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Multifocal Fixed Drug Eruption to ceftazidime in a child with cystic fibrosis

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Running title : **A multifocal Fixed Drug Eruption to ceftazidime in a child with cystic fibrosis: a case report.**

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To the editor

Introduction:

Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by well-delimited pigmented lesions of the skin and/or mucosa [1,2]. FDE is rare and frequently misdiagnosed leading to recurrent eruptions after the offending drug is re-administered [1,2]. The diagnosis hallmark is its recurrence in previously affected sites leading to a residual hyperpigmentation, however some cases without residual pigmentation have been described [2]. Many drugs have been shown to induce FDE, especially antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) [3]. To our knowledge, there is no report of FDE to ceftazidime.

Case report:

A 12-year-old girl with a DF508 homozygote cystic fibrosis (CF), was admitted in the department of Pediatric Pulmonology for an acute pulmonary exacerbation. She was chronically infected with Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and *Pseudomonas Aeruginosa*. Her maintenance therapy consisted of pristnamycin alternately with minocycline, nebulized colimycin, nebulized Drnase alpha, Saline nasal rinses, hydrocortisone, pancreatic enzymes and vitamins. She was taking daily oral itraconazole for pulmonary aspergillosis. Treatment with intravenous ceftazidime and amikacin was started at admission. Four hours after the first antibiotic infusion, she presented with a multifocal erythematous itching and burning skin eruption of the upper of the right arm, the right elbow and the right thigh. Examination revealed three round to oval-shaped, reddish-brown to violaceous macules, the biggest of which was 7 x 12 cm in size, without desquamation or vesicles (fig1). She hadn't received any other drugs than her usual treatment, especially paracetamol or NSAIDs, within the 2 weeks before the onset of the eruption. The lesions were treated with oral antihistamines and resolved within 7-8 days with residual brown pigmentation. Ceftazidime and amikacin were stopped and switched with tazocillin, gentamycin and ciprofloxacin.

Four months before, she reported similar lesions at the same sites starting 48 h after the onset of a treatment with ceftazidime and amikacin. Symptoms resolved spontaneously within 2–3 days after the drugs were stopped, leading to permanent brown residual lesions. The child previously tolerated several courses of ceftazidime and amikacin.

The diagnosis of FDE was confirmed by histopathologic examination showing lymphocytic infiltrate including CD8+ T cells at the dermo-epidermal interface, extending into the mid and upper epidermis with necrosis of keratinocytes. The upper dermis contained a large amount of melanin and melanin-

laden macrophages (fig2). Other investigations, including complete blood count, urinalysis, liver and renal function tests were normal. Two months after discharge, an allergy work-up was performed including pricks, intradermal (ID) tests, and patch tests (on the back and on the residual hyperpigmented lesions) with ceftazidime and cefuroxime, cefotaxime, and ceftriaxone, diluted with 0.9% sterile NaCl. The concentrations used were 25 mg/ml for prick tests, 0.25-25 mg/ml for ID tests, and 250 mg/ml for patch tests. Skin tests responses were negative at 15–20 min (immediate), 6–8 h (semi-late) and 48-72 h (late). Patch tests on residual hyper-pigmented lesions were negative with ceftazidime. Drug provocation test (DPT) with ceftazidime was performed and induced an itching erythematous skin eruption at the same sites of the arm and the thigh, 4 hours after the onset of the DPT. Amikacin was re-administrated without any eruption. Thus, clinical presentation together with histologic analyses and positive DPT with ceftazidime confirmed the diagnosis of ceftazidime-induced multifocal FDE.

Discussion:

FDE appear after a variable period of sensitization, usually within 1-2 weeks of drug exposure, and recur more rapidly (30 minutes to 8 hours) with subsequent exposure, generally at the same sites [4-6]. This shorter time latency may involve reactivation of memory cells located at the sites of the lesions, especially CD8+ memory T cells [4,5]. Lips, oral mucosa, hands, sole, genitals and the groin areas are the most frequently affected sites [4-6]. However, reactions can worsen in extent and severity at re-exposure, and bullous or erosive forms may be observed [4,7]. Acute lesions heal over one to two weeks leaving a residual hyperpigmentation.

In our patient, clinical presentation was compatible with the diagnosis of multiple FDE. She had been previously sensitized to ceftazidime, the first reaction occurred after 48 hours, similar lesions relapsed 4 hours after treatment with ceftazidime. The lesions were typically red to violaceous and well demarcated, and healing was followed by residual hyper pigmented lesions. Histopathologic findings were compatible with FDE, showing a lymphocytic infiltration of the dermoepidermal junction, including CD8+ T cells, with a necrosis of keratinocytes and pigment laden macrophages [4,5]. This is consistent with results showing the potential role of CD8+ T cells in FDE pathogenesis [4]. The negativity of skin test may result from a low penetration of the drug into the skin, it is also possible that our patient was sensitized to a metabolite of ceftazidime not available in the commercialized form used to perform patch testing [4].

The most frequently involved drugs are antibacterial agents and NSAIDs [3,4]. To our knowledge, there was no report of FDE to ceftazidime in the literature. However, two potential cases of ceftazidime-induced FDE have been previously declared to the French Register of

Pharmacovigilance. In the present case, amikacin and ceftazidime were suspected. Amikacin was re-administrated safely. The DPT with ceftazidime induced a relapse of acute lesions at the same sites than the previous ones, confirming its causal relationship.

Patients with cystic fibrosis (CF) may be at increased risk of drug hypersensitivity reaction. The prevalence of antibiotic allergy in CF is estimated to be 6%-25% [8], with beta-lactams being the most frequent responsible drugs. The higher incidence of hypersensitivity reaction may be explained by the increased antibiotic exposure and increased use of intravenous route. However, this prevalence may be overestimated since repeated exposure to antibiotics may induce immunological tolerance [9]. FDE to quinolones have already been reported in patients with CF [10]. To the best of our knowledge, this is the first reported case of ceftazidime-induced multifocal FDE in a child with CF.

Conclusion:

We report here the first case of FDE to ceftazidime in a child with CF. In non-severe typical forms, once the diagnosis of FDE is confirmed, the culprit drug is contraindicated to avoid the risk of potentially more severe recurrences.

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Conflict of interest

The authors declare no conflict of interest.



Figure 1. Round-to-oval-shaped, reddish-brown to violaceous macules over the right arm and the right elbow

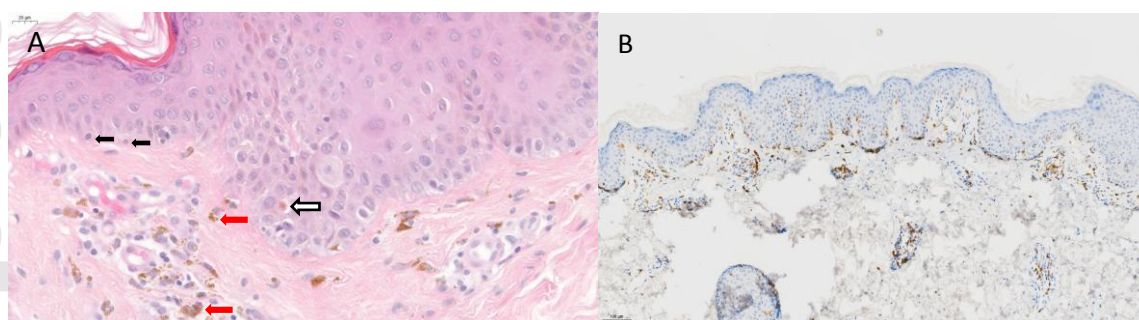


Figure 2. A: Lymphocytic infiltrate of the dermo-epidermal interface (black arrows), extending into the mid and upper epidermis with necrosis of keratinocytes (red arrows), and melanophages (black and white arrow) (H&E 50x). **B:** Immunohistochemistry with anti-CD8 (brown) showed the presence of lymphocytes CD8+ predominantly in the dermo-epidermal junction, original magnification X10.