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Association of Immunologically Confirmed Delayed Drug Reaction and Human Herpesvirus 6 Viremia in a Pediatric Case of Drug-Induced Hypersensitivity Syndrome

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Key Words

Drug-induced hypersensitivity syndrome · Drug reaction with eosinophilia and systemic symptoms · Hypersensitivity syndrome reaction · Trimethoprim/sulfamethoxazole · Human herpesvirus type 6 · Drug patch testing

We report a drug-induced hypersensitivity syndrome (DIHS) in a 2-year-old boy associating a human herpesvirus 6 (HHV-6) viremia and a drug cofactor demonstrated by patch testing. The

child was seen for febrile lower back pain. An epiduritis was suspected on clinical signs, biology and spine MRI. No bacteria were isolated from blood culture and lumbar puncture. Antibiotics were initiated with cefotaxime and rifampicin for 2 weeks. Then the child received oral rifampin and trimethoprim/sulfamethoxazole. The child had never received these antibiotics before. Four weeks later, he presented a progressive generalized rash associated with hyperthermia and severe asthenia and was referred to our unit. Exanthematous eruption, diffuse edema (fig. 1) and severe pruritus were observed on examination; in addition, polyadenitis and splenohepatomegaly were noted. The laboratory results revealed leukocytosis (WBC: 68,000/mm³, absolute eosinophil count: 1,800/mm³) with mononucleosis, cholestasis and hepatic cytolysis (alkaline phosphatase: 623 IU/l, aspartate transaminase: 430 IU/l, alanine transaminase: 265 IU/l). Polymerase chain reaction for HHV-6 performed on day 3 after the onset of the rash was positive in blood (65,000 copies/ml). Cytomegalovirus and Epstein-Barr virus serologies were negative. The diagnosis of DIHS was made, and all drugs were discontinued. Corticosteroid therapy was started (prednisone 1 mg/kg/day) resulting in a rapid resolution of DIHS symptoms without epiduritis recurrence. Corticoids were stopped within 2 weeks without relapse. Two months later, drug patch tests were performed with the commercialized forms and with the purified active agent of all suspected antibiotics (drugs series, Chemotechnique®, Sweden) in accordance with the guidelines for drug patch testing [1]. The patch tests were ap-

Fig. 1. Clinical photograph of a child with DIHS.

Fig. 2. Positive patch tests with the commercial formulation of trimethoprim/sulfamethoxazole (Bactrim) at 30% in white petrolatum and with the pure drug (cotrimoxazole) 1% in white petrolatum.

plied to the patient's upper back using Finn Chambers® on Scanpor™ tape. Readings were performed on days 2 and 3. These tests were positive (++) only with the commercial formulation of trimethoprim/sulfamethoxazole at 30% in white petrolatum and with cotrimoxazole at 1% in white petrolatum (fig. 2). The PCR for HHV-6 in blood was negative at that time.

In this case, the diagnosis of DIHS was based on the clinical signs and especially the edema of the face, the eosinophilia and the HHV-6 viremia [2]. Furthermore, positive patch tests confirmed the delayed drug reaction [3, 4]. DIHS is a severe cutaneous and systemic adverse drug reaction. The clinical characteristics of DIHS in children do not differ from those in adults [5]. There has been considerable confusion about the name of this syndrome also reported as drug hypersensitivity syndrome (DRESS), hypersensitivity syndrome reaction, drug-induced delayed multiorgan hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome – the DIHS mechanism is not fully elucidated; it is mediated by drug-specific T cells [6] and involves viral reactivation [7, 10].

HHV-6 and other viral reactivations – HHV-7, cytomegalovirus or Epstein-Barr virus – have been described to be associated with DIHS [7–10]. In this case, the HHV-6 viremia was high and was detected on day 3 after the onset. The child had no history of exanthema subitum. Thus, this HHV-6 viremia could have been associated with an HHV-6 primoinfection but HHV-6 serology was not done at that time [11]. Therefore, the likelihood of an association of an HHV-6 primoinfection and DIHS cannot be fully excluded. Anyway, this HHV-6 viremia was detected earlier than 2–3 weeks after the onset of the rash classically reported [2]. These data suggest that the HHV-6 infection in addition to drug intake is involved in the clinical feature of DIHS.

The relationship between the drug involved and HHV-6 in DIHS is supported by *in vitro* data on lymphocytes [6]. In our case, the positivity of the cotrimoxazole and commercialized trimethoprim/sulfamethoxazole dilution patch tests confirms the specific delayed drug reaction. Patch testing is the most studied test in delayed drug reaction. Currently it is a validated method to assess drug hypersensitivity reactions [1, 3, 4].

In this case, the concomitant HHV-6 viremia and the immunological delayed drug reaction demonstrated by patch testing in the same patient provide further evidence for the association of a drug and a viral factor in the pathogenesis of DIHS.

Disclosure Statement

The authors have no conflict of interest to declare.

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