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Case Report

Bacterial Infection May Trigger DRESS Syndrome: An Exceptional Case of Delayed Hypersensitivity Reaction Occurring 22 Months After Allopurinol Therapy

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Abstract

Drug-induced hypersensitivity syndrome also known as DRESS syndrome is considered as a severe and potentially life-threatening adverse drug reaction. The pathogenesis of DRESS syndrome is still partially understood. Prior research has implicated viral infection or reactivation, specifically, human herpes viruses 6 and 7, Epstein-Barr virus and cytomegalovirus.

We report a case of DRESS syndrome induced by allopurinol occurring 22 months after starting the treatment and which might have been triggered by concomitant infections.

A 72-year-old man was put on allopurinol in February 2021. Twenty months later, he was hospitalized for Klebsiella urinary tract infection associated with erysipelas that had evolved well after two weeks of antibiotherapy. On November 20, he presented a second episode of Enterococcus faecalis urinary tract infection. On December 5, he developed a pruritic maculopapular rash with fever (39.5°C). Skin examination showed a generalized infiltrated erythematous maculopapular eruption and facial edema. Complete blood counts showed total leucocyte count at 10.6 × 10^3/µl with eosinophils at 1.58 × 10^3/µl (14.9%). Histological findings were compatible with DRESS syndrome. Allopurinol was stopped. Skin condition improved within a month.

A prolonged delay between the start of treatment and the appearance of a febrile rash should never exclude the diagnosis of Dress syndrome or delay its management.

Keywords: DRESS Syndrome; Allopurinol; Infection; Pharmacovigilance; Hypersensitivity

Abbreviations

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; HHV-6: Human Herpes Viruses 6; HHV-7: Human Herpes Viruses 7; EBV: Epstein-Barr Virus; CMV: Cytomegalovirus; RegiSCAR: Registry of Severe Cutaneous Adverse Reactions; HLA: Human Leukocyte Antigen; TH1: T Helper 1

Introduction

Drug-induced hypersensitivity syndrome also known as DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, is considered as a severe and potentially life-threatening adverse drug reaction. It is characterized by skin rash, fever, hematologic abnormalities (eosinophilia, atypical lymphocytes), lymphadenopathy and internal organ involvement [1]. Currently,

the pathogenesis of DRESS syndrome is only partially understood. Prior research has implicated viral infection or reactivation. It is associated, specifically, with human herpes viruses 6 (HHV-6) and 7 (HHV-7), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) [1,2].

Materials and Methods

We report a case of DRESS syndrome induced by allopurinol occurring 22 months after starting the treatment and which might have been triggered by concomitant infections.

This case was notified to the Tunisian Center of Pharmacovigilance on December 23th2022 under the registration number 3788/22.

Results and Discussion

A 72-year-old diabetic man on insulin, with a history of coronary artery bypass surgery, was put on allopurinol in February 2021 for gout. Twenty months later, (October 22, 2022), he was hospitalized for Klebsiella urinary tract infection associated with erysipelas that had evolved well after two weeks of antibiotherapy (ciprofloxacin and piperacillin-tazobactam). On November 20, he presented a second episode of Enterococcus faecalis urinary tract infection and received teicoplanin for a week. On December 5, he developed a pruritic maculopapular rash with fever estimated at 39.5°C. The eruption first appeared on his legs and quickly proceeded to involve the majority of his body including palms and soles. Skin examination showed a generalized infiltrated erythematous maculopapular eruption (Figure 1) and facial edema without polyadenopathy. Labial mucosa and conjunctivae were not affected. The rest of the physical examination was normal. Complete blood counts showed total leucocyte count at $10.6 \times 10^3/\mu l$ with eosinophils at $1.58 \times 10^3/\mu l$ (14.9%). Renal and hepatic functions were normal. Histological findings showed vacuolisation of the epidermal basal cell layer and perivascular lymphocytic infiltrate in the dermis, compatible with DRESS syndrome. Allopurinol was stopped. Skin condition improved and laboratory parameters returned to normal rates within a month after the drug withdrawal and using oral corticosteroids (prednisolone).

The diagnosis of DRESS syndrome was made in this patient based on the criteria adopted by the European group RegiSCAR [3]. In our case, the score was four(probable case) because of: skin rash over 50% of body surface area (1 point), facial edema and infiltrated skin lesions (1 point), generalized lymphadenopathy (1 point) and eosinophilia at 14.9% (1 points). The responsibility of allopurinol in inducing DRESS syndrome was evaluated as I3 (C2S2) according to the updated French method of imputability because of the compatible delay (22 months after dug intake) and the favorable outcome after the medication withdrawal [4].

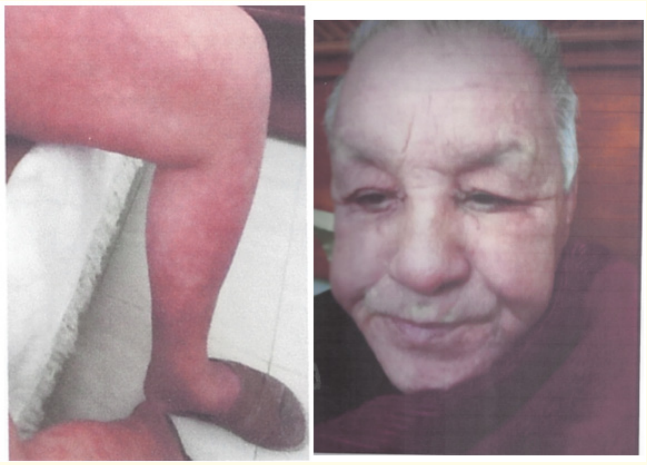

Figure 1: Maculopapular rash on leg and facial edema.

Despite that currently the pathogenesis of allopurinol-induced DRESS syndrome is only partially understood, it is thought to be multi-factorial and implicate at least three components [5]: first, the accumulation of allopurinol's metabolite which may directly cause cell damage. Second, genetic predisposition through specific human leukocyte antigen (HLA) allele's subtype. The third possible component is that DRESS syndrome, as a delayed hypersensitivity reaction, may induce the reactivation of viruses of the Herpes group by the activation of T lymphocytes. In fact, it has demonstrated that the TH1-type cytotoxic T cell response was directed against viral antigens and not against drugs. In this situation the drug promote the passage from a latent stage of infection to a viral reactivation, by increasing the viral replication either by a direct action on the virus itself, or by creating a state of immunosuppression [6]. This cascade reaction is thought to be accelerated by community-acquired bacterial and viral infections and can be observed in other stressful situations of immunosuppression such as hospitalizations in intensive care units [7].

The clinical presentation of DRESS syndrome is variable and occurs in response to a range of drugs, usually 3 weeks to 3 months after initiation. In the present case, allopurinol was being used over 22 months, but the clinical manifestations appeared, six weeks after the first urinary tract infection and 15 days after the second one, which is a suggestive delay.

Hence, we believe that these two infectious episodes, with the hospital stay, might have contributed to accelerate the cascade reaction by creating a state of immunosuppression and inducing a viral reactivation. This hypothesis might explain the longer delay, than generally accepted, between initiating allopurinol and the occurrence of DRESS syndrome. However, we could not determine the HHV-6, HHV-7, CMV and EBV reactivation, due to lack of the measurement kits at our laboratory. To the best of our knowledge, there has only been one patient diagnosed with DRESS syndrome after a long drug exposure. In that case, the patient had been treated for 12 months with sulphasalazine, and had undergone H1N1 vaccination 4 days prior to the symptoms. HHV 6 reactivation had been confirmed with a serological test [8].

Conclusion

This case fits the clinical presentation of DRESS syndrome and occurred during drug therapy with allopurinol, a known causative agent. The onset of symptoms occurring 22 months after drug initiation has not previously been reported in the literature. Thus, a prolonged delay between the start of treatment and the appearance of a febrile rash should never exclude the diagnosis of Dress syndrome or delay its management.

Conflict of Interest

the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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