5. Generalized fixed drug eruption

Fixed drug eruption (FDE), first described by Bourns in 1889, is a specific adverse reaction to medications. Usually FDE appears as a single or a few localized, sharply demarcated, round-to-oval, edematous, dusky red macules or patches hours to days after ingesting the offending drug. At times, lesions might appear locally as bullae or erosions. On rare occasions, some patients might have a severe clinical manifestation, such as extensive bullous eruptions, that needs to be differentiated from other diseases. Most patients remain asymptomatic, but some have local symptoms such as pruritus, pain, or burning sensations. Less commonly, some patients develop systemic symptoms such as general malaise, fever, anorexia, diarrhea, abdominal cramps, and dysuria. Upon re-administration of the causative agents, patients often have burning sensations before appearance of the skin lesions. Thereafter, skin eruptions appear more rapidly than after the first exposure (ranging from 30 minutes to 8 hours, often within 2 hours) in the same locations (hence the name fixed drug eruption) and elsewhere on the body. Fixed drug eruption tends to affect the lips, genitalia, and hands. The male-to-female prevalence ratio was 1 to 1.1 in a large series of 450 patients suffering from FDE.

The actual pathogenesis of FDE has not been fully elucidated. Recent research indicates that CD8+ T cells with an effector memory phenotype play an important role in reactivation of lesions with re-exposure to the offending agent. These phenotypically homogeneous T cells can directly kill surrounding keratinocytes and release large amounts of cytokines into the local microenvironment, resulting in tissue damage. Moreover, in addition to these memory T cells, the fully evolved skin lesions might result from other nonspecific recruitment of CD4+ T cells, CD8+ T cells, and neutrophils that further enhance tissue damage.

There is a long and ever expanding list of medications that cause FDE. The most common ones include nonsteroidal anti-inflammatory drugs, antiepileptic drugs, and antibiotics. The culprit medication might be absorbed intravenously, orally, rectally, or even through a plaster. Fixed drug eruption has a favourable prognosis compared with other bullous skin eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. The lesions often resolve spontaneously days to weeks after the causative drug is discontinued and might leave an area of brownish hyperpigmentation.

Differential diagnosis

Stevens-Johnson syndrome is the most important differential diagnosis, and extreme caution is required when ruling it out. Widespread bullous FDE bearing a clinical resemblance to Stevens-Johnson syndrome has been repeatedly reported. Stevens-Johnson syndrome is a serious, life-threatening, adverse skin reaction that often follows the administration of certain medications, among the most commonly reported of which are allopurinol, aromatic anticonvulsant drugs, oxicom non-steroidal anti-inflammatory drugs, penicillin, and sulfonamide antibiotics. Clinically, the eruption begins as dusky red, purpuric macules symmetrically distributed on the face, upper trunk, and proximal limbs. Soon after, they coalesce, spread to the rest of the body, and evolve into flaccid blisters and epidermal detachment associated with mucous membrane involvement. Nikolsky sign, a skin condition in which the epidermis can be easily rubbed off with lateral finger pressure, is usually positive on the erythematous areas. The mainstay of management is early identification and immediate discontinuation of suspected drugs. Treatment is mainly symptomatic.

Erythema multiforme is an acute, mild, self-limited, relapsing skin condition characterized by pathognomonic target- or iris-shaped lesions. The typical target-shaped lesions comprise 3 concentric components including a central dusky disk or blister followed by an infiltrated pale ring and a peripheral erythematous halo. The skin rash usually begins on the face and distal extremities and then spreads centripetally. Mucous membrane involvement occurs in about 70% of patients, but it is often mild and limited to the oral cavity. Erythema multiforme occurs in patients of all ages, but mostly in adolescents and young adults. The disease is usually related to an acute infection, most often a recurrent herpes simplex virus infection. Mycoplasma pneumoniae is the second most common predisposing pathogenesis. Treatment is usually not mandatory because erythema multiforme is frequently self-limiting. Symptomatic and supportive treatment is usually sufficient.

Urticaria, usually referred to as hives, is a common dermatologic disease with a typical wheal-and-flare reaction in which localized intradermal edema (a wheal) is surrounded by an area of erythema. It is characterized by numerous acute-onset, highly pruritic, blanchable, raised, annular-to-arcuate, palpable wheals. The lesions can be distributed on any skin surface and are usually transient and migratory. The causes are numerous, but in most cases the condition is the result of an allergic reaction to food or certain medications. The goal of management is early elimination of possible offending causes. Therefore, a comprehensive history taking with particular emphasis on the identification of possible pathogenesis is important. Most patients respond to antihistamines with or without a short course of corticosteroids. The skin lesions usually completely resolve within 24 to 48 hours.

Pemphigus vulgaris is a chronic, autoimmune, blistering, mucocutaneous disease in which circulating autoantibodies are directed against the surfaces of keratinocytes. In contrast with FDE, the skin rash in...
pemphigus vulgaris usually consists of painful, flaccid blisters or erosions arising on normal or erythematous skin that tend to spread at their periphery. Painful mucosal erosions are often the presenting sign. Nikolsky sign is positive when applying lateral pressure to the periphery of active lesions. Treatment includes systemic glucocorticoids and immunosuppressive drugs. Pemphigus vulgaris is associated with considerable morbidity and mortality. Only a few patients achieve complete remission and require no further therapy. Most patients tend to relapse after treatment is withdrawn. The cause of death is usually infection, and an iatrogenic immunosuppressive state caused by the therapy might have a contributory role.

Management
The primary goal of treatment for FDE is to identify and discontinue the causative agent. The patient should be instructed to avoid repeated exposure to the offending drug. In our clinic, we issue a “drug allergy card” to patients for them to keep on hand to avoid future re-exposure to the same medication. Treatment of FDE is mainly symptomatic. If the lesions are mild, treatment with systemic antihistamines and a topical steroid is sufficient. On rare occasions, patients suffering from severe conditions such as generalized bullous FDE might benefit from systemic corticosteroids.

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Competing Interests
None declared

References