

Positive basophil activation test in patient with anaphylaxis to cotrimoxazole

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Cotrimoxazole, an antibiotic also known as trimethoprim (TMP) -sulfamethoxazole (SMX), was reported to be effective against Gram-positive bacteria, Gram-negative bacteria, fungal (*Pneumocystis jirovecii*) and protozoal pathogens [1]. In HIV-infected patients, cotrimoxazole causes a higher rate of adverse drug reactions than in the general population [2]. Cotrimoxazole usually has been associated with delayed reaction but IgE mediated hypersensitivity has also been reported [3]. Although SMX is the most common culprit drug of adverse reaction to cotrimoxazole, TMP has also been involved [4, 5].

We report a case of a 38 years old woman with no history of atopy and HIV, who was referred to our Allergy Department in June 2018 for anaphylaxis. About two months earlier, she was treated with TMP-SMX 800/160 by mastitis during a week. A month later, she was again prescribed TMP-SMX 800/160, mebendazole and paracetamol as a treatment for refractory mastitis. Sixty minutes after taking the first dose of TMP-SMX 800/160, she presented otic, palms, soles and genital pruritus, generalized urticaria and dizziness. Her blood pressure was 141/87 mmHg, heart rate 135 bpm, oxygen saturation 97%. She received 100 mg of intravenous hydrocortisone, 50 mg of intravenous ranitidine, 40 mg of intravenous methylprednisolone and 6 mg of oral dexchlorpheniramine. The patient worsened and also experienced dyspnea and pharyngeal occupation despite the treatment. She immediately received intramuscular epinephrine. Vital signs were not re-measured. Hours before the reaction, she had also taken mebendazole and paracetamol. Previously, she had never taken mebendazole.

Two weeks after the reaction, the patient was initially evaluated with a detailed clinical history. In addition, the patient was informed about the risks and benefits of diagnostic work-up procedures. Unfortunately, she refused to perform skin tests to TMP-SMX due to the associated risk. Given the high suspicion of causality of TMP-SMX, a basophil activation test (BAT) was performed with three different concentrations of cotrimoxazole.

BAT was found to be strongly positive with an intermediate concentration of SMX (1 mg/mL) and TMP (0,2 mg/mL) (64% of basophils expressed CD63) (Figure 1). A second BAT was carried out to assess the basophil's activation after incubation with TMP and SMX individually: TMP alone induced a robust activation response (41% of basophils expressed CD63), whereas SMX had no effect (CD63+: <2%). BAT remains positive for TMP at 6 and 19 months after the diagnosis (CD63+ basophils: 25,9% and 18,9%, respectively)

To exclude the possibility of false-positive results, BAT was performed in 4 control patients with confirmed good tolerance to TMP-SMX. Basophils from these patients were not activated with TMP-SMX.

After knowing the positive BAT result to TMP, the patient gave his consent to the allergological study to rule out the involvement of concomitant drugs in the reaction. Drug provocation test (DPT) with mebendazol and paracetamol were carried out, both with negative results. Even though allergy workup was performed under strict hospital surveillance in a specialized setting by trained health care professionals, the patient refused to perform skin test and DPT to SMX.

Drug-induced anaphylaxis workup diagnosis includes a detailed clinical history emphasizing on severity and time elapsed between drug intake and the onset of symptoms, supplemented by skin tests and *in vitro* test [6]. There are a few *in vitro* tests available, such as serum-specific IgE and BAT, that can aid in the diagnosis and identification of the culprit drug. Specific IgE determination is only available for Beta-Lactam antibiotics and its sensitivity is low. BAT has been evaluated as a diagnostic tool for immediate hypersensitivity reactions (IHR) to β -lactam antibiotics and other antibiotics such as Quinolones [7,8]. BAT showed sensitivity between 50-60% in selective amoxicillin and clavulanic allergic patients [7] and 71% in patients with immediate hypersensitivity reactions to quinolones [8]. BAT may be particularly useful in patients with negative skin test in β -lactams. A multicenter study by De Week et al, showed that positive BAT had an important value in 13 cases of immediate-type allergy to β -lactam antibiotics with negative skin tests and serum-specific IgE. All patients were challenged and had positive results. [9]. The time between the BAT and the reaction can impact the results. BAT in Amoxicillin and clavulanic selective allergy patients lose positivity of more than 40% in tests performed over 12 months after the reaction [7]. In this case, BAT remained positive to trimethoprim 19 months after the reaction.

Anaphylaxis induced by trimethoprim is rare and in some reported cases appears mainly mediated by IgE mechanism [4, 5].

Cabañas R et al [4] described a patient with anaphylaxis to TMP-SMX who had a positive skin prick test and RAST inhibition to TMP. The patient had negative ST to SMX and no significant levels of specific IgE to SMX. Skin test to trimethoprim can trigger an anaphylaxis reaction in patients with high sensitivity to this antibiotic. Alfaya et al [5] reported a case of pruritus sickliness and hypotension after a positive skin prick test with TMP that required treatment with epinephrine. In our case, it was not possible to carry out a skin test (ST), BAT was the only diagnostic procedure available to assess the immediate hypersensitivity reaction to TMP-SMX and which allowed to TMP to be identified as a culprit drug. BAT is a diagnostic procedure that does not constitute a risk for the patient and should be the first choice of the allergy workup, especially in high-risk patients (severe reactions, patients with severe comorbid conditions) conforming to ENDA/ EAACI Drug Allergy Interest Group position paper. [10]

To our knowledge, this is the first reported case with positive BAT to trimethoprim in a patient with anaphylaxis induced to TMP-SMX. BAT could be considered a safe and useful in vitro diagnostic tool in patients who experience life-threatening reactions to TMP-SMX when specific IgE and ST are unable to be performed.

Conflicts of interest:

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Figure 1

Basophils were identified in whole blood as SSC_{low} / CD123⁺ / HLA-DR⁻ (A,B). Dot-plots of CD63 expression after challenge with PBS (negative control) (C), 0,5 µg/mL anti-IgE antibody (positive control) (D), cotrimoxazole (1 mg/mL SMX + 0.2 mg/mL TMP) (E), 1 mg/mL of SMX (F), and 0,2 mg/mL of TMP (G). Activated basophils are expressed as the percentage of CD63⁺ cells in the upper-right quadrant.

