Severe delayed hypersensitivity reaction to abiraterone acetate

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Prostate cancer (PCa) is among the most common cancers in men worldwide [1]. Androgen deprivation therapy has been the standard of care for initial management of advanced or metastatic PCa, but progression to castration resistant PCa occurs within two or three years after the initiation of androgen deprivation therapy. Newer agents that target some of these mechanisms of resistance have been recently introduced, providing additional survival benefit [2,3]. These include acetate abiraterone (AA), which interferes with androgenic stimulation of PCa growth, and pembrolizumab, an inmune checkpoint inhibitor [4]. Allergic reactions to medications are unexpected and life-threatening. This sometimes requires seeking therapeutic alternatives, in some cases avoiding the use of first-line therapies, with the consequent impact on the survival and quality of life of the patient [5].

We report a case of a 47-year-old male with current diagnosis of stage IV PCa Gleason 8, with lymph node and bone involvement, diagnosed in 2016. The patient completed treatment with oral bicalutamide, intravenous leuprorelin acetate and 6 cycles of docetaxel in 2017. Biochemical response and practical normalization of the size of lymphadenopathy with sclerotic changes in lytic bone metastases were seen after treatment. On September 2019, due to biochemical progression, he started

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treatment with oral AA 500 mg 2 tablets once daily (administered combined with oral prednisone 5 mg/12 hours in order to prevent the increase of mineralocorticosteroids caused by its mechanism of action [6]) and intravenous pembrolizumab 200 mg every 3 weeks. Ten days after the beginning of this treatment, he developed a symmetrically distributed and very pruriginous morbiliform exanthema on trunk, groins, and root of upper and lower limbs. Extremity weakness, nausea, vomiting and fever of 38.8ºC accompanied skin lesions, so he was attended at emergency room (ER). Blood count as well as hepatic and renal profile were all normal. He also referred a family epidemiological infectious environment (his child had acute gastroenteritis), reason why his oncologist suspected a possible viral condition, treating him with oral paracetamol. Two days later, he was evaluated again at the ER, revealing a pharyngeal hyperemia, enanthema and progression of the exanthema. It had spread over the back, lower limb roots and arms, originating a confluent, erythematous purplish exanthema, among with lingual, labial and eyelid edema. Fever up to 38ºC also persisted, despite treatment with paracetamol. Blood tests showed neither eosinophilia nor alteration of liver or kidney function. Serological tests for Epstein Barr virus, Cytomegalovirus, HIV, Parvovirus B19, Measles, Mycoplasma and Hepatitis C virus were performed with negative results. Antineoplastic treatment was interrupted and oral methylprednisolone 40 mg/24 hours in tapering and oral dexchlorpheniramine 2 mg/8 hours was prescribed for 14 days. The exanthema resolved one week later, with no desquamation or residual lesions.

The patient was assessed to our Allergy Department because his oncologist wanted to continue with this treatment. As a viral condition was suspected and standardized skin tests [neither skin prick test (SPT) nor intradermal tests (IDT)] with AA and

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pembrolizumab are scarce (a few cases reported in the literature), after obtaining informed consent from the patient a single blinded oral challenge test (SBOCT) with AA was performed in 2 days in order to achieve a total dose of AA of 1000 mg. On the first day, 4 hours after administrating 250 mg of AA (with prednisone 5 mg), the patient began with pruriginous erythema on the chest, bilateral eyelid edema and fever peak of 38ºC. The reaction was treated with oral paracetamol 1000 mg, subcutaneous dexchlorpheniramine 5 mg and intramuscular methylprednisolone 60 mg, lasting the reaction 24 hours. Eosinophilia, impaired liver or kidney function was not observed in this episode.

After analyzing the reaction, the possibility of desensitization with AA was considered. However, due to the presence of an intense cutaneous reaction and several general symptoms (drug fever), we decided to contraindicate a desensitization, as reported in the literature [7]. Afterwards, the administration of AA and other pregnenolone analogues was forbidden.

In order to continue with first-line therapy, a single blinded intravenous challenge test with 200 mg of pembrolizumab diluted in 200 ml of saline solution was performed in 4 hours, without developing symptoms in the following 24 hours. Therefore, treatment with pembrolizumab was subsequently administered as usual dose. Finally, he was diagnosed with delayed hypersensitivity reaction to AA.

AA is an orally administered, selective androgen synthesis inhibitor, which has demonstrated efficacy and significant increase survival in men with metastatic castration resistant PCa who had previously received docetaxel [2,3]. It is administered in combination with corticosteroids to prevent drug-induced hyperaldosteronism [6]. Hypertension, hypokalemia, hepatotoxicity, peripheral edema

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and urinary tract infections are common adverse effects [4,6]. However, hypersensitivity reactions are infrequent, and there are only few cases reported in the literature [8, 9]. Verdu et al [8] described in 2018, a patient who experienced immediate generalized urticaria to AA. They performed a rapid desensitization but without previous skin testing or graded challenge, so the underlying hypersensitivity mechanism was unknown. Núñez-Acevedo et al [9] reported a delayed mild micropapular rash in a patient treated with AA. SPT were carried out at 200 mg/ml although the results were negative. In nonimmediate reactions, we suggest delayed IDT could have been the most sensitive method to elucidate the mechanism of the reaction [10], even though a standardized concentration of IDT has not yet been published in the literature. Nevertheless, SBOCT was performed resulting positive and a successful desensitization protocol in consecutive days was performed.

Desensitization in delayed hypersensitivity reactions is less known [7]. Maculopapular exanthemas are the only delayed reactions that have been well studied and successfully desensitized. When systemic symptoms are present, desensitization is not recommended and even absolutely contraindicated if there are severe cutaneous adverse reactions [7]. In our patient, because of the presence of drug-induced fever and generalized skin reaction with angioedema, we finally considered that desensitization was contraindicated.

In conclusion, we present the case of a systemic delayed reaction to AA, with confirmed allergy with SBOCT, and unfortunately, not being possible to be desensitized, so AA was forbidden with the risk of failing treatment of his PCa. More studies are needed for standardizing skin and *in vitro* tests to perform a complete and correct allergy study in our patients, which could help us to understand the

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hypersensitivity mechanism beyond the reaction and consequently to stablish a more specific management.

Conflict of interest

Authors disclose no financial relationship with a pharmaceutical company, or laboratory products manufacturer for this study.

The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

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