

Case Report

Metrorrhagia: A Rare Manifestation of Anaphylaxis Induced by Allergen Immunotherapy

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Abstract

Allergen specific immunotherapy is the only disease-modifying treatment for allergic rhinoconjunctivitis and asthma. We present a rare clinical case of metrorrhagia as the major manifestation of anaphylaxis induced by subcutaneous immunotherapy to inhalant allergens.

Keywords: Anaphylaxis; Metrorrhagia; Immunotherapy; Allergy

1. Introduction

Allergen-specific immunotherapy is currently the only therapeutic modality able to modify Th2 immune responses and reduce symptoms elicited by environmental exposure to aeroallergens. Although subcutaneous immunotherapy (SCIT) is generally safe and effective for treating allergic rhinoconjunctivitis, asthma and Hymenoptera venom hypersensitivity with low risk of systemic allergic reactions (SRs), severe anaphylaxis may occur [1]. We present a rare clinical case of metrorrhagia as manifestation of anaphylaxis induced by subcutaneous aeroallergen immunotherapy.

2. Case Presentation

A 37-year-old, woman with a personal history of moderate/severe allergic rhinitis and well controlled allergic asthma is being treated with subcutaneous allergen immunotherapy (SIT) with two extracts: a/ mixture of pollen *Parietaria Judaica* 70%, grasses spp 30% and b/ dog hair 100%; Tyrosin TU TOP[®], Allergy Therapeutics. She has started 2,5 years ago reaching the maintenance dose (0.5 ml of each specimen) uneventfully and she is now in 4-week intervals without any adverse effect, even local reaction. Her personal medical history is free, despite a reported uterine fibroid that was surgically removed 9 years ago. Since then, her menstrual cycle was normal and her annual gynecological examination was normal. Almost 15 minutes after the simultaneous administration of both injections at the standard maintenance dose (0.5 ml), the patient developed diffuse erythema in face and trunk associated with pruritus in palms. Furthermore, she complained about gastric discomfort and within 2-3 minutes she vomited gastric secretions. The most devastating symptom was an intense sharp pain in the lower abdomen. However, her vital signs (blood pressure, heart rate and oxygen saturation) were normal and remained stable during the episode. An adrenaline dose of 0.3 ml (1/1000, 1 mg/ml) was injected IM immediately while second-line treatment with dimetindene maleate (Fenistil[®]; 4 mg/4 ml in 500cc N/S, infusion in 30 min) and methylprednisolone (Solumedrol[®]; 40 mg/ml, bolus) IV were also administered. Although all other symptoms subsided, the abdominal pain remained as intense as before adrenaline injection; therefore, a second 0.3 ml dose was injected 10 min after the first one, followed by 20 mg butyl-scopolamine (Buscopan[®]; 20 mg/ml) and ranitidine (Lumaren[®]; 50 mg/2 ml) IV. The pain subsided gradually, but metrorrhagia occurred 1 hour later. Urgent gynecological examination was immediately requested and confirmed the vaginal bleeding and moreover detected mild endometrial thickening at ultrasound imaging. The patient was on 12th day of the menstrual cycle. All performed blood tests, including coagulation testing, were normal while beta-chorionic gonadotropin measurement was negative. The metrorrhagia ceased gradually in 24 hours without any medical intervention.

No other predisposing factors as infection, emotional or physical stress, drug intake or other, were detected after the thorough revision of the episode. However, in order to avoid future reactions, the SCIT plan was modified with H1-antihistamine pre-treatment (cetirizine, Zirtek[®] 10 mg) one hour before injection, 40% dose reduction (0.3 ml of each) with 20% increase in every two uneventful administrations and sequential administration of the 2 injections with a 30-minute interval. Almost 10 months after the event she receives the standard maintenance dose without recurrence of adverse reactions.

3. Discussion

A recent subcutaneous immunotherapy surveillance study from Epstein TG et al. has shown that SRs occurred in 0.6% of patients receiving SCIT injections with the majority of them classified as mild (grade 1 and 2) while 0.005% of patients experienced life-threatening, grade-4 SRs [2]. Real life data confirm that severe SRs in SCIT are very rare but still exist.

Many factors have been implicated in the occurrence of SRs during SCIT. The treatment of patients suffering from uncontrolled and/or severe asthma, administration of pollen extracts during peak pollination season, concurrent viral infections, large local reactions to previous shots, prior history of SRs, build-up phase and especially in cluster protocols, the change of allergen's extract vial, allergen dosing mistakes and concomitant beta-blockers or angiotensin-converting-enzyme inhibitors intake are the most prevalent conditions that have been associated, individually or combined, with increased risk of a systemic reaction during immunotherapy [3]. In our case the reaction occurred on April during high *Parietaria* and grass pollen concentrations. The administration of both extracts simultaneously was adopted after the first year of uneventful SCIT as less time consuming; however, we discourage this trend in daily practice as in case of SRs the offending shot cannot be detected and the impact of the simultaneous dosing in reaction's severity cannot be excluded.

Uterine contractions and vaginal bleeding are reported as manifestations of anaphylaxis in post pubertal female patients, but they are considered non-typical and not well-documented [4, 5]. According to the World Allergy Organization, SRs to Subcutaneous Immunotherapy are classified into 5 grades and each grade is based on both system involvement and severity. Uterine cramps with metrorrhagia fall under grade 2 and are extremely rare [6]. Tubi et al. first reported two patients with immediate development of vaginal bleeding after SCIT administration followed by a limited number of reports with the majority related to venom immunotherapy and especially, to Honey-bee immunotherapy [5, 7, 8]. In Honey-bee immunotherapy associated metrorrhagia, it is suggested that specific venom allergens, especially melittin, can promote anaphylactic symptoms via nonimmune mechanisms and primarily via activation of the bradykinin pathway in addition to the IgE-mediated mechanisms [9].

In our case, the third metrorrhagia case related to pollen immunotherapy, in medical literature [5, 7], we suggest as potential cause of metrorrhagia the organ-specific effect of mast cell mediators on uterus smooth muscle, through IgE-mediated anaphylaxis to pollen extract. In this line, nowadays it is known that the kallikrein-kinin system, the clotting cascade, and the fibrinolytic system may be activated during anaphylaxis [10]. The detected concomitant endometrial dysfunction could contribute to the metrorrhagia in the absence of any other underline endocrinal or autoimmune disease.

Metrorrhagia and uterine contractions are unusual presentations of an anaphylactic reaction, but they should be considered in female patients. It is recommended that allergen immunotherapy (AIT) should not be initiated during pregnancy but, if already started, AIT can be continued through pregnancy in agreement with the patient and obstetrician if previous AIT doses have been well tolerated [1].

4. Conclusion

Our case points out that allergen immunotherapy is a specific treatment that must be performed by well trained physicians as anaphylaxis may occur even a long time after initiation. Taking into consideration the fact that our

patient developed anaphylaxis with uterine contractions and metrorrhagia after being on maintenance phase for 2.5 years without any prior adverse reaction, we suggest precise consideration of the benefit/risk ratio and thorough education of pregnant women about potential side effects before obtaining consent. Furthermore, our case supports the established contra-indication not to initiate immunotherapy during pregnancy.

Authors Contribution

M Ntakoula, C Fokoloros, C Chliva, E. Papadavid and M Makris state that they have “Substantial contribution to the conception or design of the work; AND Drafting the work and revising it critically for important intellectual content; AND Final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.”

Statement of Consent for Presentation and Publication

The authors state they have obtained patient’s informed consent for presentation and publication of the present clinical case.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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