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Case report

Evidence for human herpesvirus-6B infection of regulatory T-cells in acute systemic lymphadenitis in an immunocompetent adult with the drug reaction with eosinophilia and systemic symptoms syndrome: A case report

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ABSTRACT

We describe a fatal case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with human herpesvirus-6B (HHV-6B)-associated lymphadenitis and virus-associated hemophagocytic syndrome triggered by an over-the-counter medication to treat respiratory and influenza-like symptoms. Histologically, the structure of the lymph node was disrupted with infiltration of large lymphocytes carrying intranuclear acidophilic inclusion bodies. Immunohistochemistry and real-time PCR analysis revealed that these large lymphocytes were positive for HHV-6B. Numerous HHV-6 particles were detected in the inclusion body of the lymphocytes by electron microscopy. Interestingly, immunohistochemistry revealed that HHV-6B-infected cells in the lymph node were CD3(+), CD4(+), CD25(+), and FoxP3(+) T cells, indicating a phenotypic resemblance to regulatory T-cells. This case provides direct evidence of HHV-6 infection in CD25(+)/FoxP3(+) T cells in a case of acute lymphadenitis of DRESS syndrome, suggesting a significant role of HHV-6 infection of regulatory T-cells in the pathogenesis of DRESS syndrome.

1. Why this case is important

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is a severe adverse drug-induced reaction with symptoms including fever, skin eruption, hypereosinophilia and internal organ involvement [1]. Several weeks after taking the causative medicine, symptoms start with fever followed by erythema often progressing to exfoliative dermatitis. Lymphadenopathy or lymphadenitis and periorbital and/or facial edema is observed frequently, and reactivation of human herpes virus is found in almost all cases. Discontinuing the causative drugs and administration of anti-inflammatory drugs, including corticosteroids, reduces the symptoms in many cases. However, in other cases the prognosis can be poor. Reactivation of herpes viruses such as human herpesvirus-6 (HHV-6), Epstein–Barr virus, and cytomegalovirus is observed in almost all cases of DRESS syndrome. Indeed, HHV-6 infection is considered as an important diagnostic criterion for DRESS/DIHS [2,3].

HHV-6 is a member of the β-herpesvirus subfamily that includes cytomegalovirus and HHV-7. HHV-6A and -6B that were previously identified as two variants of HHV-6, are now recognized as distinct species [4]. HHV-6 is ubiquitous all over the world, and its primary infection occurs before 2 years of the age causing exanthema subitum [5]. HHV-6 is reactivated in immunocompromised hosts, and associated with neurological disorders, febrile illness, and hemophagocytic syndrome. Clinical studies have reported the presence of HHV-6-associated lymphadenitis in patients with

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drug-associated lymphadenopathy [1]. However, the role of HHV-6 infection in the pathogenesis of DRESS syndrome is less well known.

Here, we report an autopsy of a DRESS syndrome case with severe HHV-6B-associated lymphadenitis and fatal virus-associated hemophagocytic syndrome. In this case, HHV-6B-infected cells expressing CD3, CD4, CD25, and FoxP3, were detected in the lymph node. Thus, HHV-6B infection of lymph node cells phenotypically similar to regulatory T-cells (Tregs) may play an important role in the pathogenesis of DRESS syndrome.

2. Case description

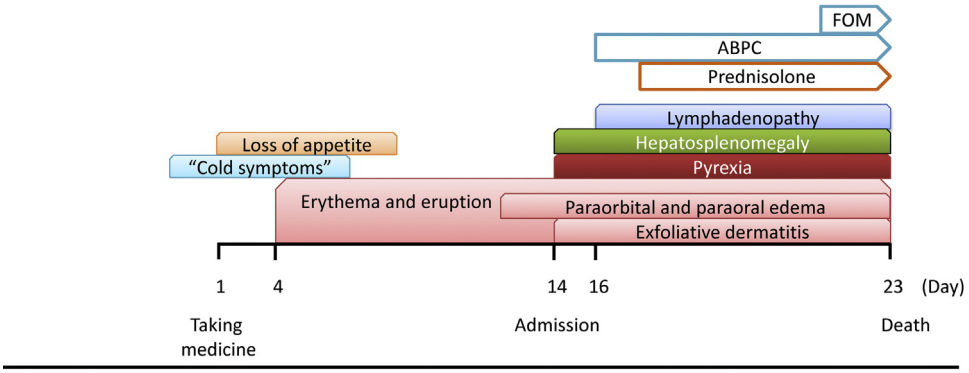
A 58-year-old Japanese man with a history of asthma, type-2 diabetes mellitus, and hypertension was admitted to our hospital because of fever, fatigue, and erythema, followed by confluent skin rash and elevated serum levels of liver enzymes (Fig. 1). Fourteen days before the erythema, he had taken an over-the-counter medicine to treat cold and influenza symptoms, which contained acetaminophen, clemastine fumarate, dihydrocodeine phosphate, noscapine, dl-methyl ephedrine hydrochloride, potassium guaiacolsulfonate, anhydrous caffeine, benfotiamine and lysozyme hydrochloride. He had experienced a skin rash after taking the same medicine 3 years earlier.

At the time of admission, he had paraorbital and paraoral edema, and swollen lymph nodes. Ultrasonography revealed hepatosplenomegaly. The notable laboratory values were high levels of white blood cells (15,600/mm^3), eosinophils (2106/mm^3), and lactic dehydrogenase (883 IU/L). Atypical lymphocytes were detected in the peripheral blood. *Staphylococcus* sp. infection was identified in skin lesion samples, for which antibacterial therapy was administered. However, he died on post-admission day 12 because of multiple organ failure, approximately 23 days from the onset of the skin symptoms. C-reactive protein increased to 22.0 mg/dL before death.

An autopsy revealed that the patient had generalized lymphadenopathy with hepatosplenomegaly. Exfoliative dermatitis with epidermolysis and blisters were observed on the trunk and limbs, and epithalaxia was severe in the oral cavity and respiratory tract. Histological analysis revealed that the structure of the lymph node was disrupted with remarkable paracortical expansion and vanishing lymphoid follicles. There were numerous large lymphocytes carrying intranuclear acidophilic inclusion bodies that had a peripheral halo (Fig. 2). These cells were observed frequently in the germinal center and sinus in the lymph node. Cells with inclusion bodies were also observed in the spleen, liver, bone marrow, and skin (data not shown). Bone marrow was hyperplastic with numerous hemophagocytic macrophages and infiltration of large lymphocytes. Immunohistochemical analysis showed that the large lymphocytes with inclusion bodies detected in the lymph nodes and other organs, were strongly positive for HHV-6 immediate early (IE) and 101K proteins (Fig. 2) [6,7]. HHV-6-associated hemophagocytic syndrome was diagnosed on the basis of the presence of HHV-6-infected cells and severe erythrophagocytosis in the bone marrow.

Immunohistochemistry revealed that the HHV-6-infected cells in the lymph nodes were CD3(+), CD4(+), CD8(−), CD20(−), CD25(+), CD56(−), CD68(−), and FoxP3(+), indicating that these cells were phenotypically similar to Tregs (Figs. 2 and 3) [8,9]. Electron microscopy revealed that inclusion bodies in the cells were composed of proteinaceous materials and numerous virions with polygonal nucleocapsids (Fig. 4). HHV-6 DNA was detected using real-time PCR in the lymph node (6.22×10^5 copies/10^6 cells), spleen (1.85×10^5 copies/10^6 cells), liver (5.7×10^4 copies/10^6 cells), gastrointestinal tract (1.02×10^5 copies/10^6 cells), skin (6.7×10^4 copies/10^6cells), kidney (1.3×10^4 copies/10^6cells) and lung (2.1×10^4 copies/10^6 cells) [10]. A real-time PCR for typing HHV-6 identified the virus to be HHV-6B, but not HHV-6A [11]. Multivirus real-time PCR, a 96-well plate system capable of simultaneously identifying 163 different viruses, including all human herpes viruses, revealed the presence of no virus other than HHV-6 in the lymph node samples [12]. *Staphylococcus* sp. were isolated from skin and lung cells in culture; however, histologically, there were no obvious signs of a bacterial focus in any organ.

Taking together the patient's entire clinical history and the autopsy report, the diagnosis was DRESS syndrome triggered by the over-the-counter medicine for cold and influenza that led to



Laboratory data

WBC (/μl)		15600	7900	6700	5400	
Eosinophils (/μl)		**2106**	**909**	**737**	**351**	
Atypical lymphocyte (/μl)		0	79	**134**	**486**	
Plt (x 10^3)		239	213	134	59	
T-Bil (mg/dl)		1.9			5.1	17.9
AST (IU/μl)	200	40			21	70
ALT (IU/μl)	140	73			21	55
LDH (IU/μl)	883	704			666	1374
γ-GTP	307	336			107	

Fig. 1. Clinical course of the case. On day 1, the patient took an over-the-counter medicine to treat cold and influenza symptoms. Fever, fatigue, and lymphadenopathy were persistent from day 4 onwards, and erythema progressed to exfoliative dermatitis by day 14. He was admitted to the hospital on day 14. On day 16, *Staphylococcus* sp. infection was diagnosed from cultures prepared from skin lesion samples, and antibacterial therapy was administered. The patient died on day 23 (12 days after admission) because of multiple organ failure. ABPC: Ampicillin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, FOM: Fosfomycin, γ-GTP: γ-glutamyltranspeptidase, LDH: lactic dehydrogenase, Plt: blood platelet count, T-Bil: total bilirubin, WBC: white blood cell count.