

# Drug-induced hypersensitivity syndrome with human herpesvirus-6 reactivation

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#### ABSTRACT

A 45-year-old man, on carbamazepine for the past 3 months, was referred as a case of atypical measles. On examination, he had high-grade fever, generalized itchy rash, cough, vomiting and jaundice. A provisional diagnosis of drug hypersensitivity syndrome to carbamazepine was made with a differential diagnosis of viral exanthema with systemic complications. Laboratory investigations revealed leukocytosis with eosinophilia and elevated liver enzymes. Real-time multiplex polymerase chain reaction (PCR) on throat swab and blood was suggestive of human herpesvirus-6 (HHV-6). Measles was ruled out by PCR and serology. The diagnosis of drug-induced hypersensitivity syndrome (DIHS) was confirmed, which could explain all the features manifested by the patient. HHV-6 infects almost all humans by age 2 years. It infects and replicates in CD4 T lymphocytes and establishes latency in human peripheral blood monocytes or macrophages and early bone marrow progenitors. In DIHS, allergic reaction to the causative drug stimulates T cells, which leads to reactivation of the herpesvirus genome. DIHS is treated by withdrawal of the culprit drug and administration of systemic steroids. Our patient responded well to steroids and HHV-6 was negative on repeat real-time multiplex PCR at the end of treatment.

**Key words:** Carbamazepine, drug-induced hypersensitivity syndrome, human herpesvirus-6

#### INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) is evoked by a drug, (usually an aromatic anticonvulsant) started 3 weeks to 3 months before the onset of symptoms.<sup>[1,2]</sup> Now, it is postulated that an interplay of a virus and a drug with the immune system of the affected person leads to this clinically challenging condition.<sup>[1]</sup> It is well documented that DIHS has been associated with reactivation of human herpesvirus-6 (HHV-6), HHV-7, Epstein Barr virus (EBV) and cytomegalo virus (CMV).

Because of multisystem involvement, it is often misdiagnosed as an infectious disease or a lymphoproliferative disease or an autoimmune disease.<sup>[1]</sup> We report this case to stress the need to include it in the differential diagnosis of pyrexia of unknown origin. Prompt withdrawal of the causative drug and steroid administration result in complete remission in most cases. To the best of our knowledge, this is the first report of HHV-6 reactivation in DIHS from India.

#### CASE REPORT

A 45-year-old man, on carbamazepine for the past 3 months, consulted a doctor nearby with high-grade fever, generalized itchy rash, cough, vomiting and jaundice. He had been advised to stop carbamazepine and prescribed antihistamines and antibiotics, without any response. He was then referred as a case of atypical measles.

On the 20<sup>th</sup> day of illness, he was admitted to the Government Medical College Hospital, Calicut.

#### Access this article online

##### Quick Response Code:



##### Website:

www.ijdvl.com

##### DOI:

10.4103/0378-6323.93635

**How to cite this article:** Riyaz N, Sarita S, Arunkumar G, Sabeena S, Manikoth N, Sivakumar CP. Drug-induced hypersensitivity syndrome with human herpesvirus-6 reactivation. Indian J Dermatol Venereol Leprol 2012;78:175-7.

**Received:** July, 2011. **Accepted:** November, 2011 **Source of Support:** Nil. **Conflict of Interest:** None declared.

Physical examination revealed high-grade fever (104°F), jaundice, cervical lymphadenopathy, facial puffiness and erythema [Figure 1] and generalized maculopapular rash [Figure 2]. Mucosal involvement was limited to scaling of the lips. Laboratory assessments showed leukocytosis (11,000/mm<sup>3</sup>), eosinophilia (17%) and elevated liver enzymes. Renal function tests, blood culture, urine culture and peripheral smear for malarial parasites were within normal limits. Serology for typhoid, rickettsial infection, leptospirosis, viral hepatitis and human immunodeficiency virus were negative. Splenomegaly was detected on ultrasound examination. With a clinical differential diagnoses of drug hypersensitivity syndrome to carbamazepine and viral exanthem with systemic complications, throat swab and blood were tested for measles, enterovirus, HHV-6, HHV-7, human parvovirus-B19, CMV, EBV and Herpes simplex virus (HSV) by real-time multiplex polymerase chain reaction (PCR) (Fast Track Diagnostics, Luxembourg). Both throat and blood tested positive for HHV-6.

Diagnosis of typical DIHS was confirmed as per the criteria proposed by the Japanese consensus group<sup>[1,2]</sup> [Table 1], which could explain all the features manifested by our patient, including HHV-6 reactivation.

The patient was started on 50 mg prednisolone and he responded well [Table 2]. The steroid was slowly tapered and stopped over 3 months. HHV-6 was negative on repeat real-time multiplex PCR at the end of treatment.

## DISCUSSION

DRESS was defined by Bocquet *et al.* as a constellation of symptoms and signs, the main features being a

cutaneous eruption after exposure to the offending drug (carbamazepine in our case), associated with fever and organ involvement.<sup>[2]</sup> Drugs commonly associated with DRESS are carbamazepine, phenytoin, phenobarbitone, lamotrigine, minocycline, allopurinol, dapsone, diltiazem, abacavir, nevirapine and non-steroidal anti-inflammatory drugs like ibuprofen, etc.<sup>[1,3,4]</sup>

A simple drug etiology cannot explain all the features of DIHS, like its delayed onset, paradoxical worsening of clinical symptoms after stopping the causative drug and multiple organ system failures in a stepwise manner.<sup>[5]</sup> Now, it is postulated that an interplay of a virus and a drug with the immune system of the affected person leads to this clinically challenging condition.<sup>[1]</sup>

Drugs like phenytoin, phenobarbitone and carbamazepine are metabolized to reactive aromatic epoxides by the cytochrome P<sub>450</sub> system. These toxic metabolites are detoxified by epoxide hydroxylase, which may be defective in DIHS. Therefore, a high level of the drug or a reactive metabolite may initiate the immune response.

It is well documented that DIHS has been associated with reactivation of HHV-6, HHV-7, EBV and CMV. DIHS patients having HHV-6 reactivation developed a more severe and prolonged form of the disease.<sup>[6,7]</sup>

HHV-6 infects nearly all humans by age 2 years. It infects and replicates in the CD4 T lymphocytes and establishes latency in human peripheral blood monocytes or macrophages and early bone marrow progenitors.<sup>[8]</sup> In DIHS, allergic reaction to the causative drug stimulates T cells, and this T cell stimulation leads to reactivation of the herpesvirus genome.<sup>[1]</sup>



**Figure 1: Edema and erythema of face**



**Figure 2: Erythematous maculopapular rash all over the body**

**Table 1: Various diagnostic criteria proposed for drug-induced hypersensitivity syndrome**

| RegiSCAR study group <sup>[2]</sup>   | Japanese consensus group <sup>[1,2]</sup>   | Bocquet et al. <sup>[2]</sup>  |
|---|---|--|
| 1. Hospitalisation  | 1. Maculopapular rash developing more than 3 weeks after starting therapy with a limited number of drugs                                    | 1. Cutaneous drug eruption   |
| 2. Reaction suspected to be drug related  | 2. Prolonged clinical symptoms after discontinuation of the causative drug  | 2. Adenopathies $\geq 2$ cm in diameter or hepatitis (liver transaminases $\geq 2$ -times the upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis |
| 3. Acute rash*  | 3. Fever ( $>38^{\circ}\text{C}$ )  | 3. Hematologic abnormalities eosinophilia $\geq 1.5 \times 10^9/\text{L}$ or atypical lymphocytes  |
| 4. Fever above $38^{\circ}\text{C}^*$   | 4. Hepatitis (ALT $>100$ units/L) or renal involvement  | <i>Presence of 1, 2 and 3 is required for the diagnosis of DRESS</i>   |
| 5. Enlarged lymph nodes involving at least two sites*   | 5. Leukocyte abnormalities [leukocytosis $>11,000/\text{mm}^3$ ; atypical lymphocytosis $>5\%$ ; eosinophilia (1500 cells/ $\text{mm}^3$ )] |  |
| 6. Involvement of at least one internal organ*  | 6. Lymphadenopathy  |  |
| 7. Blood count abnormalities:   | 7. HHV-6 reactivation   |  |
| a. Lymphocytes above or below laboratory limits*  | <i>Presence of all 7 criteria -&gt; typical DIHS</i>  |  |
| b. Eosinophils above laboratory limits (in percentage or absolute count)*                                       | <i>Atypical DIHS -&gt; except lymphadenopathy and HHV-6 reactivation</i>  |  |
| c. Platelets below laboratory limits* $\geq 3$ of the criteria marked** are required for the diagnosis of DRESS |   |  |

**Table 2: Liver function test results of the patient**

|                              | At the time of admission | 4 weeks after starting steroids | After completion of treatment |
|------------------------------|--------------------------|---------------------------------|-------------------------------|
| Total bilirubin (mg%)        | 8.2                      | 2.09                            | 0.5                           |
| Direct bilirubin (mg%)       | 4.4                      | 0.64                            | 0.1                           |
| Total protein (gm%)          | 6.4                      | 7.39                            | 6.5                           |
| Albumin (gm%)                | 3.2                      | 4.51                            | 3.6                           |
| SGOT (IU/ml)                 | 807                      | 24                              | 31                            |
| SGPT (IU/ml)                 | 243                      | 74                              | 45                            |
| Alkaline phosphatase (IU/ml) | 231                      | 91                              | 56                            |

Diagnosing DIHS early is of utmost importance as delay in treatment can be fatal. Various diagnostic criteria are proposed for DIHS [Table 1].

The initial manifestation of DIHS is fever ( $38^{\circ}\text{C}$ – $40^{\circ}\text{C}$ ). Majority of the patients subsequently develop an erythematous morbilliform rash with facial edema. In some cases, especially when the offending drug is not withdrawn, a severe exfoliative dermatitis occurs.<sup>[1]</sup> Hepatomegaly, hepatitis, splenomegaly and hematological abnormalities are common, whereas mucosal involvement is minimal. Pneumonitis, interstitial nephritis and myocarditis are also reported. A high mortality rate of 10–20% is seen in DIHS due to multiorgan failure.

Withdrawal of the causative drug and administration of prednisolone 1–1.5 mg/kg body weight are curative in most cases. Steroids act by suppressing T cell stimulation and inhibiting release of cytokines.<sup>[9]</sup> Rapid tapering of steroids may result in rebound flare up.

Although there are many reports of DIHS with herpesvirus reactivation in the foreign literature, we did not come across any such reports from India.

## ACKNOWLEDGMENT

\*The virological part of the work was supported by the ICMR research grant of Dr. G. Arunkumar (File No. 5/8/7/15/2010/ECD-I).

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