Dimethyl fumarate induced Wells syndrome. A case report

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Introduction. Wells syndrome, also known as eosinophilic cellulitis, is a rare dermatosis with approximately 200 cases previously described in the literature. Here, we present a case of a patient with multiple sclerosis with Wells syndrome induced by dimethyl fumarate (DMF).

Case report. A 41-year-old Caucasian woman was treated with DMF in July 2021. One week later, she experienced itching on her upper and lower right arm, followed by the appearance of erythematous plaques covered with vesicles. The complete blood count showed an increased eosinophil count of up to 2,000 μL. The histological images demonstrated dermal eosinophil infiltration concordant with Wells syndrome. The clinical course was benign, with complete resolution of the lesions and normalization of the eosinophil count within four weeks. Administration of corticosteroids was not necessary.

Conclusions. Eosinophilia is rare in patients with multiple sclerosis treated with DMF and usually does not require dosage adjustments. Although clinical manifestations of eosinophilia in these patients are very rare, it is important for practitioners to recognize the symptoms. Many neuroleptic drugs can induce eosinophilia and systemic symptoms; therefore, physicians must be aware of the risks associated with DMF and neuroleptic drugs, particularly for quetiapine, which contains fumarate.

Key words. Dimethyl fumarate. Eosinophilia. Multiple sclerosis. Neuroleptics. Quetiapine. Wells syndrome.

Introduction

Wells syndrome, also known as eosinophilic cellulitis, is a rare dermatosis with approximately 200 cases described in the literature.

This syndrome usually affects adults and is most common in females in their 40s; however, it has also been described in children.

The typical skin manifestation is the occurrence of cellulitis/erisipela-type lesions that affect the extremities. Skin lesions are usually associated with peripheral eosinophilia.

Histologically, the 'flame-figures', located in the mid to deep dermis, are common but not specific to Wells syndrome. The flame figures are composed of a central part consisting of collagen fibers and eosinophilic granules surrounded by a histiocytic and eosinophilic infiltrate.

The etiology and pathogenesis of Wells syndrome is unknown, and antigenic stimuli probably cause the activation of Th2-like T lymphocyte clones, as well as the synthesis of interleukin 5 and eosinophil-stimulating cytokines.

Many factors such as viral, parasitic, bacterial, or fungal infections, insect bites, drugs and vaccines have all been reported as triggering factors [1]. There are no reports of Wells syndrome induced by multiple sclerosis drugs.

Case report

A 41-year-old Caucasian woman was diagnosed with multiple sclerosis in 2011 and she was taking mirtazapine and quetiapine 50 mg/day for mood disorders.

She started DMF treatment in July 2021 and experienced nausea and abdominal pain as side effects. One week after the first dose (taking DMF 240 mg/day), she noted itching on her upper right arm, followed by the development of erythematous plaques covered with vesicles (Fig. 1). She presented to the clinic for an evaluation one week later as the plaques had spread to the lower right arm. The patient did not report any fever or systemic symptoms. We proceeded to stop DMF and performed a blood test and biopsy of the lesion. The complete blood count showed an increase in eosinophils up to 2,000 μL. The histological images showed the presence of papillary dermal edema with lymphocytic and eosinophil inflammatory cell infiltrates concordant with Wells syndrome (Fig. 2). The clini-

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Figure 1. Skin lesions.

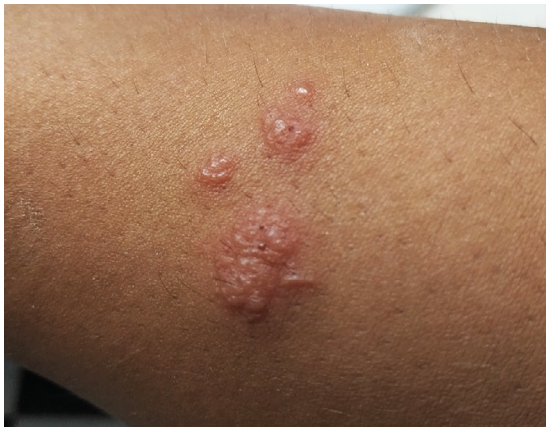
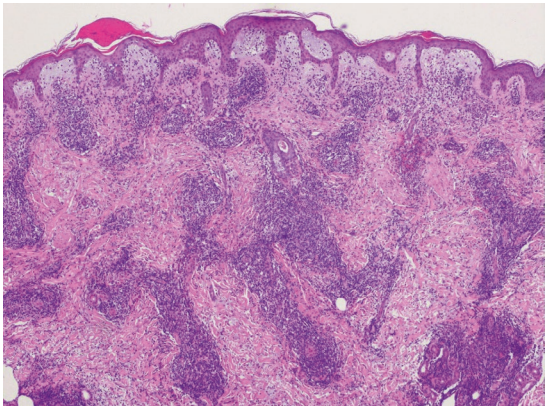


Figure 2. Papillary dermal edema with a lymphocytic and eosinophil inflammatory.



cal course was benign, with complete resolution of the lesions and normalization of the eosinophil count within 4 weeks. Administration of corticosteroids was not necessary.

Discussion

Many drugs have been associated with the onset of Wells syndrome. Antibiotics, anticholinergic agents, anesthetics, non-steroidal anti-inflammatory agents, thyroid medications, chemotherapeutic agents, thiomersal-containing vaccinations, and anti-TNF agents have all been reported as trigger factors for Wells syndrome [1].

Thus far, there have been no descriptions of Wells syndrome cases in either multiple sclerosis patients or in association with multiple sclerosis drugs. However, after reviewing the literature, we found a case of eosinophilic cardiac injury [2], eosinophilic gastroenteritis [3]and eosinophilic fasciitis [4] induced by DMF in multiple sclerosis patients.

DMF causes a reduction in lymphocytes; however, only few works have studied its effects on eosinophils. A recent review of lymphopenia induced by DMF in multiple sclerosis showed that only two works so far have been conducted to study the effect of DMF on eosinophils. One of these showed that eosinophil levels decreased by 54.1%, while the other found that DMF treatment did not exert any significant effects on eosinophils [5].

In contrast, studies on patients with psoriasis observed eosinophilia in the first three months of treatment with DMF, with stabilization or improvement in the long term without dose adjustment [6]. The composition of DMF is different from that of Fumaderm®, which contains DMF and zinc salts of monoethyl fumarate (MEF). In 2017, the European Medicines Agency (EMA) approved Skilarence® for the treatment of moderate-to-severe plaque psoriasis. This drug contains the same amount of DMF as Fumaderm®, but does not contain MEF salts. Despite the differences in composition, eosinophilia has been reported as a common adverse effect of Skilarence®, as with Fumaderm®. A transient increase in the mean eosinophil count was noted as early as week 3, reaching a maximum at weeks 5 and 8, and returned to baseline values at week 16. To improve the tolerability of these drugs, it is recommended to begin treatment with an initial dose with subsequent gradual increases every week to 90 mg at week 3, 240 mg at week 5, and 600 mg at week 8. (https://www.ema.europa.eu/en/documents/product-information/skilarence-epar-product-information_en.pdf).

Our patient presented symptoms with a dosage of 240 mg/day of DMF, so we can speculate that eosinophilia is a dose-dependent drug reaction and the higher dosage of DMF used in psoriasis (up to 720 mg/day) could explain the higher incidence reported in these patients with respect to multiple sclerosis.

It is important to keep in mind that the commercial formulation of quetiapine is quetiapine fumarate and that the 50 mg pills therefore contain approximately 8 mg of fumarate. In addition, most

atypical neuroleptic drugs can cause eosinophilia and systemic symptoms. Clozapine-induced eosinophilia is well documented, and there have been several reports of the involvement of quetiapine, risperidone, ziprasidone, haloperidol, aripiprazole, and olanzapine [7-10]. We did not find reports of ansenapine induced eosinophilia.

In conclusion, eosinophilia is rare in patients with multiple sclerosis treated with DMF and usually does not require dose adjustments. Although clinical manifestations of eosinophilia in this group of patients are very rare, it is important for practitioners to recognize the symptoms. Many neuroleptic drugs can induce eosinophilia and systemic symptoms; therefore, physicians must be aware of the risks associated with DMF and neuroleptic drugs, particularly for quetiapine, which contains fumarate.

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Síndrome de Wells secundario a dimetilfumarato. A propósito de un caso clínico

Introducción. El síndrome de Wells, también conocido como celulitis eosinofílica, es una rara dermatosis con aproximadamente 200 casos descritos en la bibliografía. Aquí presentamos un caso clínico de un paciente con esclerosis múltiple y síndrome de Wells secundario a dimetilfumarato (DMF).

Caso clínico. Mujer de 41 años que en julio de 2021 inició el tratamiento con DMF. Una semana más tarde, comenzó con prurito en las extremidades derechas, seguido por la aparición de zonas eritematosas con vesículas. El hemograma mostró elevación del recuento de los eosinófilos hasta 2.000 μL. El estudio anatomopatológico evidenció un infiltrado eosinófilo a nivel de la dermis compatible con síndrome de Wells. La evolución clínica fue favorable, con resolución de las lesiones y normalización de la eosinofilia aproximadamente en cuatro semanas. No fue necesario administrar corticoesteroides.

Conclusiones. La eosinofilia es rara en los pacientes con EM tratados con DMF y generalmente no precisa ajuste de dosis. A pesar de que las manifestaciones clínicas de la eosinofilia en estos pacientes sean raras, es importante que el médico reconozca los síntomas. Numerosos neurolépticos pueden causar eosinofilia y síntomas sistémicos; por lo tanto, los facultativos deben conocer los riesgos de la asociación entre DMF y neurolépticos, en particular por la quetiapina, que contiene fumarato.

Palabras clave. Dimetilfumarato. Eosinofilia. Esclerosis múltiple. Neurolépticos. Quetiapina. Síndrome de Wells.