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CASO CLÍNICO/CASE REPORT

Drug-induced hypersensitivity syndrome associated with minocycline prescribed for acne treatment. Case report

Síndrome de hipersensibilidad inducido por drogas asociado a minociclina prescrita para tratamiento de acné. Caso clínico

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RESUMEN

Las reacciones adversas a medicamentos o drogas (RAM) son inesperadas y suponen un desafío diagnóstico importante para cualquier médico. Algunas RAM ocurren instantáneamente posterior a la exposición a un fármaco, sin embargo, otras, como en este caso, ocurren muchas semanas después de iniciar tratamiento. Presentamos el caso de un síndrome de hipersensibilidad inducida por drogas posterior a la exposición del paciente a minociclina en contexto de tratamiento de acné.

ABSTRACT

Adverse drug reactions (ADR) are unexpected, unpleasant, and comprise a diagnostic challenge for any physician. Some ADRs occur instantly after being exposed to a certain medication, but others, as described in this case, can present weeks after treatment is started. We present a case of severe drug-induced hypersensitivity syndrome after exposure to minocycline prescribed for acne treatment.

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INTRODUCCIÓN

Adverse drug reactions (ADR) are unexpected, unpleasant, and comprise a diagnostic challenge for any physician. Some ADRs occur instantly after being exposed to a certain medication, but others, as described in this case, can present weeks after treatment is started. Minocycline has been indicated as a rare cause of adverse reactions and drug induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS) is included in the ADR profile[1].

We aim to present the diagnostic process of a patient admitted to our intermediate care unit with fever and hypereosinophilia. This case posed a significant diagnostic challenge due to the marked eosinophilia, prompting our team to consider a broad range of differential diagnoses.

CASE PRESENTATION

We present a 30-year-old male patient, under treatment with minocycline for common acne in outpatient dermatology care. Four weeks after starting treatment, the patient developed a fever of up to 38ºC and upper respiratory symptoms (sore throat, runny nose, nasal congestion and ear pain). He was evaluated by a general practitioner and was diagnosed with acute rhinopharyngitis. A treatment based on antihistamines, paracetamol, and celecoxib at usual doses was prescribed. A progressively ascending maculopapular rash on the lower extremities appeared one day later. The patient, under no medical advice, decided to discontinue celecoxib under the suspicion of an allergic reaction.

Two days before admission, the rash involved the chest as well as both auricles and eyelids. In a new outpatient consultation, an evolution of the rash and multiple cervical adenopathy is observed; prednisone 20 mg/day, amoxicillin-clavulanate, antihistamines, and paracetamol were started. At this point, the patient decides to discontinue minocycline without medical supervision. The patient's overall condition deteriorated, with an increase in the maculopapular rash which reached erythroderma level, as well as facial edema. This lead to a consult at our emergency unit and admission to the intermediate care unit six weeks after initiating minocycline.

Upon admission to the unit, the patient seemed in fair condition, tachycardic, well-perfused, feverish up to 38.6ºC and oxygen supplementation via nasal cannula at 2 l/min resulted in $SatO_2$ 96%. On physical examination, facial edema (figure 1A), symmetric bilateral eyelid edema, left auricular edema (figure 1B), and purulent otorrhea were evident. The throat was erythematous without mucosal lesions or pharyngeal tonsil exudate. Multiple cervical adenopathy was present. The patient had a polymorphic confluent maculopapular rash on both anterior and posterior regions of his chest and abdomen and extremities (figure 1C). Mild hepatosplenomegaly is noted. Admission laboratory results are summarized in table 1.

Laboratory work-up was notable for severe hypereosinophilia, and the admission diagnosis of hypereosinophilic syndrome was made, suggesting a drug hypersensitivity reaction. Dexamethasone 12 mg intravenous (IV) per day and antihistamines were initiated. An external otitis was successfully treated with oral flucloxacillin. Additional studies were performed, including chest, abdomen, and pelvis computed tomography (CT) and a total body PET-CT. A summary of tests, microbiologic studies, and images are shown in table 2. A left anterior cervical lymph node and a skin biopsy were carried out, in addition to a flow cytometry.

During days 1 to 3 of hospitalization, the patient's inflammatory parameters increased, and he remained febrile (figure 2). Transaminases continued to rise, and a more significant hepatosplenomegaly became apparent. Severe odynophagia developed, and oral ulcers were discovered in the anterior pillar of

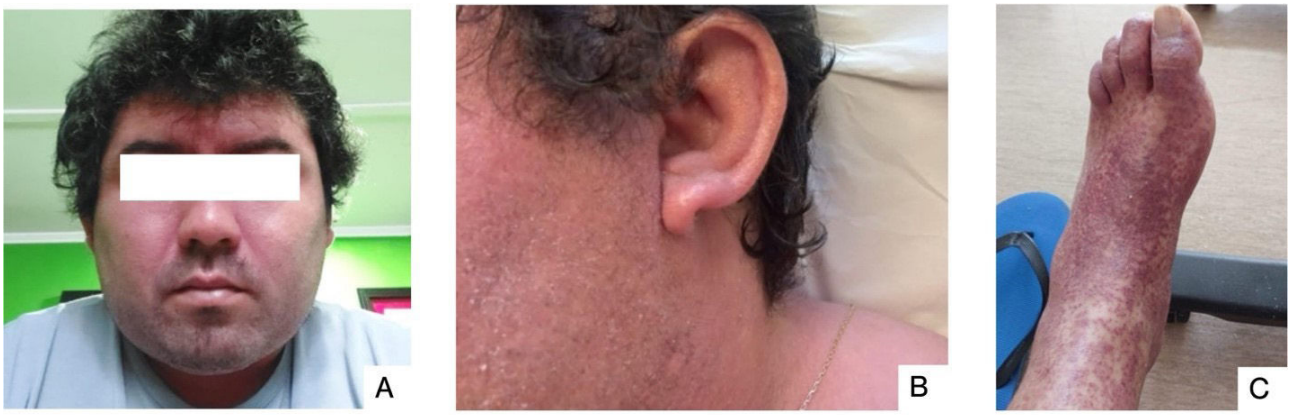

Figure 1. (A) facial edema and erythroderma; (B) preauricular and auricular edema; (C) purpura in foot.

Parameter	Values	Units
Hemoglobin	16.2	g/dl
Hematocrit	47.8	%
Mean Corpuscular Volume (MCV)	83.1	fl
Mean Corpuscular Hemoglobin (MCH)	28.1	pg
Mean Corpuscular Hemoglobin Concentration (MCHC)	33.8	g/dl
Leucocyte count	31630	cells/ul
Lymphocytes	Atypical	
Eosinophils	11(3479)	% (cells/ul)
Lactate dehydrogenase (LDH)	753	IU/ml
Alkaline Phosphatase (ALP)	195	IU/ml
Aspartate Aminotransferase (AST)	819,2	IU/ml
Creatinine	1.0	mg/dl
C-reactive protein	56	mg/dl (normal <0.5 mg/dl)
Procalcitonin	<0.05	ng/ml

Table 1. Summary of admission laboratory tests.

Test	Values
Blood Cultures (Aerobic and Anaerobic)	Negative
Urine culture	Negative
IgM Epstein-Barr Virus	Negative
IgG Epstein-Barr Virus	Positive
IgM/IgG Cytomegalovirus	Negative
HBsAg	Negative
Anti-HVC	Negative
IgM/IgG Parvovirus B19	Negative
Ear swab culture	Positive to methicillin-sensitive *Staphylococcus aureus* (MSSA)
Chest, Abdomen and Pelvis Computed Tomography	Supra and infra diaphragmatic adenopathy, areas of ground-glass opacities in both lower lobes of inflammatory-infectious origin, periportal and perivascular edema, cervical soft tissue edema, and pansinusitis.
Positron Emission Tomography-Computed Tomography	multiple hypermetabolic adenopathy above and below the diaphragm, hypermetabolic splenomegaly, mild normometabolic hepatomegaly, diffuse hypermetabolism of the bone marrow, pansinusitis, and diffuse inflammatory appearing hypermetabolism in the skin of the head, scrotum, and to a lesser extent, the trunk and extremities (dermatitis).

Table 2. Summary of microbiologic, serologic, and imaging studies.

the pharynx and oropharynx. PCR for human herpes virus (HHV) 1 and 2 was negative. Flow cytometry results were negative for lymphoproliferative disease. Due to the history of exposure to a tetracycline, suspicion of DiHS/DRESS arose. In addition, a PCR for human herpesvirus 6 (HHV-6) resulted positive.

With this information, the diagnosis of a drug reaction with eosinophilia and systemic symptoms DiHS/DRESS was made. At this point, liver, lungs, mucous membranes and skin were involved. Myocardial involvement was ruled out through normal levels of highly sensitive troponin T and ProBNP. The lymph node biopsy reported secondary lymphadenitis. The skin biopsy showed psoriasiform, spongiotic and vacuolar superficial and mid-perivascular dermatitis with abundant eosinophils plus focal pustular elements (figures 3A, 3B, 3C).

Treatment was initiated with intravenous immunoglobulin (IVIG) 1 g/kg (total of 70 g), and dexamethasone 12 mg IV/day was continued.

On the fifth day of hospitalization, the patient remained febrile with intense erythroderma and there was a recurrence of eosinophilia. A pulse of methylprednisolone with 500 mg on day 1, 250 mg on day 2, and 250 mg on day 3 was administered in addition to a second course of IVIG at 1 g/kg (70 g in total).

On the patient's seventh day in care, clinical improvement was observed and the eosinophilia resolved. The patient was transferred from the intermediate care unit to the medical hospitalization ward and was discharged on the 12th day since admission.

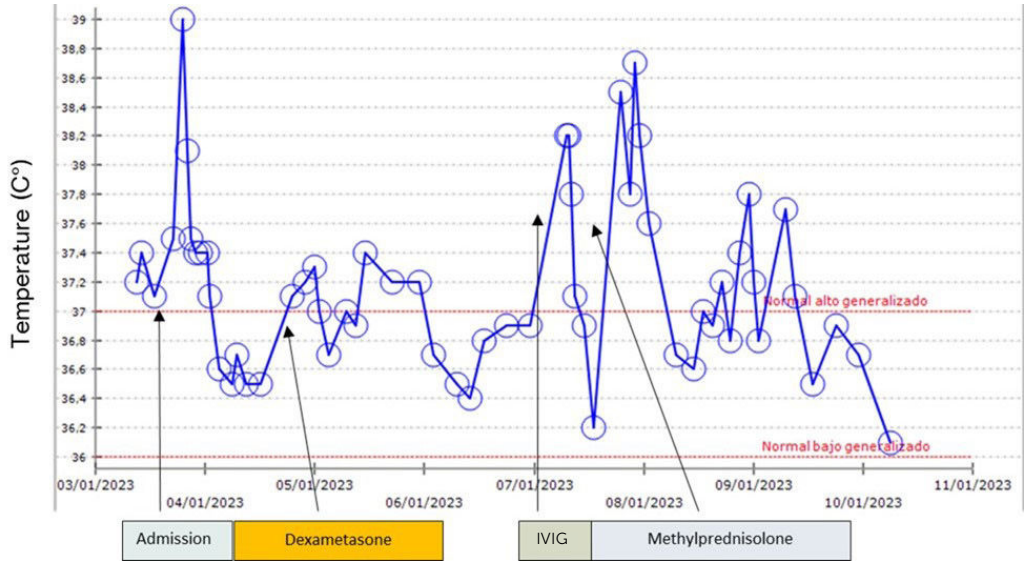

Figure 2. Axilary temperature evolution from admission to discharge, highlighting the IVIG + methylprednisolone pulse treatment effect.

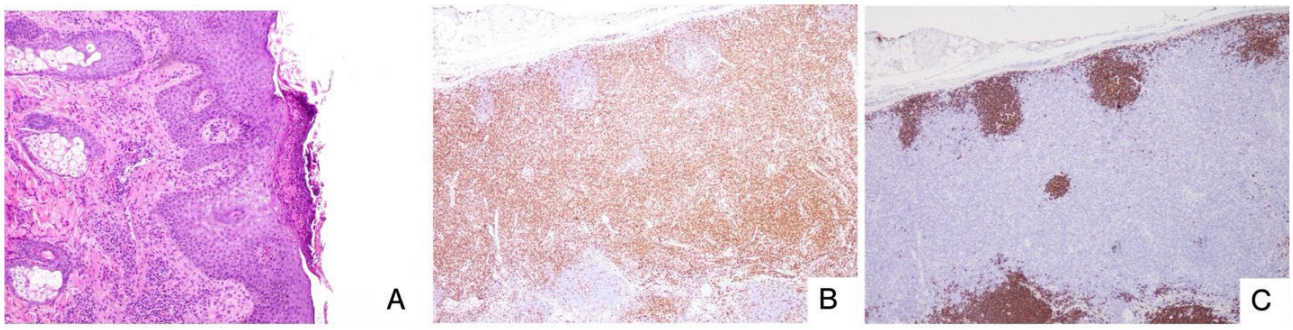

Figure 3. Skin and lymph node biopsies.

(A) cutaneous biopsy (40x), with hematoxylin-eosin stain showing psoriasiform spongiotic and vacuolar dermatitis, mid and superficial perivascular eosinophilic infiltration and lymphocyte-perivascular infiltration (B) immunohistochemistry in optical microscopy (10x), left cervical lymph node showing follicular hyperplasia and intense TCD3+ clonal expansion in the parafollicular zone (C) immunohistochemistry in optical microscopy (10x) with atypical CD30+ lymphocytes with Sternbergoid aspect.

DISCUSSION

DiHS/DRESS, constitutes a challenging diagnosis with a low prevalence (0.9 to 2 per 100,000 patients/year) and an incidence that can increase from 1 in 1,000 to 1 in 10,000 exposures to high-risk medications[2]. In a systematic review, 4% of DiHS/DRESS cases were associated with tetracyclines, with minocycline being the least common[3]. There is no gender or age predisposition. The main drugs involved in this reaction have remained consistent over the past 15 years, including allopurinol, vancomycin, carbamazepine, tetracyclines, sulfamethoxazole, and lamotrigine[4]. Proposed mechanisms that increase the risk include CYP450 polymorphisms that lead to decreased glutathione levels and immunosuppression and the reactivation of HHV, specifically HHV-6. It has been suggested that other viruses such as Epstein-Barr virus or citomegalovirus could also reactivate in the acute and post-corticosteroid tapering phases[5]. There are two widely recognized diagnostic criteria, RegiSCAR and the Japanese criteria, both of which the patient, in this case, met[6]. In our patient, the availability of a positive PCR for HHV-6 contributed to a more precise diagnosis.

Differential diagnoses include Stevens-Johnson syndrome, neutrophilic dermatoses like Sweet syndrome, and acute eosinophilic leukemia. As in this case, the clinical presentation typically occurs 4 to 6 weeks after starting the drug, with cutaneous involvement, lymphadenopathy, fever, and at least one systemic involvement.

Hepatitis is commonly seen, but there may also be eosinophilic pneumonia, cardiac involvement, and interstitial nephritis[7]. The severity assessment is important, and clinical series have reported an association between the intensity of erythroderma or purpura in the lower limbs and the presence of multisystemic involvement, even proposing a score to predict poor outcomes and risk of severe or fatal cytomegalovirus infection[8]. In line with all findings described, we had access to the the skin biopsy results which showed spongiotic dermatitis with eosinophilic infiltration and perivascular lymphocytic infiltrate[9], which confirmed DiHS/DRESS

The treatment approach involved discontinuing all medications due to the risk of potentiation of the adverse reaction, as DiHS/DRESS can sensitize patients to other drugs different from the trigger. The dexamethasone equivalent to 75 mg of oral prednisone was initiated, without achieving adequate control. Subsequently, 1 g/kg of IVIG over two days and a pulse of methylprednisolone were administered[10]. In follow-up appointments, cutaneous involvement gradually improved, but hepatic abnormalities persisted, leading to the addition of low-dose cyclosporine[11,12], which allowed prednisone tapering nearly three months after diagnosis. Ultimately, the patient showed favorable progress, leading to discharge and disease remission.

In summary, this clinical case highlights the importance of conducting thorough assessments in patients with rapid deterioration and severe eosinophilia. The observed worsening of symptoms underscores the necessity for clinicians to gather all relevant information concerning medications and other kinds of exposures.

Even in the absence of a definitive diagnosis, the implementation of decisive actions grounded in the understanding of the underlying pathophysiology must be warranted to mitigate adverse outcomes and enhance patient care.

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