## Positive Basophil Activation Test Result in a Patient With Anaphylaxis to Cotrimoxazole

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The antibiotic cotrimoxazole, also known as trimethoprim-sulfamethoxazole (TMP-SMX), is effective against gram-positive bacteria, gram-negative bacteria, fungi (*Pneumocystis jiroveci*), and protozoan pathogens [1]. TMP-SMX causes adverse drug reactions in HIV-infected patients more frequently than in the general population [2]. While it is usually associated with delayed reactions, IgE-mediated hypersensitivity has also been reported [3]. Although SMX is the most common culprit drug in adverse reactions to cotrimoxazole, TMP has been found to play a role [4,5].

We report the case of a 38-year-old woman with no history of atopy or HIV infection who was referred to our Allergy Department in June 2018 for anaphylaxis. About 2 months earlier, she had received a week's therapy with TMP-SMX 800 mg/160 mg for mastitis. A month later, she was again prescribed TMP-SMX 800/160, mebendazole, and paracetamol as treatment for refractory mastitis. Sixty minutes after taking the first dose of TMP-SMX 800 mg/160 mg, she developed pruritus affecting the ear, palms, soles, and genitals, as well as generalized urticaria and dizziness. Her blood pressure was 141/87 mmHg, heart rate 135 bpm, and 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's condition worsened, with dyspnea and globus sensation despite treatment. She was immediately given intramuscular epinephrine. Her vital signs were not remeasured. Hours before the reaction, she had also taken mebendazole and paracetamol. She had never previously taken mebendazole.

Two weeks after the reaction, the patient was initially evaluated by means of a detailed clinical history. She was also informed about the risks and benefits of diagnostic work-up procedures and refused to undergo skin tests with TMP-SMX owing to the associated risk. Given the high suspicion of causality for TMP-SMX, a basophil activation test (BAT) was performed with 3 different concentrations.

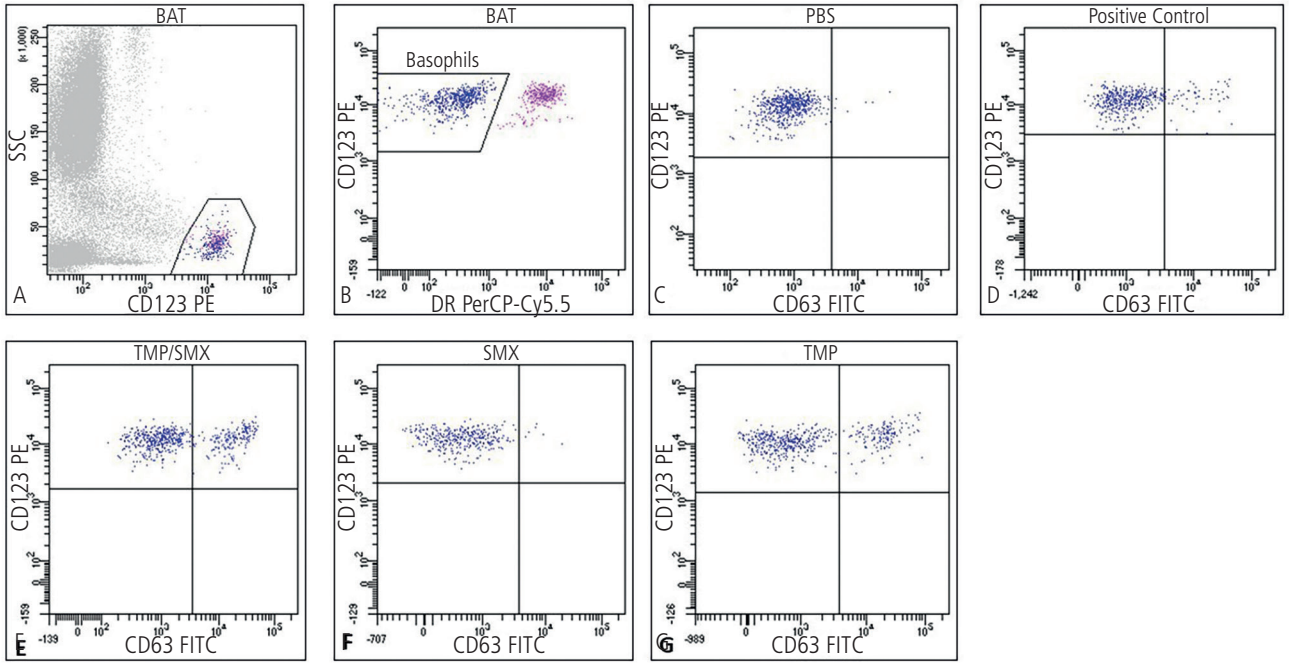


**Figure.** Basophils were identified in whole blood as SSClow/CD123+/HLA-DR– (A,B). Dot plots of CD63 expression after challenge with phosphate-buffered saline (negative control) (C), 0.5 µg/mL anti-IgE antibody (positive control) (D), cotrimoxazole (1 mg/mL SMX + 0.2 mg/mL TMP) (E), 1 mg/mL of SMX (F), and 0.2 mg/mL of TMP (G). Activated basophils are expressed as the percentage of CD63+ cells in the upper right quadrant.

 

The BAT result was strongly positive, with an intermediate concentration of SMX (1 mg/mL) and TMP (0.2 mg/mL) (64% of basophils expressed CD63) (Figure). A second BAT was carried out to assess basophil 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 remained 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.

Once the positive BAT result to TMP was known, the patient gave her consent to undergo an allergology work-up to rule out the involvement of concomitant drugs in the reaction. A drug provocation test (DPT) with mebendazole and paracetamol yielded negative results. Even though the allergology work-up was performed under strict hospital surveillance in a specialized setting by trained health care professionals, the patient refused to undergo skin testing and DPT with SMX.

Diagnosis of drug-induced anaphylaxis includes a detailed clinical history, with emphasis on severity and time between drug intake and onset of symptoms, supplemented by skin and in vitro tests [6]. Few available in vitro tests (eg, serum-specific IgE and BAT) can aid in the diagnosis and identification of the culprit drug. Determination of specific IgE is only available for β-lactam antibiotics, and its sensitivity is low. BAT has been evaluated as a diagnostic tool for immediate hypersensitivity reactions to β-lactam antibiotics and other antibiotics such as quinolones [7,8]. BAT showed sensitivity of 50%-60% in selective amoxicillin-clavulanic acid–allergic patients [7] and 71% in patients with immediate hypersensitivity reactions to quinolones [8]. BAT may prove particularly useful in patients with negative skin test results for β-lactams. A multicenter study by De Week at al [9] showed that a positive BAT result had considerable value in 13 cases of immediate-type allergy to β-lactam antibiotics with negative skin test and serum specific IgE results. All patients were challenged and had positive results. The time between the BAT and the reaction can impact the results. In selective amoxicillin-clavulanic acid–allergic patients, BAT loses positivity in more than 40% of tests performed over 12 months after the reaction [7]. In the present case, BAT remained positive to TMP 19 months after the reaction.

Anaphylaxis induced by TMP is rare, and, in some cases, IgE-mediated [4,5]. Cabañas et al [4] reported the case of a patient with anaphylaxis to TMP-SMX who had a positive skin prick test result, with inhibition of TMP in the radioallergosorbent test. The patient had negative skin test results with SMX and no significant levels of specific IgE to SMX. Skin testing with TMP can trigger an anaphylactic reaction in patients with high sensitivity to this antibiotic. Alfaya et al [5] reported the case of a patient who experienced pruritus, nausea, and hypotension after a positive skin prick test with TMP that required treatment with epinephrine. In the case we report, it was not possible to carry out a skin test; BAT was the only diagnostic procedure available to assess the immediate hypersensitivity reaction to TMP-SMX and that enabled TMP to be identified as a culprit drug. BAT does not constitute a risk for the patient and should be the first choice in the allergology work-up, especially in high-risk patients (severe reactions, patients with severe comorbid conditions), consistent with the ENDA/EAACI Drug Allergy Interest Group position paper [10].

To our knowledge, this is the first reported case of a positive BAT result for TMP in a patient with anaphylaxis induced by TMP-SMX. BAT can be considered a safe and useful in vitro diagnostic tool in patients who experience life-threatening reactions to TMP-SMX when determination of specific IgE and skin testing cannot be performed.

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*Conflicts of Interest*

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