

# Galcanzumab-induced fixed drug eruption



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## INTRODUCTION

Fixed drug eruptions (FDEs) are defined by the recurrence of one or several skin lesions in a fixed location following exposure to an offending drug. Most FDEs occur following oral rather than parenteral drugs. However, FDEs following biologic therapy have been rarely reported.<sup>1</sup>

We present a case of a 48-year-old woman, whose clinical and pathologic findings were consistent with the diagnosis of FDE due to injections of galcanzumab-gnlm, a monoclonal antibody directed against calcitonin gene-related peptide (CGRP) which was approved in 2018 for the treatment of migraines. To our knowledge, this is the first reported case of FDE associated with galcanzumab-gnlm to date.

## CASE DESCRIPTION

A 48-year-old female with history of migraines, depression, and narcolepsy presented to the clinic for evaluation of a chronic persistent rash on the left upper arm. Several months prior to presentation, the patient began monthly galcanzumab-gnlm 120 mg/mL subcutaneous injection therapy for management of chronic migraines. The patient reported developing erythema and pruritus of the left upper arm within 24 hours of self-injection at remote sites, lasting up to 3 days. This then evolved into a non-pruritic, non-painful, chronic, brown-to-blue patch. Each monthly injection of galcanzumab-gnlm resulted in the same clinical course at the identical site on the left arm, despite injecting different areas on the body including the abdomen and thighs. No reaction was seen at the site of the injection. The patient denied any new changes or additions to her other medications, which included over-the-counter daily vitamins, calcium, and biotin as well as prescribed bupropion 300 mg, dextroamphetamine-amphetamine 30 mg, escitalopram oxalate 20 mg,

### Abbreviations used:

FDE: fixed drug eruption  
CGRP: calcitonin gene-related peptide

and omeprazole 20 mg. The patient also denied any illicit drug use.

On physical exam, there was a single, sharply demarcated, round plaque with a dusky violaceous hue and hyperpigmentation on the left upper arm (Fig 1). There was no evidence of bullae or dermal erosion, nor any areas of mucocutaneous involvement.

A 4-mm punch biopsy of the lesion on the left arm revealed mixed spongiotic and interface dermatitis with neutrophils, eosinophils and melanophages most consistent with a FDE (Fig 2). A periodic acid–Schiff stain was negative for fungal elements.

No additional sites of involvement were observed during ongoing treatment with galcanzumab-gnlm. Given the focality of the eruption and efficacy for the patient's migraines, the patient had initially decided to continue therapy with close clinical monitoring. However, at her last follow-up visit, she stated that she had discontinued the medication due to loss of efficacy for the treatment of her migraines.

## DISCUSSION

The humanized monoclonal antibody galcanzumab-gnlm is a CGRP inhibitor approved in 2018 for the management of migraines. Galcanzumab-gnlm binds CGRP, a neuropeptide, and prevents its activity without blocking the CGRP receptor.

While FDEs were not observed in phase 3 clinical trials, there were reports of other systemic and localized hypersensitivity reactions secondary to galcanzumab-gnlm, including the development of anti-drug antibodies and injection site reactions.<sup>2-5</sup> Though not seen in this case, at a dose of 120 mg/mL,

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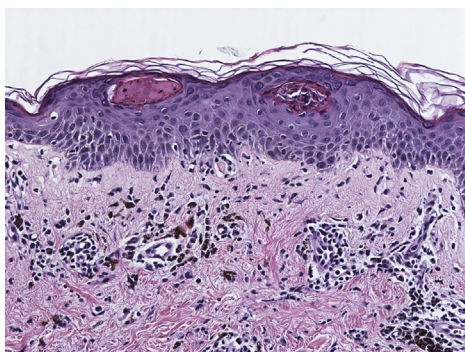
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**Fig 1.** FDE on left upper arm presenting as a well-circumscribed, violaceous plaque. FDE, Fixed drug eruption.



**Fig 2.** Interface dermatitis with necrotic keratinocytes, melanophages, and scattered eosinophils (Stain: hematoxylin and eosin, magnification  $\times 20$ ).

6.0%-17.1% of patients in galcanezumab-gnlm clinical trials experienced injection site pain, 3.0%-11.6% had an injection site reaction, and 1.0%-7.0% developed injection site erythema.<sup>2-4</sup>

FDEs are delayed hypersensitivity reactions that typically present within days to months of initial drug exposure and within 24 hours of subsequent exposures, resulting in well-defined, round-to-oval, violaceous plaques that resolve into post-inflammatory hyperpigmented patches. The most commonly reported drugs to induce FDEs include sulfonamides, such as trimethoprim/sulfamethoxazole, tetracyclines, naproxen, acetaminophen, ibuprofen,

carbamazepine, pseudoephedrine, mefenamic acid, and barbituates.<sup>6</sup>

The exact pathogenesis of FDE due to galcanezumab-gnlm remains unclear. Indeed, the pathogenesis of FDEs is not completely understood but is hypothesized to be related to antigen activation of intraepidermal CD8<sup>+</sup> T cells and prolonged ICAM-1 expression in lesional keratinocytes.<sup>6</sup> The activation of CD8<sup>+</sup> T cells leads to local release of immunological mediators including interferons, granzymes, and perforin, which, along with recruitment of CD4<sup>+</sup> cells and neutrophils, result in tissue damage. Mizukawa et al. identified persistent populations of early interferon-gamma producing effector-memory CD8<sup>+</sup> T cells within FDE lesions.<sup>7</sup> The researchers found that these intraepidermal T cell populations persist in a state of activation even in resting lesions, allowing for the rapid release of cytotoxic mediators upon antigen re-exposure.

The involvement of galcanezumab-gnlm in FDE induction is unique in several aspects. First, to our knowledge, there has not been a report of FDE associated with galcanezumab-gnlm or any other CGRP inhibitor to date. Further, FDEs are most often associated with oral medications, though parenteral agents, including botulinum toxin type-A, iodinated contrast, interferon-beta-1b, and adalimumab, have been reported to induce FDEs.<sup>8-10</sup>

Future large-scale studies on the immunogenicity of galcanezumab and identification of possible FDEs elicited by the drug may provide a better understanding of galcanezumab-gnlm's role in drug reactions. We encourage patients to discuss potential alternatives with their prescribing physician if they develop galcanezumab-gnlm FDE before discontinuation of the offending drug.

#### Conflicts of interest

None disclosed.

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