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CASE REPORT

Hydroxychloroquine-induced DRESS syndrome

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Abstract The authors describe the first case of drug rash with eosinophilia and systemic symptoms syndrome caused by hydroxychloroquine treatment in a male patient affected by seronegative arthritis.

Keywords Adverse reactions · DRESS syndrome · Eosinophilia · Hydroxychloroquine

Introduction

Hydroxychloroquine (HXQ) sulfate is a synthetic antimalarial drug, widely used in rheumatology due to its immunosuppressive properties. Antimalarials are well known to cause adverse reactions, ocular and cutaneous side effects being the most frequent. The most frequently noted cutaneous manifestation is skin pigmentation [1].

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, acute drug reaction. This syndrome was first described with anticonvulsant drugs (carbamazepine, phenytoin, and phenobarbitone) and was therefore named anticonvulsant hypersensitivity syndrome. The same symptoms were subsequently observed with a variety of other drugs, such as allopurinol, sulfasalazine, dapsone, and minocycline. The clinical manifestations typically occur within 2–6 weeks after initiating therapy and, in most cases, resolve when the drug is discontinued, without sequelae. However, a fatal outcome has been reported in 10–40% of cases [2, 3]. DRESS syndrome has been recently classified under a delayed type IVb hypersensitivity reaction where T helper type 2 cells play a significant role [4].

The clinical spectrum of DRESS syndrome is broad and protean, and the manifestations may appear in sequence. Fever is usually present. Skin eruption may vary from a diffuse maculopapular inflammatory rash to erythroderma; less frequently, cutaneous involvement presents with toxic epidermal necrolysis, Stevens–Johnson syndrome, or erythema multiform. Concerning organ involvement, lymph nodes, liver, and kidney are frequently affected; lung and heart are involved in a minority of the cases. The percentage and the type of visceral involvement differ in relation to the offending drug. Eosinophilia is the most common laboratory abnormality [3]. However, no symptom nor sign nor laboratory test is always present. Instead, the syndrome is a constellation of clinical manifestations and laboratory findings, and the diagnosis may be difficult to obtain.

Nevertheless, recent studies have strongly suggested that viral infections, especially reactivation of human herpesvirus 6 (HHV-6), commonly occur 2–3 weeks after onset of rash; therefore, the demonstration of HHV-6 reactivation is of high diagnostic value, regardless of whether virus reactivation plays a causal role or represents a consequence of DRESS syndrome [5, 6].

We present a case of DRESS syndrome secondary to HXQ administration.

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Case report

A 62-year-old man was started on HXQ (400 mg/day) for a seronegative polyarthritis. Two weeks later, he developed a rash starting with pruriginous infiltrated papules and facial edema that in a few days evolved into a diffuse dermatitis and thus was admitted to hospital.

His past history included alcoholic steatohepatitis and hypercholesterolemia on rosuvastatin. On physical examination, there was diffuse, erythematous-exfoliative rash involving trunk and limbs. No lymph node enlargement was observed; the temperature was 36.5°C. HXQ therapy was withdrawn.

Blood tests showed leukocyte count of 11,300 per mm^3 (normal range 4,200–12,400), eosinophils 2,400 per mm^3 (normal <450), basophils 470 per mm^3 (normal <200), no atypical lynphocytosis. Erythrocyte sedimentation rate and C-reactive protein were elevated at 66 mm/h (normal <34) and 21 mg/l (normal <5), respectively. Liver function test revealed alanine transfaminase 91 U/l (normal <40 U/l) and gamma-glutamyltranspeptidase 726 U/l (normal <61). BUN and creatinine levels were normal, while urinalysis showed proteinuria 70 mg/dl (normal <5). Blood culture, serology for rheumatoid factor, antinuclear factor, anti-DNA, anti-smooth muscle, and antimitochondria antibodies were negative as well as HBsAg and anti-HCV antibodies. He developed fever (39°C) after 5 days, and therapy with ceftriaxone (1 g/day) was started.

A diagnosis of DRESS syndrome due to HXQ was made. Unfortunately, at our institution, tests for HHV-6 are not performed.

The rash improved slowly after HXQ discontinuation. Ten days later, because of persistence of eosinophilia and elevation of acute-phase reactants, prednisolone 12 mg/day was prescribed with tapering of the dose over 4 weeks.

At discharge from the hospital, the rash and abnormal laboratory values were improving. The rash eventually resolved after 60 days.

Discussion

To our knowledge this is the first report of DRESS syndrome induced by HXQ. The knowledge of this association is remarkable because DRESS syndrome is a severe and life-threatening drug reaction.

In recent years, the diagnostic criteria of the DRESS syndrome were debated. However, it is generally accepted that DRESS syndrome is characterized by a variable combination of: (1) drug-induced immunological background; (2) later onset than other drug reactions; (3) longer duration than common “drug rashes”; (4) multiorgan involvement; (5) lymphocyte activation (node enlargement, lymphocytosis, atypical lymphocytes); (6) eosinophilia; and (7) frequent virus reactivation [7]. Moreover, the importance of HHV-6 reactivation has recently been highlighted above all by Japanese authors, not only for the supposed pathogenetic role, but also from a diagnostic point of view [6].

In conclusion, although the abovementioned criteria are generally accepted, definite diagnostic criteria for the syndrome are still lacking, as well as the relationship between the clinical and laboratory findings and the causative drug. The main features of the DRESS syndrome like fever, severe skin reaction, eosinophilia, and multisystemic organ involvement [2] were all present in our patient, alongside other features which are commonly regarded as typical (later onset and longer duration). Moreover, high temperature appeared some days after HXQ treatment discontinuation; a paradoxical worsening of the clinical picture after interruption of the causal drug has been reported [8].

HXQ is known to produce other cutaneous reactions, some of which, like the DRESS syndrome, are of the delayed type, more commonly acute generalized exanthematous pustulosis but also fatal toxic epidermal necrolysis, contact dermatitis, and phototoxic and photoallergic dermatitis [1].

Maybe other cases of DRESS syndrome provoked by HXQ may not have been recognized because many patients are advised by their rheumatologists to immediately stop the drug if a rash develops; moreover, other cases may have been misdiagnosed as other forms of cutaneous HXQ-induced reactions.

The knowledge of DRESS syndrome related to HXQ treatment is relevant, as the drug is frequently used in patients suffering from systemic lupus erythematosus, and the occurrence of the DRESS syndrome might be mistaken for a flare of SLE, which also may present with fever, skin rash, adenopathy, liver, and renal involvement. However, the presence of eosinophilia and lymphocytosis are more typical of DRESS syndrome, and the detection of HHV-6 reactivation could be diagnostic.

Rheumatologists should be aware of this syndrome, as it is potentially severe and associated with other commonly prescribed drugs in rheumatology such as allopurinol and sulfasalazine.

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