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Toxic epidermal necrolysis induced by cystic fibrosis transmembrane conductance regulator modulators

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Cystic fibrosis (CF) is an autosomal recessive disorder characterized by defects in the chloride ion transport caused by mutations in those genes encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.¹ Approximately 2000 genetic variants of the disease have been identified, with F508del being the predominant mutation.¹ TRIKAFTA (Vertex Pharmaceuticals, Boston, Massachusetts) is the first triple combination of the transmembrane conductance regulator correctors VX-661 (tezacaftor 50 mg) and VX-445 (elexacaftor 100 mg) together with the gating potentiator VX-770 (ivacaftor 75 mg), and is used to treat patients with CF with at least one copy of the F508del mutation.² TRIKAFTA confers a gain in lung function, resulting in a reduction of pulmonary exacerbations and improving patient-reported quality-of-life scores.³

CASE REPORT

A 39-year-old man with a history of CF and F508d/G542X mutation presented with a generalized rash, angioedema, fever, and dyspnoea requiring hospitalization in the intensive care unit 10 days after starting therapy with TRIKAFTA (two tablets in the morning) and KALYDECO (Vertex Pharmaceuticals, Boston, Massachusetts) containing ivacaftor 150 mg (one tablet in the evening). The drugs were immediately discontinued. Blood test displayed neutropenia, lymphopenia, increased bilirubin, and C-reactive protein. At hospitalization, the patient had fever, hypotension, and bilateral pneumonia with no isolated pathogens. However, his condition progressed into a severe respiratory insufficiency that required orotracheal intubation. Three days after the intensive care unit admission, the generalized rash turned into blisters that became flaccid with large areas of skin peeling off. An early biopsy of the skin tissue confirmed a suspected diagnosis of toxic epidermal necrolysis (TEN). After 20 days of treatment with high doses of corticosteroids, piperacillin/tazobactam,

and paracetamol, the patient was transferred to a normal ward where treatment was continued. The patient was discharged after complete recovery 1.5 months later. A month later, the patient presented to the Allergy Department for diagnostic work-up, including a patch test with TRIKAFTA and KALYDECO at 20% in physiological saline solution and petrolatum (pet). The patches remained on the patient's back for 48 hours and readings were taken at day (D) 2 and D4. Both drugs induced doubtful reactions at D2 (?+) and positive reactions at D4 (+), but similar tests in five controls were negative. The strength of the patch test reactions based on the ICDRG criteria was stronger when tested in saline compared with pet. (Figure 1).



FIGURE 1

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Patch tests readings at day 4 with TRIKAFTA and KALYDECO. SS, saline solution and pet, petrolatum

DISCUSSION

TEN is a rare, but severe cutaneous adverse reaction, mostly caused by drugs. Genetic factors associated with drug hypersensitivity are a complex issue that has been studied in different populations, suggesting a putative association between, for example, the human

leucocyte antigen (HLA)-B*58:01 allele and allopurinol hypersensitivity, or HLA-B*15:02 and carbamazepine hypersensitivity.⁴ Whether hypersensitivity to CFTR modulators is related to a genetic factor remains uncertain. However, it seems that some critical factors may act synergistically, such as drug interactions, or viral infections, leading to drug-induced TEN reactions.⁵

Because drug re-exposure tests are contraindicated for TEN, patch testing has proven to be a useful and safe diagnostic tool to reveal the causative drug.^{6, 7} The positive patch test reactions to both TRIKAFTA and KALYDECO suggest an underlying T-cell-mediated immune reaction to ivacaftor or other common ingredients (Table 1), although drug cross-reactivity among the different CFTR modulators could not be ruled out. Herein, we present the first report of TEN induced by drugs containing CFTR modulators, not previously mentioned as a side effect in the drug package inserts, diagnosed by specific epicutaneous testing.

TABLE 1. Comparative table with ingredients of TRIKAFTA and KALYDECO

TRIKAFTA	KALYDECO
75 mg Ivacaftor	75 mg Ivacaftor
50 mg tezacaftor	
100 mg elexacaftor	

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AUTHOR CONTRIBUTIONS

Elena Mederos Luis: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (lead). **Ruperto Conzález Pérez:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); supervision (lead); validation (equal); writing – review and editing (equal). **Paloma Poza Guedes:** Conceptualization (equal). **Cristina Álava Cruz:** Conceptualization (equal). **Víctor Matheu:** Conceptualization (equal). **Inmaculada Sánchez Machín:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); supervision (lead); validation (lead); visualization (lead); writing – review and editing (equal).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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