Anaphylactic Reactions With 3 Nonrelated Drugs (Gadoteridol, Paclitaxel, Bevacizumab) in a Patient With Severe Comorbidities

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Multiple drug hypersensitivity syndrome (MDHS) confirmed by a positive allergy study is unusual. The few cases reported in the literature mainly involve delayed reactions, while immediate IgE-mediated cases are exceptional [1]. We report a case of MDHS where all episodes were immediate reactions.

The patient was a 66-year-old woman with high-grade ovarian and fallopian tube carcinoma, high blood pressure, and ankylosing spondylitis treated with prednisone 5 mg and an angiotensin II receptor blocker. She had no history of allergic diseases. Immediately after the first administration of gadoteridol during magnetic resonance imaging, she experienced anaphylactic shock (skin and respiratory involvement, hypotension, Glasgow score 3) requiring admission to the intensive care unit.

One month later, after an infusion of 5 mL of paclitaxel during her first chemotherapy cycle, she experienced immediate, severe anaphylaxis (skin and digestive involvement, hypotension) requiring antihistamines, corticosteroids, intravenous fluid, and oxygen treatment. The remaining drugs (carboplatin and bevacizumab) were administered the following day without complications.

During the second chemotherapy cycle, she experienced a new anaphylactic episode 3 minutes after starting the bevacizumab infusion. This consisted of facial erythema, itching palmar erythema, abdominal pain, nausea/vomiting, and dyspnea (baseline SaO_2, 88%). She recovered after receiving antihistamines, corticosteroids, and oxygen treatment. The patient tolerated carboplatin the following day.

We carried out an allergy work-up including basal serum tryptase (4 µg/L), total IgE (44 IU/mL), skin prick tests (SPTs) to aeroallergens and hazelnut (negative), and skin tests to gadoteric acid, gadoteridol, paclitaxel, and bevacizumab, which were positive for gadoteridol in the SPT and paclitaxel in the intradermal test (IDT) (Table).

Because paclitaxel was the most effective option for the patient's carcinoma, desensitization with premedication (corticosteroids and antihistamines) was programmed. Two minutes after starting the first step at the first session (calculated dose administered, 1.7 µg), the patient presented an anaphylactic episode with skin, digestive, and respiratory involvement requiring epinephrine. Serum tryptase increased to 22.8 µg/L at 2 hours after onset of symptoms, with a subsequent decrease to 3.39 µg/L in 24 hours.

Paclitaxel was discontinued after a risk-benefit analysis by the oncologist and allergist. The oncologist scheduled an alternative chemotherapy regimen with gemcitabine and carboplatin, which was administered in 6 cycles without complications, followed by surgery. The carcinoma went into remission.

In an attempt to find an explanation for these 4 episodes of severe anaphylaxis, we first considered the possibility of a clonal mast cell activation disorder as an underlying cause. We calculated the Spanish Network on Mastocytosis

Table. Skin Tests to Drugs and Excipients

	SPT 1/10	SPT 1/1	IDT 1/1000	IDT 1/100	IDT 1/10
Gadoteric acid (279.3 mg/mL)	–	–	–	–	–
Gadoteridol (279.3 mg/mL)	+ (6-mm wheal)	NP	NP	NP	NP
Paclitaxel (6 mg/mL)	NP	–	NP	–	+ (8-mm wheal)
Bevacizumab (25 mg/mL)	–	–	–	–	–
Polyethylene glycol 1500 (0.5 g/mL)	NP	–	NP	NP	NP
Polyethylene glycol 3350 (0.5 g/mL)	NP	–	NP	NP	NP
Polyethylene glycol 4000 (0.5 g/mL)	NP	–	NP	NP	NP
Polysorbate 80 (1 g/mL)	NP	–	NP	NP	NP

Abbreviations: IDT, intradermal test; NP, not performed; SPT, skin prick test.

(REMA) score for each reaction, obtaining negative values in all episodes except for that involving gadoteridol (+2), thus indicating a high risk of clonal mast cell activation disorder and the need for further mast cell clonality studies [2]. According to the REMA recommendations, a peripheral blood sample was sent to the Spanish Mastocytosis Reference Center (CLMast) to investigate the presence of the D816V KIT mutation using allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR). The mutation was not detected.

Second, we considered potential sensitization to excipients as the cause of reactions to nonrelated drugs. We reviewed the composition of each of the 3 drugs involved but were unable to find a common excipient. Nevertheless, Cremophor EL (CrEL; macrogolglycerol-ricinoleate), a component of paclitaxel, has been considered a cause of IgE-mediated allergic reactions owing to the polyethylene glycol (macrogol) it contains. In addition, cross-reactivity between CrEL and the polysorbate contained in bevacizumab has been reported [3]. Subsequent SPTs with polyethylene glycol and polysorbate yielded negative results (Table). Therefore, we reasonably ruled out sensitization to excipients as cause of the reactions to nonrelated drugs.

Finally, we suspected MDHS, which is a rare entity (prevalence of 0.6%-2.5%) involving a positive result with ≥2 chemically different drugs. This condition is more frequent in severe delayed skin reactions such as DRESS syndrome (10%-18%) [1].

The positive skin test result to paclitaxel and gadoteridol points to an IgE-mediated mechanism as the cause of the immediate reactions. Immediate hypersensitivity is uncommon in MDHS. In a recent retrospective study of >9000 patients with a suggestive history of drug allergy, only 45 were confirmed to have MDHS, and, exceptionally, the reactions were immediate in 10 patients [1].

We report the case of a patient who experienced 4 severe episodes of anaphylaxis after administration of 3 nonrelated drugs that are uncommon causes of anaphylaxis (gadoteridol, paclitaxel, bevacizumab).

The prevalence of immediate reactions to magnetic resonance contrast media ranges from 0.04% to 2.2%, and around 0.004%-0.01% of cases involve anaphylactic reactions [4]. Both high osmolality–related complement activation and IgE-mediated mechanisms have been involved in the pathogenesis of these reactions [4].

Immediate hypersensitivity reactions to paclitaxel occur in <10% of premedicated patients and generally present as flushing, back or abdominal pain, and respiratory symptoms, mostly after the first dose [5-7], with atopy described as a risk factor [6,7]. It has been postulated that yew tree pollen [5-7] and hazelnut tree pollen (and hazelnuts) [6] are potential sources of first exposure and sensitization to taxane molecules, although reactions are generally attributed to surfactants used in the formulation of paclitaxel (CrEL) through complement activation [5-7]. Skin testing seems to be a useful tool, yielding positive results to paclitaxel in 10%-70% of cases [5,6,8] or to CrEL [3], suggesting an IgE-mediated mechanism. Although desensitization based on a 3-bag, 12-step protocol is highly efficacious and safe [6,7], a severe reaction was recorded at a minimum dose of the drug.

Infusion reactions to bevacizumab are rare (<6.1%) [7,9]. The first case of anaphylaxis due to bevacizumab was recently reported [9]; the present case is the second to date. Patients with cancer and chronic inflammatory diseases treated with monoclonal antibodies and antineoplastic agents are susceptible to immediate reactions to their drugs [7]. The reactions may be due to mechanisms other than those included in the classic Gell and Coombs classification of hypersensitivity reactions. Consequently, it has been suggested that different underlying endotypes/phenotypes might be involved in the development of immediate reactions to these agents [7,10].

In summary, we report a case of MDHS with 3 nonrelated drugs presenting as immediate anaphylaxis.

Studies that explain susceptibility to developing MDHS are lacking. It is necessary to investigate and clarify the predisposing mechanisms of this rare condition, which exceptionally involves immediate reactions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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