DIFFICULTIES IN THE DIAGNOSIS AND MANAGEMENT OF FIXED DRUG ERUPTION - CASE PRESENTATION

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Summary

Fixed drug eruption is a cutaneous allergic reaction characterized by the clinical appearance of a single or multiple erythematous-violaceous plaques, occurring each time upon exposure to the implicated agent and with the same location. These lesions can be difficult to diagnose due to their resemblance to other pathologies (autoimmune bullous diseases, erythema multiforme, vasculitic urticaria etc).

We present the case of a 59-year-old patient with numerous comorbidities who presented with the occurrence of an eruption consisting of multiple well-demarcated erythematous-violaceous plaques on the trunk and arms, evolving for approximately 2 months. We note the difficulty in obtaining a medical history, as the patient had bilateral conductive hearing loss. Thus, communication was facilitated through written language and family members, highlighting a possible correlation between the onset of lesions and the administration of gastroenterological treatment with antispasmodics and proton pump inhibitors.

Based on the patient's complaints, medication history, and clinical manifestations, suspicion of fixed drug eruption was raised and confirmed through histopathological examination. Although the clinical and paraclinical data support the diagnosis of fixed drug eruption, it was not possible to identify a specific implicated medication, leading to the administration of symptomatic corticosteroid treatment with favorable evolution.

Fixed drug eruption represents a delayed-type hypersensitivity reaction (type IV) with cutaneous clinical manifestations that are difficult to diagnose due to their heterogeneous appearance, requiring a high degree of suspicion (especially in cases where the disease history and medication consumption cannot be easily determined).

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Introduction

Fixed drug eruption represents a distinctive type of hypersensitivity reaction characterized by the appearance of isolated plaques or a small number of erythematous-violaceous plaques that recur at the same location upon re-exposure to the implicated drug. After the resolution of the plaques, post-inflammatory hyperpigmentation becomes evident.

There are also rare and atypical variants, such as multiple, non-pigmentary, or severe forms (generalized bullous) that share common elements with Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN). [1]

Epidemiology

From an epidemiological standpoint, cutaneous hypersensitivity reactions occur in 2-3% of patients receiving medication. They can occur in all age groups, with no predilection for sex. Exanthematous or morbilliform eruptions are more common than fixed drug eruptions, accounting for approximately 95% of all cutaneous hypersensitivity reactions. [2]

Pathogenesis

The classes of drugs that can cause fixed drug eruption vary depending on the country, availability, and consumption rate. The most common classes of drugs involved in the occurrence of fixed drug eruption are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and hypnotics (Table 1).

Rare cases of fixed drug eruption have been reported with the administration of levocetirizine, certain foods, and food additives. There have also been reports of cases associated with structurally similar substances (cross-reactivity)

Table 1. Main classes of drugs involved in the occurrence of fixed drug eruption

- Antibiotics (trimethoprim-sulfamethoxazole, penicillins, tetracyclines, quinolones, dapsone)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin, naproxen, ibuprofen)
- Analgesics (Acetaminophen)
- Barbiturates
- Anticonvulsants (carbamazepine)
- Antimalarials

and those that are chemically unrelated (polysensitivity). [5] Fixed drug eruption can be a manifestation of innate immune system activation, as a few cases have been reported following COVID-19 vaccination (without prior exposure to a specific medication). [6]

Immunological mechanisms

- Intraepidermal CD8+ T cells (effector phenotype with memory) play a crucial role in mediating localized epidermal lesions, being abundant at the dermo-epidermal junction in active lesions and persisting in healed lesions for an extended period.
- CD8+ T cells remain latent until the therapy is re-administered, at which point they directly contribute to epidermal destruction by releasing interferon-gamma and cytotoxic granules: granzyme b and perforin. [7]
- In addition to CD8+ T cells, cytokines and adhesion molecules recruit CD4+ T cells, CD8+ T cells, and neutrophils to contribute to tissue destruction in active lesions.
- In a late stage, regulatory CD4+CD25+ Foxp3+ cells participate in immune response homeostasis by inducing apoptosis of cytotoxic cells, but a subset of CD8+ T cells is protected from apoptosis through interleukin-15 secreted by basal keratinocytes, becoming memory cells.
- Mast cells contribute to the activation of CD8+ T cells through adhesion molecules surrounding basal keratinocytes and the activity of tumor necrosis factor-alpha. [8]

Histopathology

Fixed drug eruption represents a lichenoid tissue reaction, and the histopathological appearance varies depending on the stage of the lesion and the type of implicated medication, although they share common features.

At the onset of the disease, skin biopsy may reveal a moderate degree of spongiosis, perivascular lymphocytic inflammatory infiltrate, and interface dermatitis. In the late stage, evidence of pigment incontinence and epidermal hyperpigmentation can be observed (Table 2).

Atypical histological patterns, such as neutrophilic reaction, leukocytoclastic vasculitis, and non-pigmented fixed drug eruption, have been identified in fixed drug eruption. [9]

In the non-pigmented variant of fixed drug eruption, epidermal changes are mild or absent, and there is an inflammatory infiltrate in the reticular dermis consisting of lymphocytes, eosinophils, and melanophages.

The generalized bullous variant shows similar characteristics to the blisters seen in Stevens-Johnson syndrome or toxic epidermal necrolysis (full-thickness epidermal necrosis without pigmentary incontinence). [10]

Therefore, it can be concluded that the histopathological changes in fixed drug eruption are not specific and can be observed in other conditions. To establish a definitive diagnosis, the identified histopathological characteristics should be correlated with the clinical aspects, lesion distribution, disease history, and temporal correlation between drug exposure and eruption.

Table 2. Fixed Drug Eruption. Histopathological Features Based on Stages.

Early stage
• Moderate spongiosis (intercellular edema) and diffuse or localized epidermal necrosis.
• Inflammatory infiltrate that consists of lymphocytes, macrophages, and occasional eosinophils, primarily located in the perivascular area and the upper portion of the dermis.
• Interface dermatitis is observed, characterized by vacuolization of the basal layer (separation of keratinocytes from the basal membrane) and the presence of apoptotic bodies.
Late stage
• Post-inflammatory hyperpigmentation due to the accumulation of melanin in macrophages located in the upper portion of the dermis.
• Other histopathological findings include apoptotic keratinocytes, vacuolization of the basal layer, inflammatory infiltrate with rare eosinophils, and pigmentary incontinence.

Clinical manifestations

The clinical presentation of fixed drug eruption predominantly consists of well-demarcated round-oval erythematous-violaceous macules, either singular or in a limited number, which can evolve into edematous plaques with or without the development of blisters.

Generally, patients do not associate systemic symptoms such as general malaise or fever, but local symptoms such as itching or burning sensation may predominate. Predilection sites include the genital and perianal regions, lips, and extremities. Mucosal involvement (such as oral mucosa) can lead to erosions and ulcers. Erythematous lesions can occur in previously traumatized areas (e.g., puncture sites, burns) or in areas of herpes virus reactivation (herpes simplex or herpes zoster). [9]

The onset of the rash occurs within a shorter interval as the frequency of exposure to the implicated therapy increases. Acute lesions generally appear within 30 minutes to 8 hours after drug administration but can also occur later (up to 2 weeks after exposure). After the discontinuation of the therapy, the resolution of lesions occurs spontaneously within 7-10 days, with residual post-inflammatory hyperpigmentation. Upon re-exposure, the lesions reappear in the same regions but can also develop in other areas. After multiple episodes, fixed drug eruption can resemble the appearance of generalized bullous diseases (TEN/SJS).

Table 3. Background Medication of the patient

Levothyroxine	Hydrochlorothiazide	Olmesartan medoxomil/ amlodipine	Atorvastatin
Acenocoumarol	Pantoprazole	Platelet aggregation inhibitor (Thrombo ASS)	Bioflavonoids (Detralex)

Clinical variants

Fixed drug eruption can present with various clinical variants, including:

1. Erythema multiforme-like: lesions resembling target lesions seen in erythema multiforme. In contrast to erythema multiforme, the central color of the lesions in the erythema multiforme-like variant is darker.
2. Generalized variant: diffuse distribution throughout the body. The lesions can be numerous and affect multiple body regions simultaneously.
3. Fixed drug eruption with multiple lesions: these can appear simultaneously or successively in different regions of the body after exposure to the implicated drug.
4. Bullous variant of fixed drug eruption: an extremely rare form characterized by the development of erythematous-violaceous plaques that overlay flaccid or vesicular blisters, which can rupture and result in erosions and crusts. Systemic symptoms such as malaise, fever, and arthralgia can be present, and it is more frequently associated with the use of antibacterial sulfonamides and nonsteroidal anti-inflammatory drugs. In contrast to SJS/TEN, in the bullous variant of fixed drug eruption, the involvement of the oral mucosa is spared, and the clinical course is favorable after the discontinuation of the therapy.
5. Non-pigmentary variant: described in a small number of patients, most commonly associated with the administration of pseudoephedrine. The clinical picture consists of a single or multiple well-demarcated erythematous plaques that heal without residual post-inflammatory hyperpigmentation. [3,9]

Case presentation

We describe the clinical case of a 59-year-old patient with numerous comorbidities who presented with an eruption consisting of multiple well-demarcated erythematous-violaceous plaques on the trunk and arms, evolving for approximately 2 months.

Regarding the personal medical history, the following conditions are noted: bilateral conductive hearing loss, NYHA class 2 congestive heart failure, bilateral carotid atheromatosis without hemodynamic significance, mild mitral and tricuspid regurgitation, grade 2 hypertension with intermediate risk, history of pulmonary embolism (PE) and deep vein thrombosis (DVT), complex thrombophilia, minor thalassemia, and hypothyroidism.

The patient's background therapy consisted of multiple classes of medications (Table 3).

We note the difficulty in obtaining a medical history, as the patient had bilateral conductive hearing loss. Thus, communication was facilitated through written language and family members, highlighting a possible correlation between the onset of lesions and the administration of gastroenterological treatment with antispasmodics and pantoprazole.

During the general clinical examination, no abnormalities were detected, and the dermatological examination revealed erythematous-violaceous plaques, multiple, well-demarcated, located on the trunk and arms (Figure 1, Figure 2).

Laboratory tests were performed, but no significant abnormalities were found. Clinical findings, in combination with the patient's history, raised suspicion of fixed drug eruption, which was confirmed by histopathological examination. However, the identification of a specific implicated medication was not possible, which led to the administration of symptomatic corticosteroid treatment with a favorable outcome.

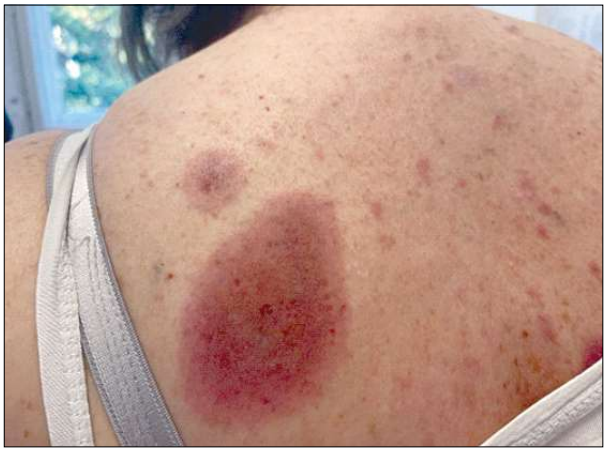

Figure 1. Clinical manifestations in fixed drug eruption

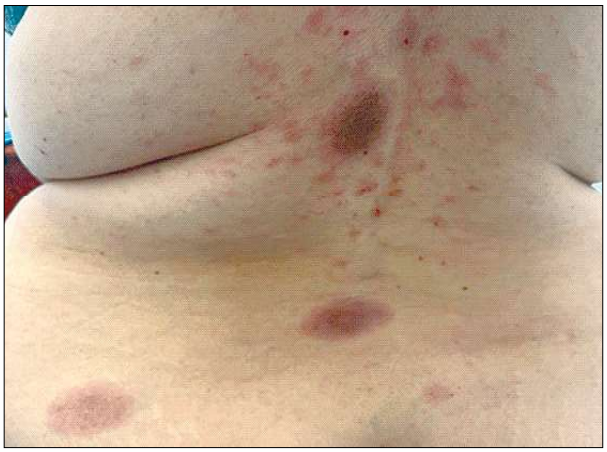

Figure 2. Clinical manifestations in fixed drug eruption

Other diagnostic methods used include provocation testing: systemic (oral) and topical (patch testing), which can aid in identifying the causative medication when multiple medications are suspected or when the patient's history is unclear. Oral provocation testing is preferred as it replicates the conditions of exposure, but it is contraindicated in patients with generalized fixed drug eruption (due to the high risk of severe adverse reactions). The testing starts with a dose that is one-tenth of the therapeutic dose administered 2-4 weeks after lesion resolution, and the dose is gradually increased at intervals of 12-24 hours. Oral provocation testing is considered positive when the eruption appears at previously latent sites of fixed drug eruption. Patch testing is considered safe as the eruption is localized and is performed when there is a history of generalized fixed drug eruption or when the patient refuses oral testing. [11]

Differential diagnosis

Fixed drug eruption shares similarities with other conditions, and differential diagnosis is necessary, considering the number, distribution, and morphology of the lesions. The differential diagnosis includes:

1. Autoimmune bullous diseases such as Stevens-Johnson syndrome or toxic epidermal necrolysis, as they may exhibit some common features (although the lesions are not as well-demarcated and

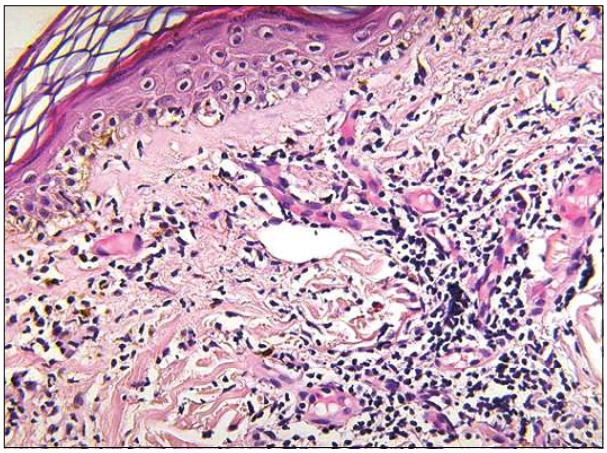

Figure 3. Vacuolar interface dermatitis, apoptotic bodies, chronic inflammation, HE 40x

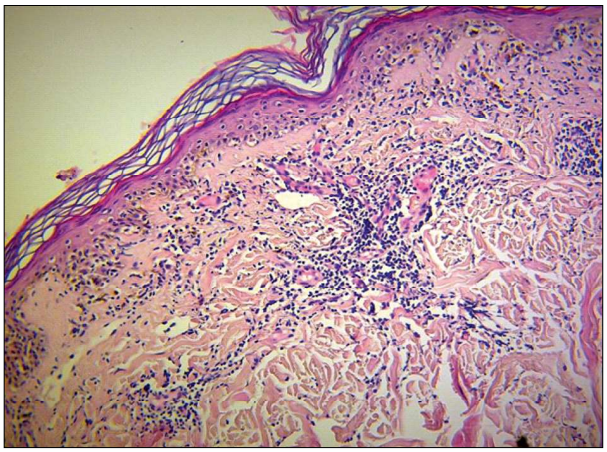

Figure 4. Apoptotic keratinocytes, basal layer vacuolization, inflammation with rare eosinophils, pigmentary incontinence, HE 100x

tend to coalesce, systemic symptoms are dominant, and the disease course is rapidly progressive).
2. Erythema multiforme: a hypersensitivity reaction to certain medications, infections, or other factors, characterized by target-like lesions. In erythema multiforme, the lesions have a symmetric appearance and tend to affect mucous membranes.
3. Bullous pemphigoid: Involvement of bullous pemphigoid presents with pruritic inflammatory plaques, progressing to extensive lesions with tense blisters that rupture and heal without scarring. The skin biopsy reveals a lymphocytic and neutrophilic inflammatory infiltrate, and direct immunofluorescence examination shows linear deposits of IgG along the basement membrane, which are absent in fixed drug eruption lesions.
4. Large plaque parapsoriasis.

Management

Due to the patient's comorbidities, the background medication could not be discontinued. Although clinical and paraclinical data supported the diagnosis of fixed drug eruption, the identification of a specific implicated medication was not possible, leading to the administration of symptomatic systemic corticosteroid treatment with a favorable outcome. The lesions improved, with the resolution of erythematous-violaceous plaques without the development of new lesions, but with residual post-inflammatory hyperpigmentation (Figure 5).

The most important aspect in managing fixed drug eruption is the cessation and avoidance of the implicated therapy or chemically related medications. In general, treatment is symptomatic and aims to alleviate pruritus.

- For patients with a single lesion or a limited number of lesions, topical corticosteroids and systemic antihistamines are recommended for 7-10 days, with two applications per day.
- For patients with atypical or generalized variants, a short course of systemic corticosteroids (prednisone at a dose of 0.5-1 mg/kg/day for 3-5 days) is recommended, although there is a lack of studies supporting their use. [11]

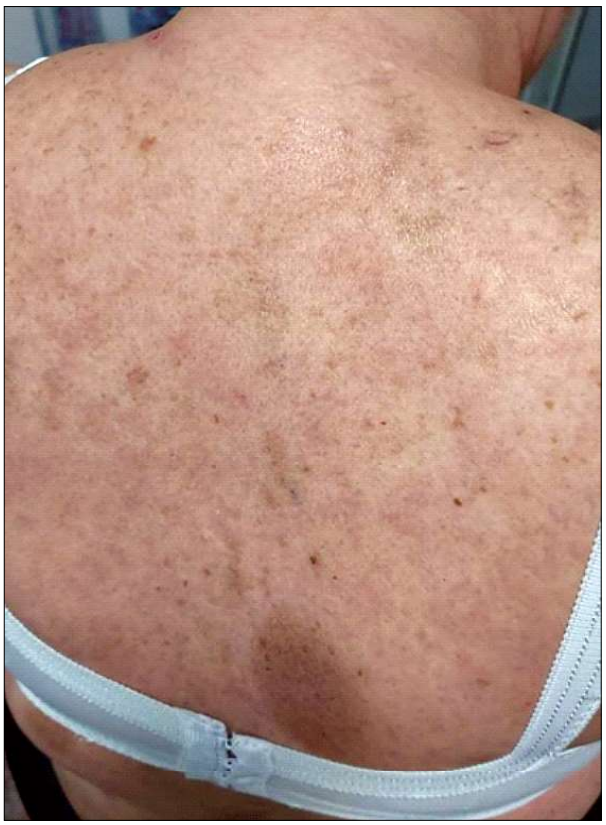

Figure 5. Residual post-inflammatory hyperpigmentation

Conclusions

Fixed drug eruption is a less common entity among drug reactions. The cutaneous clinical manifestations are challenging to diagnose due to

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Conflict of interest
NONE DECLARED

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