Clinical commentary

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Epidiolex-induced skin rash

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ABSTRACT – Epidiolex® (cannabidiol, aka CBD) is a recently approved FDA prescription drug for the treatment of epilepsy associated with Lennox-Gastaut and Dravet syndromes, and is increasingly used for treatment-resistant epilepsy. Rash was rarely reported in Epidiolex® clinical trial data. We report a case of Epidiolex®-related skin rash that developed in a delayed fashion in a 23-year-old female with medically refractory epilepsy. We also review the potential mechanism of Epidiolex®-related skin rash.

Key words: Epidiolex, cannabinoid, skin, rash, hypersensitivity reaction, antiepileptics, drug interaction, CBD, Epidiolex® (cannabidiol)

Epidiolex® (*Epidiolex® brand name utilized to avoid confusion with other CBD products*) is a 99% pure, oral CBD extract in sesame oil that was approved in June 2018 by the FDA for treatment of two epilepsy syndromes - Lennox-Gastaut syndrome (LGS) and Dravet syndrome. In four randomized, double-blind, parallel-group, adjunctive-therapy trials, Epidiolex® was found to be superior to placebo in reducing the frequency of drop seizures in patients with LGS and convulsive seizures in patients with DS (Thiele *et al*., 2018). The most common side effects reported in trials included pyrexia, upper respiratory tract infection, somnolence, decreased appetite, diarrhea, vomiting, nasopharyngitis, status epilepticus, fatigue, and lethargy (Devinsky *et al*., 2016, 2018; Sekar and Pack, 2019). Rash was reported as a side effect in the Dravet trial (Devinsky *et al*., 2018); in which a total of six patients (18%) experienced a rash, five in the CBD group and one in the placebo group, with no cases showing mucosal involvement or evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis. However, the literature on the underlying mechanism of Epidiolex®-related skin rash is limited. We report a skin rash that developed in a 23-year-old female after initiation of Epidiolex® as adjunctive treatment for LGS. To our knowledge, this is the first case report of Epidiolex®-related skin rash (ERSR) outside the clinical trials. We will also review the possible mechanisms by which Epidiolex® may cause skin reactions.

Case study

The patient is a 23-year-old female with a history significant for refractory focal epilepsy status post vagal nerve stimulator placement. Prior to initiation of Epidiolex®, the patient received lacosamide 150 mg BID, topiramate 200 mg BID, clobazam 25 mg AM and 30 mg PM. She was started on Epidiolex® at 2.9 mL (100 mg/mL solution) BID for seven days, then increased

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to 5.8 ml BID; given her weight of 117 kg. Initially, she tolerated the medication well with decreased seizure frequency. Five weeks after starting Epidiolex®, the patient developed a morbilliform rash on her left forearm, spreading to all extremities and the trunk (*figure 1*). The patient had not started any other new medications, did not have any other known exposures, and did not have any known hypersensitivity reactions to other medications in the past. After developing the rash, she was seen in the clinic during which perampanel was prescribed and an Epidiolex® wean was initiated. The patient subsequently presented to our emergency department with complaints of shortness of breath and diarrhea in addition to rash. Laboratory work was unremarkable with no eosinophilia or signs of end organ damage suggesting DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome or drug-induced hypersensitivity syndrome (DIHS). Epidiolex® was discontinued and the patient was admitted to the hospital for close monitoring and treatment. After three days, the rash had almost entirely faded and the patient's shortness of breath and diarrhea symptoms had also resolved, so the patient was discharged home.

Discussion

Around 3% of patients receiving antiseizure drugs (ASDs) experience skin-related side effects (Błaszczyk *et al*., 2015). Although the exact pathogenesis of skin eruption remains largely unknown, it is suspected to be an allergic hypersensitivity reaction. Classically, older aromatic ASDs, such as carbamazepine, phenytoin and phenobarbital, are commonly associated with a skin rash but relatively newer ASDs, including lamotrigine, zonisamide, oxcarbazepine and lacosamide, are also implicated. Hypersensitivity reactions range from immediate to delayed. Most ASD allergic reactions are delayed hypersensitivity reactions. Delayed reactions are believed to be T-cell-mediated that vary in severity from a simple rash to severe systemic involvement, such as Stevens Johnson syndrome and toxic epidermal necrosis (Krauss, 2006). The actual mechanism for ASD hypersensitivity syndrome is not entirely understood but hypothesized to result from toxic ASD intermediaries due to inadequate drug clearance with elevated dose or CYP pathway inhibition. Toxic intermediaries can trigger immune-mediated responses or direct cell death at the sites where metabolic processes occur. The skin, liver, and mucosa are the primary sites of ASD metabolism (Fowler *et al*., 2019).

This patient developed a morbilliform rash as well as shortness of breath and diarrhea within five weeks of starting Epidiolex®. These symptoms could suggest drug-induced hypersensitivity syndrome (DIHS) which is characterized by late onset, infectious mononucleosis-like symptoms, and herpesvirus 6 (HHV-6) or Epstein Barr virus reactivation (Tohyama and Hashimoto, 2011). DIHS is commonly associated

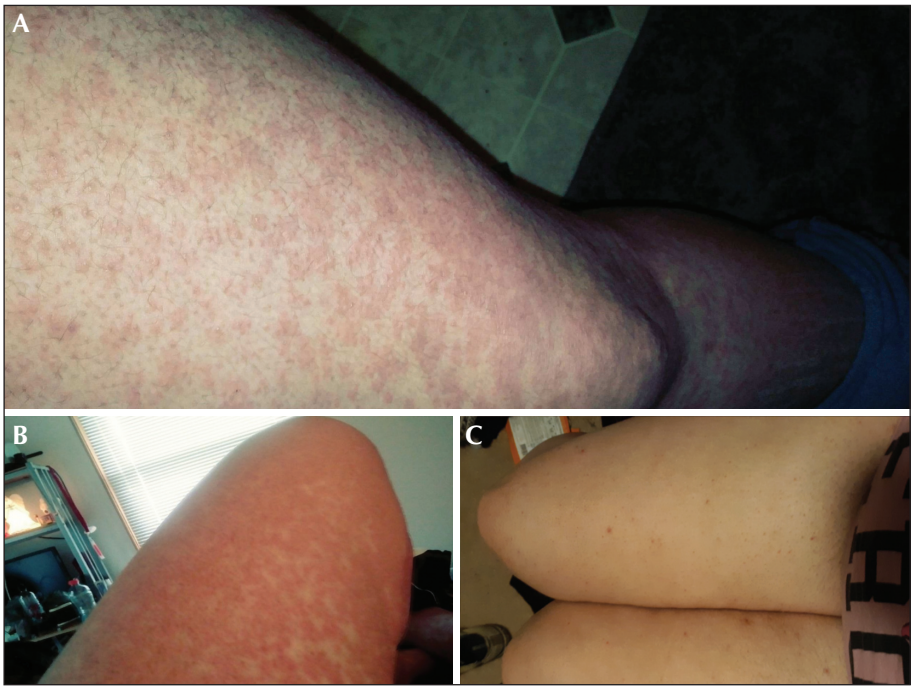

Figure 1. Erythematous papules over the thigh (A, B) and resolution of the rash after discontinuation of the drug (C).

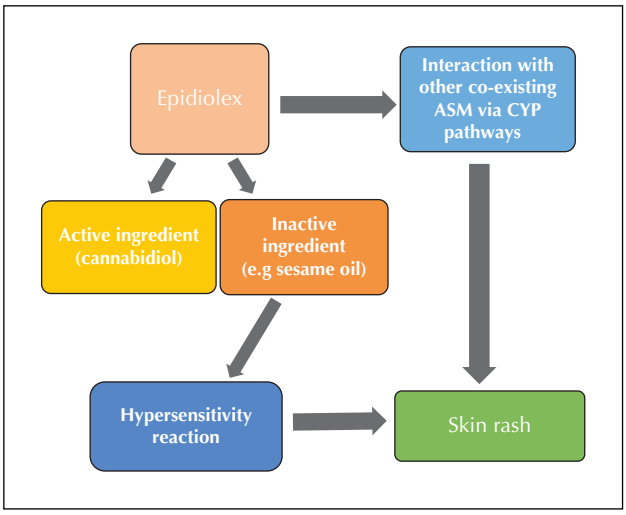

Figure 2. Schematic representation of potential mechanisms of Epidiolex® related skin rash, including hypersensitivity reaction to the active ingredient cannabidiol, an inactive ingredient such as sesame oil, or interaction with other anti-seizure medication via CYP pathways.

with fever, liver disturbances and leukocyte abnormalities. However, our patient had no signs of systemic involvement, and her symptoms resolved relatively quickly after discontinuing Epidiolex®. Therefore, the temporal relationship with Epidiolex® initiation favors Epidiolex® as the causative factor. Furthermore, based on the WHO-Uppsalla Monitoring Centre causality assessment system, this would meet the criteria for probable/likely adverse drug reaction due to Epidiolex®. There are a few possible explanations for the development of the skin rash in relationship to the initiation of Epidiolex®, summarized in *figure 2*. Firstly, a delayed hypersensitivity reaction to the CBD itself, as described above, is a possibility; this would fit the clinical picture and time course of this case. However, another consideration that must be taken into account is the possibility that the hypersensitivity reaction occurred in response to medication excipients in the Epidiolex® formulation, such as sesame oil. While anaphylaxis to sesame oil has been reported in several patients, this is less likely to occur with pharmaceutical-grade sesame oil. Sesame oil for cooking is generally unrefined, in order to preserve taste, and was found to contain 3-13 µg/g allergenic protein. In comparison, pharmaceutical-grade sesame oil is refined and therefore considered to be non-allergenic unless it is contaminated with residual protein (Kelso, 2014). A third consideration is the potential for Epidiolex® to cause drug-drug interactions through the CYP enzyme pathways. Epidiolex® can inhibit CYP 2C9 and 2C19, among other metabolic pathways, and the prescribing information recommends dose reductions of concurrent drugs that are substrates of these CYP pathways (Epidiolex®, 2019). Clobazam is metabolized by CYP3A4 to an active metabolite N-desmethylclobazam, which is extensively metabolized by CYP2C19 (Onfi®, 2018); its co-administration with Epidiolex® could cause a three-fold increase in plasma concentration of N-Desmethylclobazam. Likewise, lacosamide (Vimpat®) is a CYP2C9 and CYP2C19 substrate and its level can increase if co-administered with CYP2C inhibitor, such as Epidiolex. Although we did not check levels in our patient, it is possible that Epidiolex® may have led to elevated lacosamide and/or clobazam levels via inhibition of CYP2C19/CYP2C9 enzyme, either of which could have been the cause of the adverse dermatological effects that our patient experienced.

The time frame between the initiation of Epidiolex® and the development of the morbilliform rash fits the description of a delayed hypersensitivity reaction to Epidiolex®. However, given Epidiolex®'s ability to inhibit metabolic pathways, one must consider interactions with co-administered ASDs as a possible underlying mechanism. This is clinically relevant because Epidiolex® is typically an adjunctive ASD, and therefore the patients most likely to use Epidiolex® are those on multiple ASDs. Hence, physicians should be alert about this adverse event as they counsel their patients upon initiating Epidiolex®. □

Disclosures.
None of the authors have any conflict of interest to declare.

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