Dear Editor,

Hypereosinophilia (i.e. a blood eosinophil count exceeding 1.5 \times 10^9/L) can be caused by various triggers including numerous allergic, infectious, and neoplastic disorders, and intrinsically cause tissue and organ damage, regardless of underlying cause. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome/drug-induced hypersensitivity syndrome (DIHS) is a rare, potentially life-threatening adverse drug-induced reaction with cutaneous manifestations and internal organ involvement.\(^1,2\) Reactivation of herpesviruses, including human herpesvirus-6 (HHV-6), HHV-7, cytomegalovirus (CMV), and Epstein–Barr virus (EBV), has been shown to play a role in DRESS/DIHS pathogenesis.\(^2,3\) Here, we report an infant case with severe hypereosinophilia accompanied by cutaneous, cardiac, and pulmonary manifestations, and reactivation of CMV and BK virus (BKV).

A previously healthy 17-month-old girl was referred to our institute on the 2nd day of illness because of high-grade fever and skin eruption. The patient had a cough and low-grade fever, and thus received pranlukast and azithromycin (AZM) from ten days and four days before the visit, respectively. The patient had no history of allergies, but had a family history of drug allergy. On admission, her temperature was 38.8 °C; blood pressure, 108/62; heart rate, 180; respiratory rate, 38; and oxygen saturation, 94% in room air. Reticulated erythema spread from trunk to extremities, but not into mucosa and conjunctivae. Physical examination revealed cervical lymphadenopathy without hepatosplenomegaly. Laboratory findings revealed leukocytosis and eosinophilia with white blood cell count of 39.8 \times 10^9/L with 54% eosinophils (21.5 \times 10^9/L), 20% neutrophils, 21% lymphocytes, and 1.0% atypical lymphocytes. The blood chemistry results including hepatic enzymes were not notable. Immunoglobulin G, A, M and E were within the age-appropriate range. Pathogens were not isolated from blood, urine, or stool culture. Rapid antigen tests for respiratory syncytial virus, mycoplasma, and adenovirus were negative. Serologic tests revealed absence of active infection of CMV, EBV, human parvovirus B19 (hPV-B19), human immunodeficiency virus, hepatitis viruses, and HHV-6.

Pneumonia was observed on the chest radiograph, and deteriorated with progression of desaturation, in spite of treatment with ampicillin/sublactam. A chest computed tomography scan on the 4th hospital day revealed a mixture of ground-glass opacities and nodular shadows with hilar lymphadenopathy (Fig. 1). Furthermore, an echocardiography revealed myocardial hypertrophy: IVSd, 7.9 mm (5.07 SD); LVIDd, 27.0 mm (0.40 SD); LVPWd, 7.3 mm (4.77 SD); LVIDs, 15.9 mm (−0.10 SD); and EF, 79.6%. Serum NT-proBNP was elevated: 1334 pg/ml [<125 pg/ml], but neither TnT nor CK-MB. Skin biopsy revealed evidence of eosinophilic infiltration into subcutaneous tissue without vasculitis. These results indicated multiple organ failure with hypereosinophilia.

Bone marrow examination revealed normocellular bone marrow with eosinophil proliferation (26.2%) but not immature or monoclonal cell proliferation, which indicated the absence of myeloproliferative neoplasms.\(^4\) Primary hypereosinophilic syndrome-associated gene analysis, including FISH and RT-PCR of the FIP1L1-PDGFRA fusion gene and direct sequencing of PDGFRα and PDGFRβ, were negative. Anti-nuclear and anti-neutrophil cytoplasmic antibodies were negative. Parasite examination of stool was negative. Serologic and sputum tests for Aspergillus were negative. There was no elevation of serum beta-D glucan. Multiplex PCR analysis for viral DNA of whole blood samples detected CMV and BKV DNA on the 2nd hospital day (52 copies/ml and 32 copies/ml, respectively), which increased on day 32 (1.0 \times 10^4 copies/ml and 37 copies/ml, respectively). On the 4th day, lymphocyte transformation test (LTT) for pranlukast and AZM were positive (2.31 and 2.16 [stimulation index: <1.81], respectively).

The patient was treated with administration of prednisolone (2 mg/kg/day) from the 6th day, and her symptoms, including fever, skin eruption, and desaturation, markedly improved on the next day. Hypereosinophilia also improved (0/L; leukocyte count, 9.5 \times 10^9/L) on the 9th day and did not relapse through tapering and withdrawal of prednisolone (Fig. 2A). Systemic corticosteroid therapy rapidly improved pneumonia and gradually improved myocardial hypertrophy; thus, the patient left the hospital on the 28th day. However, pulmonary arterial hypertension persisted and required treatment with sildenafil from 33 days after discharge. Cardiac catheterization revealed pulmonary arterial hypertension one month after discharge: mean pulmonary artery pressure (PAP), 45 mmHg [<25 mmHg]; pulmonary vascular resistance (Rp), 11.61 Um²; pulmonary artery wedge pressure (PAWP), 9 mmHg; systemic blood flow (Qs), 3.10 L/min/m², and improvement of that after four months: PAP, 28 mmHg; Rp, 2.79 Um²; PAWP, 11 mmHg; Qs, 5.74 L/min/m².

In this case, systemic corticosteroid therapy rapidly improved hypereosinophilia accompanied by improvement of associated manifestations, thus that therapeutic response and transient...
which are relatively short. A few cases with AZM-associated DRESS/DIHS were previously reported and these cases had relative short latency period (7–10 days). Furthermore, it was suggested that DRESS/DIHS might be correlated with multiple drug hypersensitivity (MDH). Therefore, we speculated that DRESS of this patient might be associated with MDH to AZM and pranlukast, although a possibility of non-specific reactions could not deny completely.

It was suggested that imbalance and abnormal proliferation of regulatory T cells would lead to eosinophilia, and expansion of regulatory T cells would occur far before DRESS/DIHS onset, which would contribute to reactivations of herpes viruses. Sequential reactivations of various herpesviruses have exclusively been demonstrated during the acute stage of DRESS/DIHS as with graft-versus-host diseases (GVHD). Our multiplex PCR system covered herpes simplex virus, HHV-6, -7, and -8, varicella-zoster virus, CMV, EBV, HPV-B19, JC virus, and BKV. Interestingly, in this case, CMV and BKV, but not HHV-6, were detected. Thus, we serologically confirmed that the patient had a past infection of CMV but not HHV-6, which might be the cause of lack of HHV-6 reactivation. BKV, which is a member of the polyomavirus family, infects most people subclinically during early childhood and, in immunocompetent individuals, the infection is completely asymptomatic; however, in immunocompromised patients including hematopoietic bone marrow transplant and kidney transplant patients/recipients, BKV reactivation followed by high-level viral replication could cause hemorrhagic cystitis and nephropathy. BKV reactivation was observed in patients with immunodeficiency or GVHD, furthermore, it was reported that active HHV6 reactivation might be associated with GVHD and co-reactivations of CMV and BKV. In this case, slight elevation of BKV DNA loads might lead to asymptomatic course, however BKV reactivation might support the hypothesis regarding clinical and immunological similarity between DRESS/DIHS and GVHD. The elevation of viral DNA loads, which indicated CMV and BKV viremias, spontaneously faded out after several months without a specific therapy (Fig. 2B).

In conclusion, we report an infant case of severe hypereosinophilia and systemic symptoms with MDH for AZM and pranlukast associated with reactivation of cytomegalovirus and BK virus. LTT and multiplex virus PCR were used to diagnose DRESS, and our case might provide novel insight regarding BKV reactivation in DRESS/DIHS.

Conflict of interest

The authors have no conflict of interest to declare.

References


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