CLINICAL VIGNETTE

Multifocal Fixed Drug Eruption in an Atopic Patient

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Introduction

Fixed drug eruption (FDE) is a common type of cutaneous adverse drug reaction. It is characterized by recurrent lesions at the same site of the skin or mucous membranes upon repeated uptake of the causative drug.[1,2] Acute episodes typically present as either a solitary or a small number of pruritic, sharply demarcated, erythematous macules that evolve into edematous plaques.[2,3] The lesions occur with a mean onset of time of two hours from exposure to the causative drug, and resolve spontaneously after cessation, leaving post-inflammatory hyperpigmentation which can persist for prolonged periods.[3] FDE commonly occurs on the lips and genitalia but may affect any area of the body.[4]

The pathogenesis of FDE is thought to be a form of delayed-type hypersensitivity, mediated by cytotoxic CD8+ T-cells with an effector-memory phenotype.[2,3] Tissue damage occurs when these cells are activated to directly kill surrounding keratinocytes, releasing large amounts of cytokines such as IFN$_\gamma$ into the local microenvironment.[3] Following the initial activation phase, the continued presence of CD8+ T-cells may infer a protective immune mechanism. This is supported by multiple studies demonstrating that T-cells with an effector-memory phenotype are consistently found at significant levels following infection in tissues such as the lung, and preferentially migrate into sites of infection, such as mucosal sites, persisting for long periods of time following infection.[3,5-8]

Diagnosis of FDE is primarily based on history, involving a careful review of both prescribed and over-the-counter medications to identify potential culprit drugs.[9] The most often implicated drugs are cotrimoxazole, paracetamol, NSAIDs, and various antibiotics.[10] Treatment of FDE includes culprit drug discontinuation, patient counseling, and medications for symptomatic relief.[11] For post-inflammatory hyperpigmentation, topical lightening agents are commonly used, such as hydroquinone, azelaic acid, and retinoids.[12]

We present a case of suspected FDE in a patient with a history of atopy, highlighting the challenge of diagnosing FDE when lesions are multifocal and do not recur in the exact same locations.

Case Description

A 58-year-old woman presented for evaluation of intermittent episodes of skin hyperpigmentation for the past five years. Each episode consisted of erythematous, pruritic plaques on her face, chest, and groin, followed by hyperpigmentation. The plaques arose in different locations each episode, and usually resolved in days to weeks, with hyperpigmentation lasting months. Potential triggers that she identified included NSAIDs, pseudoephedrine, or multivitamins, though she was not able to identify a clear correlation with symptoms. To treat her skin hyperpigmentation, she has tried sunscreen, hydroquinone, and tretinoin creams with no improvement.

The patient's past medical history includes aspirin exacerbated respiratory disease, multiple nasal polypectomies, atopic dermatitis, chronic urticaria, allergic rhinitis, moderate persistent asthma, and hypertension. She underwent aspirin desensitization and had been tolerating aspirin 325mg daily for six months prior to presentation. She has had three past nasal polypectomies. Her moderate persistent asthma has been well-controlled on Dupixent for the past four years. Symptoms of allergic rhinitis, atopic dermatitis, and chronic urticaria also improved significantly since starting Dupixent. Other medications at presentation included losartan, verapamil, conjugated estrogens-medroxyprogesterone, levocetirizine, and albuterol inhaler as needed. Her allergies include NSAIDs, to which she had a previous FDE, and sulfites. Family history was non-contributory. She reported occasional alcohol and edible cannabis use but no tobacco use.

On presentation, vital signs were normal. Physical examination showed skin hyperpigmentation on her forehead, cheeks, nose, periorbital area, chest, and hands with well-demarcated violaceous patches. Laboratory studies including a comprehensive metabolic panel and complete blood count were only significant for mild microcytic anemia and basophilia. Environmental aeroallergen skin prick testing was positive for a variety of pollens (grasses, trees, and weeds), dust mite, and cat.

The patient was referred to Dermatology for further evaluation. Due to her history of FDE with NSAIDs and her frequent pseudoephedrine use, the well-demarcated annular violaceous appearance of lesions, and location on the hands and labia major, an FDE was favored as the most likely diagnosis. Given that her lesions on presentation were most consistent with post-inflammatory hyperpigmentation rather than active FDE, biopsy was not pursued. It was advised that the patient continue to avoid NSAIDs, pseudoephedrine, and other supplements as well.

Discussion

This patient's presentation is most consistent with multifocal FDE with post-inflammatory hyperpigmentation. The case presented a diagnostic challenge for the following reasons: the fact that these multifocal lesions did not recur in the same locations with each episode, a history that did not clearly correlate symptoms with any specific medication trigger, and an inability to biopsy due to the absence of active lesions at the time of presentation.

FDE typically presents with lesions that recur at the same location with each repeated uptake of the causative drug.[1] Recent studies demonstrate that multiple lesions, as seen in this case, are more common than a solitary lesion in FDE, with the percentage of patients presenting with multifocal lesions cited at 75.6%, 64%, and 83.8%, in three studies.[9,10,13] However, the recurrence of lesions at different sites is infrequently described. One study describes two patients presenting with a confirmed FDE to acetaminophen, where involved sites did not necessarily flare with each exposure, nor did activity always appear in the same sites with repeated flares.[14] This was deemed a wandering fixed drug eruption, which is not otherwise described in literature, but may occur quite frequently. This phenomenon is thought to occur as certain sites of recent flares become refractory, and thus new flares develop in new sites with each subsequent drug exposure.[15] This is notably different from the polysensitive fixed drug eruption, where more than one causative drug is involved and causes lesions at multiple different locations with each episode,[16] which of note has also rarely been previously described in medical literature.[16,17]

The pathogenesis of either the wandering or polysensitive FDE presentations are not described in literature. Based on the pattern of lesions and pathogenesis of classic FDE, it may be hypothesized that in the wandering presentation, the continued presence of effector-memory CD8+ T-cells at the original sites of lesions infers a more protective than hypersensitive immune mechanism, preventing subsequent flares at those specific sites. In the polysensitive FDE, various hypersensitivity reactions occur at different sites, mediated by cytotoxic CD8+ cells in the pattern described in the literature, with each site corresponding to a different drug exposure and therefore initial immune activation.

This case presents a diagnostic challenge in that it remains unclear whether it represents the wandering versus polysensitive FDE. The patient was able to identify multiple potential triggers, including pseudoephedrine, NSAIDs, and multivitamins of various brands, but was not able to provide a history with a clear relationship between a causative drug and symptoms. Though pseudoephedrine and NSAIDs are known to be associated with FDE,[10,18] an association with multivitamins has only been described in a case report.[19] Given the absence of a clear medication history, it remains indistinguishable whether she is reacting to the same medication upon repeat exposures, or if each episode is a reaction to a different causative medication. Since the patient did not have active lesions at presentation, skin biopsy could not be performed to confirm or further elucidate the diagnosis.

This patient presentation demonstrates the challenge of diagnosing FDE when lesions are multifocal and recur in different locations, medication history is unclear, and further diagnostic data is not available. Unfortunately, FDE in these cases often remains underdiagnosed and undertreated because it does not fit the usual pattern, and the pathogenesis remains uncharacterized. This case highlights the importance of including a wandering or polysensitive FDE on the differential diagnosis of any patient with a similar presentation.

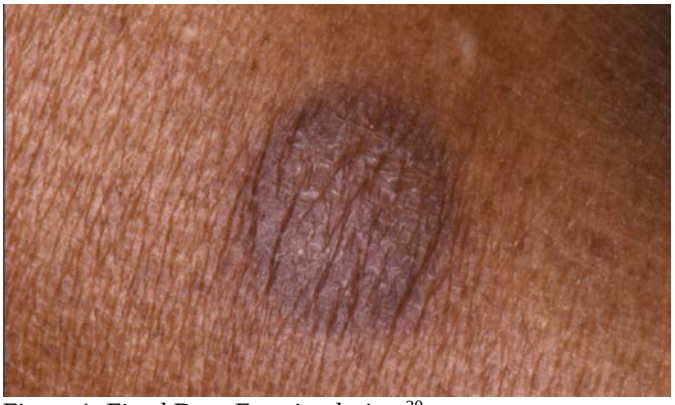

Figure 1: Fixed Drug Eruption lesion.[20]

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