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CASE REPORT

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Agranulocytosis-complicated DRESS with medullar HHV-6 replication

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Abstract

HHV-6B is the subtype most often involved in the systemic manifestations of the DRESS, but also in myelosuppression in bone marrow transplant. We report a new observation of its myelosuppressive effect: a case of DRESS complicated by agranulocytosis with detectable HHV-6 RNA in bone marrow.

KEYWORDS

agranulocytosis, bone marrow, drug reaction with eosinophilia and systemic symptoms, HHV-6

1 | INTRODUCTION

We report a case of DRESS complicated by isolated agranulocytosis with detectable HHV-6 RNA in polymerase chain reaction (PCR) analysis from bone marrow and without hemophagocytosis, which suggests that HHV-6 reactivation in the bone marrow of patients with DRESS syndrome may induce agranulocytosis.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potential life-threatening drug hypersensitivity syndrome. One of its particularities is the long-term course of symptoms with periods of remission and flare-up until several months after withdrawal of the culprit drug.[1]

Clinical manifestations of DRESS are high fever, facial edema, nonspecific skin eruption, and diffuse lymphadenopathy. Blood abnormalities are often observed too, such as blood eosinophilia, atypical lymphocytes, kidney (acute renal failure), and liver (hepatitis) dysfunctions. Involvement of the myeloid stem cells may occur and is usually related to the direct toxicity of the drug or a hemophagocytosis syndrome.

HHV-6 virus, the most often reactivated virus in DRESS syndrome, plays a role in clinical and visceral manifestations of DRESS.

We report a case of DRESS complicated by isolated agranulocytosis with detectable HHV-6 RNA in polymerase chain reaction (PCR) analysis from bone marrow.

2 | CASE REPORT

A 32-year-old Philippine woman was recently referred to the psychiatry department for bipolar postpartum disorder treated by lithium, antidepressants (serotonin reuptake inhibitors), and several benzodiazepines sequentially. Four weeks after treatment initiation, she presented a febrile rash associated with facial edema and cervical lymphadenopathy (Figure 1). Blood tests showed cytolytic hepatitis (transaminase X 3N)

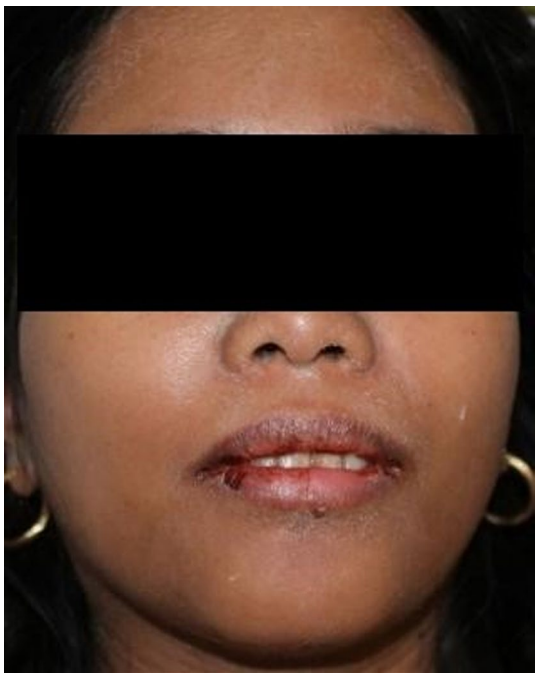

FIGURE 1 Facial edema and cheilitis characteristic of DRESS

and hyper eosinophilia at 1.5G/L. DRESS syndrome was suggested despite negative blood PCR analyses for HHV-6, HHV-7, CMV, and EBV. All psychotropic drugs were stopped and clorazepate was started to prevent a syndrome of weaning, in agreement with her psychiatrist and the pharmacovigilance department.

Two weeks after the onset, whereas DRESS-related clinical symptoms were almost completely resolved and the patient was only treated with clorazepate, she relapsed with a new febrile skin eruption. A concomitant agranulocytosis (polymorphonuclear neutrophils, 200/mm3) was observed, without infectious complications.

PCR analysis performed on bone marrow aspiration was positive for HHV-6 (1500 copies/ml) and negative for HHV-7 and CMV. No hematological arguments for hemophagocytosis or for drug toxicity were observed.

After the clorazepate withdrawal and with G-CSF injections, a normal neutrophil count was obtained in five days. Complete remission of symptoms was observed within 3 weeks.

Probability scores for DRESS showed a REGISCAR score calculated at 6 (definite DRESS), and the DIHS (drug-induced hypersensitivity syndrome) of the Japanese group was calculated at 7 (typical DRESS).[2,3]

Due to a dramatic evolution of her bipolar syndrome and the need for lithium treatment, we decided to prematurely practice cyamamezine and lithium patch tests (30% pet).[4] Cyamamezine patch test was positive, and oral lithium was therefore reintroduced sequentially every week without complications according to this protocol: 1/4 of a dose, 1/2 of a dose, and whole dose.

3 | DISCUSSION

We report a case of DRESS syndrome complicated by an agranulocytosis with positive HHV-6 reactivation in bone marrow.

DRESS syndrome is a type IV hypersensitivity reaction. The pathogenesis of DRESS remains incompletely understood. Many reports have suggested the role of reactivations of viruses from the herpes virus family (HHV6, HHV7, CMV, and EBV). Genetic susceptibility to some drugs has also been identified in particular in southeast Asian populations, like in our Philippine patient.[5] Mechanisms of viral reactivation are still controversial. It has been suggested that drugs induce transient immunosuppression leading to viral reactivation.[1] Indeed, transient hypogammaglobulinemia has been demonstrated at the very beginning of DRESS.[6,7] Another hypothesis is that some drugs may directly lead to viral reactivation and replication such as sodium valproate or amoxicillin, which are able to induce direct HHV-6 replication in vitro.[8]

HHV-6 virus, the most often reactivated virus in DRESS syndrome, is a latent virus known to be able to reactivate, especially when immunodepression occurs. Thus HHV-6 viral replication seems to play a role in visceral manifestations of DRESS as demonstrated in hepatitis or encephalitis.[9] Additionally, it may be responsible for the development of multiorgan failure occurring concomitantly or even after discontinuation of the culprit drug.[10] Such that HHV-6 reactivation is considered as a diagnostic and prognostic marker in DRESS syndrome, as suggested by a Japanese study.[11]

There are two types of HHV-6, A and B, which are differentiated by specific cell receptors. HHV-6B whose the cellular receptor is the CD134 (OX40), an immune costimulatory molecule, is the subtype involved in DRESS syndrome.[12] It has been shown that the CD134 was preferentially expressed on CD4 T cells in patients suffering from a DRESS syndrome, at the time of acute symptoms.[13]

In the present case, viral replication of HHV-6 was not initially found in blood but secondarily in bone marrow at the time of agranulocytosis. Longitudinal follow-up of blood HHV-6 was not performed due to the initial high evidence of DRESS syndrome. However, the initial negativity of HHV-6 in blood could be explained by the late of positivity that can be observed until 1-2 weeks after the rash onset.[11]

The myelosuppressive effect of HHV-6 has been demonstrated in adults as in pediatric. Its myelosuppressive role is not fully understood. Indeed, genomic HHV-6 can be detected in bone marrow samples from healthy subjects.[14] Nevertheless, in bone marrow transplantation, HHV-6B medullar tropism on the graft can be the cause of delay or even absence of granulopoiesis in the host.[15-17] In vitro, HHV-6B could inhibit bone marrow progenitors.[18]

In pediatric, HHV-6 is the main cause of infection-associated neutropenia.[19] The precise mechanisms underlying HHV-6B–associated neutropenia remain unclear, but

chemokines may play an important role in the pathogenesis of severe neutropenia in patients with primary HHV-6B infection.[20] As well as in adults population, HHV6-B is responsible of more graft failures in hematopoietic cell transplantation, and especially neutropenic graft failures.[21]

Hematologic dysfunctions in DRESS usually involve the three myelopoiesis lineages by mechanisms of drug-induced hemophagocytosis or direct drug toxicity.[1,22] In our case, isolated agranulocytosis was observed, without involvement of lymphocytic or megakaryocytic lineages. Moreover, cyamamezine is not known to provide hematotoxicity. Finally, bone marrow aspiration did not show any microscopic signs in favor of hemophagocytosis.

Thus, we hypothesized that medullar HHV-6 reactivation could be responsible for agranulocytosis in our patient.

Finally, lithium was successfully reintroduced and cannot be suspected to be involved in the occurrence of DRESS in our patient. Moreover, it has been suggested that small molecules such as lithium were not able to trigger allergy.

Overall, this case report strongly suggests that HHV-6 reactivation in the bone marrow of patients with DRESS syndrome may induce agranulocytosis.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

ML: served as the primary author, saw the patient in clinic, and is responsible for the literature review and construction of the manuscript; FT: served as allergologist referent who managed this case and refined the final shape of the report; PC and OB: saw the patient in clinic and refined the final shape of the report; CH: served as pharmacist who conducted the drug survey; PJ and VH: served as the senior author managing the construction and edits of the manuscript and guiding the primary author through the submission process.

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