ondansetron 8 mg were added as part of the premedication protocol by the oncologist, and as a result, the administration of pertuzumab was achieved without incident. The patient was administered one additional cycle of pertuzumab as part of the desensitisation protocol without incident.

We present the case of a patient who presented with an immune-mediated reaction after the first and second pertuzumab cycle administration, presumably due to cytokine release, based on her clinical symptoms (chills, headache, and low-grade fever, cough, facial flushing, and headache). After the allergological study, we confirmed a positive intradermal reaction at a concentration of 1/100. With this clinical presentation and the results of the in vivo tests, we suspected a mixed phenotype hypersensitivity drug reaction. Evidence exists in the literature that the symptoms of the reactions presented in the mixed phenotype can be controlled by desensitisation protocols [5], indicating that the administration in desensitisation is successful.

Additional cases of hypersensitivity reactions to monoclonal antibodies have been reported, with different mechanisms involved in these reactions. In addition to the classic hypersensitivity reaction IgE-mediated mechanism, Valdecillas and Castells commented on the possible non-IgE-mediated mechanisms (IgG-mediated or cytokine release) associated with hypersensitivity reactions to biologics, and how sometimes both IgE and non-IgE mechanisms can coexist [6], as in our case, which presented with the clinical symptoms consistent with a cytokine release syndrome and the result of an in vivo test. We believe that the positive skin test is due to exposure to pertuzumab and its consequent sensitisation. It is important to recognise and classify such patients for allergological management, with desensitisation as an effective therapeutic option[5, 7, 8].

Various protocols have been published that have achieved desensitisation to these drugs, without the ability, in some cases, to demonstrate the mechanism involved with an objective test. González de Olano et al. were the first to report a case of anaphylaxis after the administration of pertuzumab and demonstrate an IgE mechanism mediated by the basophil activation test (BAT), for which it was possible to administer the desensitisation protocol [3]. As in the case of this group, we decided the administration of additional corticosteroids doses to prevent the symptoms caused by the release of mast cell mediators as premedication.

In our case, we emphasise the importance of increasingly frequent hypersensitivity reactions to monoclonal antibodies and of carrying out an allergological study at the appropriate time. It is important to be able to classify drug hypersensitivity reactions into different phenotypes and endotypes to optimise therapeutic

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management.Desensitisation is a useful therapeutic option in the hypersensitivity reactions to drugs with different mechanisms involved.

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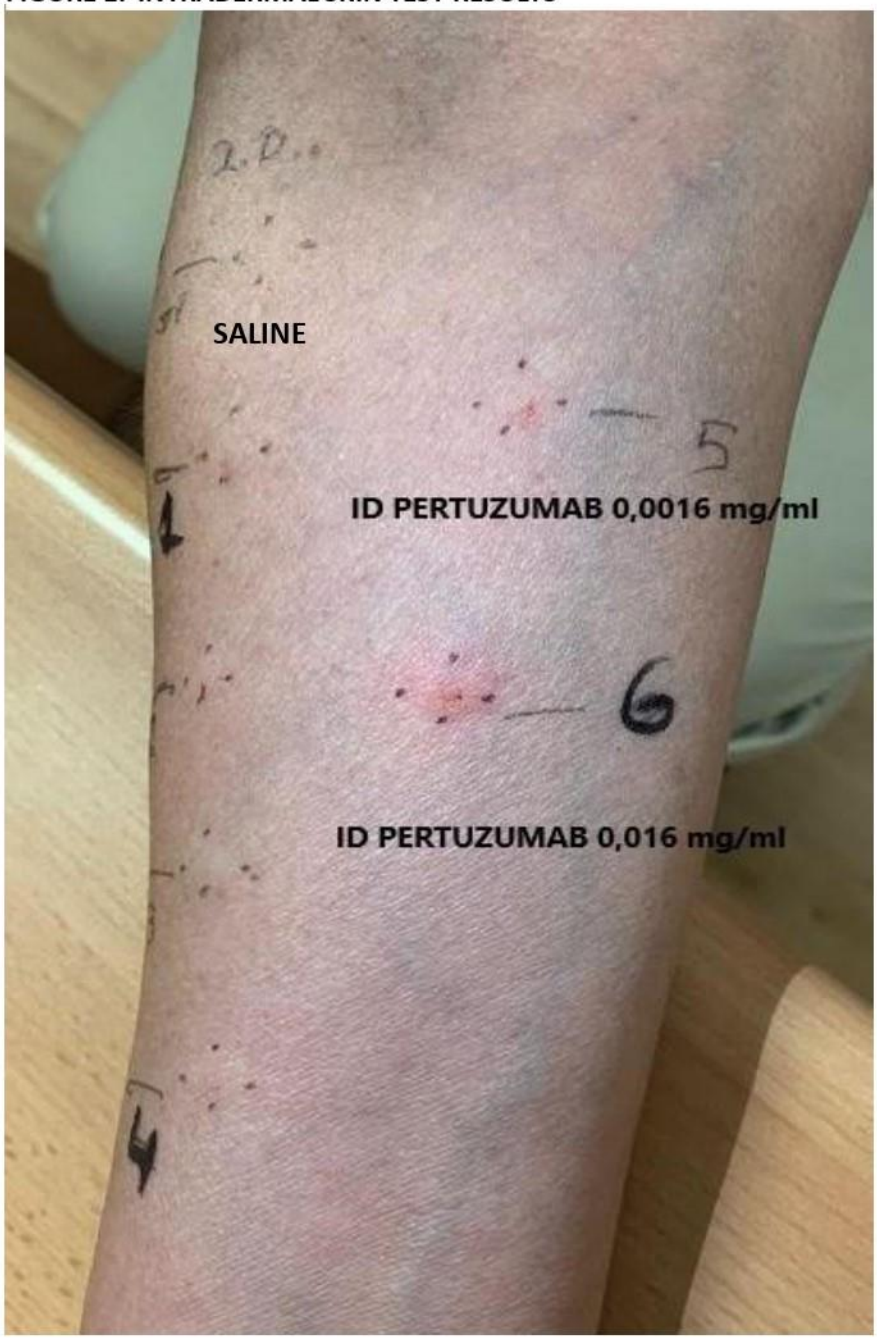
Figure 1. Intradermal skin tests results.

FIGURE 1. INTRADERMAL SKIN TEST RESULTS



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