

Drug Hypersensitivity Syndrome Caused by Minocycline

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Background: Minocycline is a commonly prescribed drug for the treatment of acne. Its use is generally not associated with systemic side effects.

Objective: To describe a case of minocycline-induced drug hypersensitivity syndrome in a 20-year-old Japanese woman.

Methods and Results: Following 2 months of minocycline treatment, the patient developed skin lesions composed of exudative maculopapules, purpuratous macules, and target-like, erythema multiforme-like plaques over most of her body. In addition, she had fever, abnormal liver function tests, eosinophilia, and atypical lymphocytosis. Laboratory tests indicated no elevation of antibody titers against cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Her ongoing exposure to minocycline was stopped, and treatment with oral prednisolone was begun. Her signs, symptoms, and laboratory abnormalities then began to resolve. Subsequently, the syndrome was observed to return briefly in response to an oral challenge with minocycline.

Conclusions: Minocycline is able to elicit a drug hypersensitivity syndrome that can resemble infectious mononucleosis. This drug reaction can be treated effectively by cessation of exposure to this drug and steroid therapy.

Antécédents: La minocycline est un médicament souvent prescrit dans le traitement de l'acné. Son utilisation n'est généralement pas associée à des effets secondaires systémiques.

Objectif: Le présent article décrit le cas d'un syndrome d'hypersensibilité aux médicaments, engendré par l'utilisation de la minocycline chez une jeune femme japonaise de 20 ans.

Méthodes et résultats: Après deux mois de traitement à la minocycline, la patiente a développé des lésions cutanées composées de maculo-papules exsudatives, de taches rouges et de plaques érythémateuses en cocarde multiformes sur la majeure partie de son corps. En outre, elle faisait de la fièvre, ses tests présentaient une fonction hépatique anormale et elle souffrait d'éosinophilie et de lymphocytoses atypiques. Les tests de laboratoire n'indiquaient aucune élévation du niveau des anticorps du cytomégalovirus, du virus d'Epstein-Barr et du herpèsvirus humain de type 6. Le traitement continu à la minocycline a été arrêté et remplacé par un traitement oral à la prednisolone. Les signes, les symptômes et les résultats de laboratoire ont commencé à s'améliorer. Plus tard, à la suite d'un test de provocation orale par minocycline, le syndrome a réapparu.

Conclusions: La minocycline peut produire un syndrome d'hypersensibilité qui peut ressembler à la mononucléose infectieuse. Cette hypersensibilité au médicament peut être traitée de façon efficace grâce à l'arrêt du traitement et à la prise de stéroïdes.

MINOCYCLINE is a tetracycline derivative with broad-spectrum, antimicrobial activity. It is commonly prescribed for the treatment of acne because it is active against *Propionibacterium acnes*, the bacterial species considered to be most prominent in the pathogenesis of acne.¹ In addition to its bacteriostatic action, minocycline has been reported to act by decreasing chemotaxis of poly-

morphonuclear leukocytes, modifying the complement pathways and inhibiting lipase production by *P. acnes*.² Adverse effects are uncommon with minocycline, although serious life-threatening reactions, such as drug hypersensitivity syndrome (DHS), acute generalized eruptive pustulosis, and drug-induced lupus, have been reported.^{3–8} Here we describe a patient in whom minocycline caused DHS characterized by a reversible fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, and generalized rash. Oral readministration of minocycline resulted in symptoms similar to those of the initial reaction.

Case Report

In 1993, a 20-year-old woman had been receiving 150 mg daily of minocycline and flavin adenine dinucleotide (FAD,

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vitamin B₂) for treatment of acne for 2 months when she developed a sore throat, cervical lymphadenopathy, and fever (40°C). At a local hospital, the patient was diagnosed as having a common cold, and was prescribed a combination of salicylamide, acetaminophen, caffeine, and methylenedisalicylate promethazine. Meanwhile, she continued to take minocycline and FAD for her acne. Her symptoms did not improve, and 2 days after the start of her fever, she developed pruritic, exudative maculopapules on both forearms and the dorsa of both hands. Within 3 days, these same lesions covered her abdomen (Figure 1A), arms, and legs (Figure 1B), and she also developed exudative, elevated, skin-colored plaques (Figure 1C) and target-like

lesions (Figure 1D) on her palms, fingers, and the dorsa of her hands. She then visited a dermatologist, who made the diagnosis of an adverse drug reaction. This doctor ordered a stop to all medications that the patient had been receiving, including FAD and minocycline, and began treatment with oral antihistamines (oxatomide, mequitazine, and d-chlorpheniramine maleate) and betamethasone. The response was poor, however.

There were no skin symptoms or swellings on her face, as is sometimes seen in patients with DHS.⁹ Laboratory tests run on the fifth day of her symptoms showed liver dysfunction: alanine aminotransferase was 114 U/L (normal 5–50 IU/L), aspartate aminotransferase was 266 U/L



Figure 1. Scattered erythema and macules covering the patient's (A) abdomen and (B) legs. Additional findings include (C) exudative elevated skin-colored plaques and (D) target-like lesions on the palms, fingers, and dorsa of the patient's hands.

(normal 5–50 IU/L), and lactate dehydrogenase was 841 U/L (normal 50–450 IU/L). A complete blood cell count revealed, in addition, the presence of atypical lymphocytosis ($162/\mu\text{L}$) and eosinophilia ($1,334/\mu\text{L}$). The total white blood cell count was $3,900/\mu\text{L}$. Based on these findings and the development of tonsillitis, the diagnosis was changed to infectious mononucleosis (IM), and the patient was referred to our hospital for further examination and treatment. She presented to us 7 days after she first became symptomatic.

An incisional skin biopsy specimen was taken from the left leg, and it revealed liquefaction degeneration of the basal cells and focal epithelial cell necrosis concomitant with the presence of dermal lymphocytic perivascular infiltrates. These findings were consistent with a diagnosis of erythema exudativum multiforme. Laboratory tests were run for antibody titers against Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus type 6 (HHV-6). These titers were determined both at the time of the patient's initial presentation (7 days from the initial symptom) and 14 days later (21 days from the initial symptom). Acute infection was ruled out because immunoglobulin (Ig)M against these viruses was lacking and IgG titers indicated previous infections. At the same time, we also tested the patient's urine and serum for the presence of genomic deoxyribonucleic acid (DNA) of these viruses using the polymerase chain reaction. These findings were also negative.

Treatment was begun with oral prednisolone (1 mg/kg/d), cefaclor (antibiotics), loxoprofen sodium (nonsteroidal anti-inflammatory drug), glycyrrhizin (for liver disease), ketotifen fumarate (antihistamine), d-chlorpheniramine maleate (antihistamine), and topical difluprednate (steroidal ointment). Over the next 3 days, all of the patient's symptoms and liver function abnormalities improved, and we tapered down the prednisolone in steps as follows: 1 mg/kg for 3 days, 0.6 mg/kg for 4 days, 0.3 mg/kg for 7 days, 0.2 mg/kg for 7 days, and no prednisolone thereafter.

On day 25 after her symptoms began, we ran patch tests for minocycline and FAD, as well as a drug lymphocyte stimulation test (DLST) for minocycline. All results were negative (the titer for DLST was 77%). One week after the last dose of prednisolone had been given, the patient was given an oral dose of 50 mg minocycline to test for hypersensitivity. Two days later, groups of tiny papules on an erythematous base were observed over both knees. Abnormal liver function tests were detected, and the patient developed a sore throat and a high fever (39.5°C). One day later, the skin abnormalities matured into erythema multiforme-like plaques. Oral administration of 15 mg

prednisolone led to resolution of both the fever and skin eruptions within 3 days.

Based on the patient's response to this oral challenge with minocycline, we concluded that the previous diagnosis of IM was incorrect and that the patient was suffering instead from a DHS. The patient was instructed to avoid minocycline and other tetracycline derivatives in the future and has had no recurrence of disease.

Discussion

We report here the differential diagnosis and treatment of DHS in a 20-year-old patient who had been receiving minocycline for the preceding 8 weeks as a treatment for acne. DHS is characterized by rapidly progressing erythema and multiple systemic symptoms that include fever, abnormal liver or kidney function, hepatitis, nephritis, atypical lymphocytosis, eosinophilia, leukocytosis, and lymphadenopathy, although all of these symptoms do not always present. In rare cases, abnormalities are also seen in other organ systems. This syndrome typically begins 1 to 8 weeks after initiation of exposure to the causative agent, and internal organ involvement occurs within 4 to 12 weeks after starting the medication.^{4,9–11} Only a limited number of drugs are known to cause DHS, among them being aromatic anticonvulsants, sulfonamide, allopurinol, mexiletine, and minocycline.^{12,13} The systemic symptoms of DHS are severe and can be fatal. Thus, DHS is categorized as a severe drug-reaction syndrome, in a group that also includes Stevens-Johnson syndrome and toxic epidermal necrolysis.¹⁴ Bocquet and colleagues and Roujeau proposed that severe cutaneous adverse reactions be divided into the following five categories: bullous fixed drug eruptions, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis.^{15,16} By this classification system, DHS is a form of DRESS.

Recently, it was proposed that the cutaneous and systemic symptoms of DHS are often associated with reactivation of HHV-6.^{17–19} According to this hypothesis, DHS has two clinical phases, an early phase characterized by an allergic drug reaction and a later phase in which there is HHV-6 reactivation. Consistent with this hypothesis, Tohyama and Hashimoto proposed to rename DHS as HHV-6-associated drug eruption.²⁰ However, the laboratory findings in our patient were not consistent with reactivation of HHV-6, nor did we observe any consequent systemic and skin symptoms that would normally be associated with such reactivation. We propose two possible

explanations for this: (1) our timely treatment with appropriate doses of steroid may have aborted immunosuppression and thereby prevented late-phase reactivation of HHV-6 and (2) late-phase reactivation of HHV-6 may have eventually occurred in our patient, but the serologic tests were run at times too early to detect this. In the case that we have described, late assessment of HHV-6 titer was not possible because this phenomenon was unknown at that time (in 1993). It is now thought that it may be necessary to wait 4 weeks after the onset of DHS before using the DLST to identify causative agents and that a similar wait is needed before measurements of IgG titers are able to reveal HHV-6 reactivation.¹⁹

The pathogenic mechanisms underlying DHS are still not known with any precision, but the following mechanistic sequence has been proposed: minocycline may be metabolized into reactive iminoquinones that then elicit T-cell activation.⁴ This then triggers release of HHV-6 from monocytes or salivary glands, with the end result being a late-phase reaction that resembles IM.¹⁸ This same sequence of events has also been proposed as a mechanism of allergic hypersensitivity and immunity-related graft-versus-host type.²¹ Inflammatory cytokines and activated eosinophils may also play a role in the induction of DHS.^{22,23} In contrast to minocycline, neither tetracycline nor doxycycline is metabolized into iminoquinone derivatives. Thus, it is possible that these antibiotics could be safely given to a patient who was hypersensitive to minocycline. However, we are aware of no present evidence that such a substitution can be made safely.

The differential diagnosis of this patient includes IM. IM is characterized by fever, lymphadenopathy, hepatosplenomegaly, leukocytosis, lymphocytosis, atypical lymphocytosis, and skin symptoms that include maculopapules, scarlatiniform, herpetiform, erythema multiforme-like plaques, urticaria, and purpura.²⁴ There is, therefore, a significant overlap between the signs and symptoms of IM and DHS. However, IM is caused by acute, primary infection with EBV, and correct diagnosis is thus aided by the presence in IM of elevated titers of anti-EBV IgM antibodies.²⁴ CMV mononucleosis and HHV-6 mononucleosis cause similar symptoms.²⁴ The patch test and DLST also aid in this differential diagnosis in that they are typically negative in IM. There is an exception, however, in that the DLST for amoxicillin is often positive in IM patients with amoxicillin-induced erythema.²⁵ Although our patient had some symptoms and laboratory abnormalities compatible with IM, our diagnosis of DHS was correct because IgM antibodies for EBV, CMV, and HHV-6 were not elevated; atypical lymphocytes were not elevated over 10%;

reaction was resolved within 3 days; and a subsequent challenge with minocycline led to a return of symptoms. A similar case of DHS was described in one previous report.⁷

In conclusion, we have reported here a case of DHS that was caused by minocycline. Following the exclusion of an infectious etiology, the patient was effectively treated with steroids, which is not always but is often necessary for the treatment of minocycline hypersensitivity. Given that DHS is a severe disorder and potentially life-threatening, it is important to recognize this syndrome and to diagnose it correctly. Therefore, to diagnose it, we must do liver and kidney function tests, assess body temperature, and perform patch testing and DLST once we suspect a DHS. Once it is diagnosed, the indicated treatment is withdrawal of exposure to the causative medication and adequate steroid therapy.

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