

Neutrophilic Generalized Fixed Drug Eruption Induced By Etoricoxib

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Fixed drug eruption (FDE) is a type IV hypersensitivity characterized by recurrent lesions in the same site after drug re-exposure, showing a lymphocytic infiltration of the affected skin. Generalized bullous presentation of FDE (GBFDE) is a rare variant, characteristically presenting with generalized bullae accompanying the distinctive FDE lesions. It can resemble a Stevens-Johnson Syndrome (SJS), but usually less severe and without systemic symptoms[1].

In recent years, the use of selective COX-2 inhibitor non-steroidal anti-inflammatory drugs (NSAIDs) has increased worldwide. There are a few cases reported on FDE induced by selective COX-2 inhibitors [2-5]. Here we present 2 patients with certain characteristics that suggest a different kind of potentially severe etoricoxib-induced GBFDE.

Case #1: A 43-year-old woman who developed 2 cutaneous lesions consisting in hyperpigmented plaques with peripheral erythema over left buttock(5 cm) and right wrist (3 cm), 1 day after the intake of ibuprofen 600 mg and 30 min after etoricoxib 60 mg, administered for a wrist injury. Skin lesions progressed to blisters and resolved after treatment with oral corticosteroids (CS)in 2-3 weeks. Two months later, she took etoricoxib 60 mg and both skin lesions reappeared after 30 min, together with 5 new

similar lesions in her trunk and upper limbs. Recovery was achieved in 10 days with oral CS, with residual hyperpigmentation.

Another two months later, an allergy study was started, after obtaining informed consent. Patch-tests (PT) were done with etoricoxib (10% in petrolatum) on both residual pigmented lesion and healthy skin, with negative results. Then, a single-blind drug oral challenge-test (DCT) with etoricoxib 60 mg was carried out, and the skin lesions reappeared 30 min later, as well as new lesions in the neck, trunk, upper and lower limbs, and genital area. Skin biopsy was performed, showing a perivascular dermatitis pattern with a neutrophilic inflammation of the papillary dermis, and scattered melanophages (Figure 1). She was treated with oral CS, with improvement in 7 days (Figure 1 supplemental materials). Then, DCT was performed with ibuprofen 600 mg, showing good tolerance. Finally, to confirm selective allergy to etoricoxib, additional DCT were performed on separate days with acetaminophen 1 g., AAS 500 mg, and celecoxib 200 mg, with negative results.

Case #2: A 48-year-old woman developed a generalized rash, characterized by erythematous-macular lesions in the abdomen, neck, upper and lower limbs, including left ankle, evolving to bullous lesions, with neither mucosal involvement nor systemic symptoms. Skin lesions appeared 1 week after a diclofenac injection, and 1-2 hours after an oral etoricoxib intake, administered for shoulder pain. She had been previously treated with both drugs, noticing one transient hyperpigmented lesion in left ankle that she had thought to have no relation to this treatment. She was initially diagnosed as SJS, but blood test results were within normal limits, and lesion biopsy showed epithelial erosion with intense neutrophilic inflammation of the papillary dermis. Lesions fully recovered in 10 days with oral CS.

After obtaining informed consent, PT with etoricoxib was performed in previous lesional and normal skin, with negative results. DCT with ibuprofen (600 mg), diclofenac (50 mg), and celecoxib (200 mg) were negative. DCT with etoricoxib was not performed because it is contraindicated in case of GBFDE. Final diagnose was GBFDE due to etoricoxib hypersensitivity and she was advised to avoid etoricoxib intake, with no recurrence of skin lesions.

We present 2 patients with etoricoxib-induced FDE, evolving to GBFDE after drug re-exposure. This is a selective allergy, since both our patients tolerated celecoxib and other NSAIDs. Noteworthy, they showed a rare neutrophilic inflammatory pattern, suggesting a new condition, different from the classic FDE. Differential diagnosis was made with other bullous disorders andwith neutrophilic dermatoses, such as drug-related Sweet syndrome [6].

FDE is characterized by lesion recurrence in the same site after drug re-exposure, without mucosal involvement. Good general status in GBFDE contrasts with severe systemic toxicity of SJS [1].Challenge-test is the gold standard diagnostic procedure for FDE, but it is contraindicated in case of GBFDE, and this is the reason why our second patient was not challenged with etoricoxib. Patch-testing, both in affected and healthy skin, is a safer alternative to identify the offending drug, but a negative result – as both our patients showed - does not rule out the diagnosis[7].

Biopsy helps to reject other dermatoses, but it is not a specific test. Typical FDE histology shows a perivascular lymphocytic infiltration with melanophages. It is sometimes indistinguishable from SJS, being the clinical features the main diagnostic support [1]. However, both our cases showed extensive neutrophil infiltration, a rare

FDE pattern that has been previously reported in association with other drugs, but never before related to selective COX-2 inhibitors[8].

You can postulate that the presence of a neutrophil infiltration in a FDE lesion is just an early phase of inflammation, but by sequential biopsies after DCT, the lymphocytic infiltration is present even in early biopsies, meanwhile a neutrophil one is not present in typical FDE [9].The latency periods observed in our patients were as in an immediate reaction (minutes to 1-2 hours), whereas the FDE usually shows a longer latency, which could be related to the fact that neutrophils are more involved.

There are a few previous reports on etoricoxib-induced FDE [2-5], only 1 of them corresponding to GBFDE [5], but a neutrophil infiltration had not been previously notified. However, etoricoxib-induced FDE may be more frequent than supposed, and have a possible genetic predisposition[10].

Previous articles have reported a possible cross-reactivity between etoricoxib and celecoxib, according to patch-test results. However, by DCT etoricoxib showed no cross-reactivity with celecoxib and parecoxib in a case of FDE [3].In line with this result, both our patients tolerated celecoxib, which can be explained by the structural differences between these drugs [3,4].

In conclusion, etoricoxib can induce a specific selective and potentially severe form of FDE, characterized by a neutrophil infiltration that can progress to a generalized form. Given that selective Cox-2 inhibitors are increasingly used, more cases of GBFDE due to etoricoxib should be expected.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Figure legends

Figure 1. Histopathology of left buttock lesion after DCT with etoricoxib. Findings include vacuolar alteration of the basal layer, with both superficial and deep dermal neutrophilic inflammatory infiltrate, and with scattered melanophages. Hematoxylin and eosin stain at 400X. DCT, drug challenge-test.

