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Carbamazepine-induced DiHS/DRESS syndrome leading to hemophagocytic lymphohistiocytosis in a woman carrying the HLA-B*1301 gene

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Here, we present a case of hemophagocytic lymphohistiocytosis secondary to DiHS/DRESS syndrome after using carbamazepine in a woman who carried the HLA-B*1301 gene. A 66-year-old woman developed skin allergies and a high fever 20 days after taking carbamazepine for tinnitus. During hospitalization, there were three peaks of skin lesions, including patches and plaques, even blister and skin loosening. Moreover, skin lesions were accompanied by liver damage and hemophagocytic lymphohistiocytosis syndrome. She was cured after the application of systemic glucocorticoid methylprednisolone, antibiotics, and ganciclovir to prevent activation of the herpes virus. Moreover, she got support from plasma, gamma globulin, and exogenous fibrinogen. According to the medical history, physical examination, and histopathological examination, the patient was diagnosed as carbamazepine-induced DiHS/DRESS syndrome, resulting in hemophagocytic lymphohistiocytosis. Furthermore, the blood analysis showed she carried the HLA-B*1301 gene.

1. Introduction

Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but life-threatening reaction induced by drugs such as phenytoin, phenobarbital, carbamazepine, valproate, and allopurinol. It is an acute severe adverse drug reaction with fever, skin rash, and visceral involvement triad (Shiohara and Mizukawa 2019). The disease is characterized by skin rashes, fever, hematological abnormalities, lymphadenopathy, and organ failure, i.e. hepatic dysfunction (Shiohara and Mizukawa 2019). The exact incidence rate of DiHS/DRESS is unknown, and the DRESS induced by antiepileptic drugs and sulfonamides is about 1/10000 (Hiransuthikul et al. 2016). However, its mortality rate is as high as up to 10% (Watanabe 2018). The clinical manifestations are diverse and easy to be misdiagnosed.

Carbamazepine has been widely used as an anti-epileptic medicine in patients with neurological diseases. Many reports have shown adverse reactions, i.e. DiHS/DRESS syndrome due to the use of carbamazepine. However, there is no previous report about hemophagocytic lymphohistiocytosis due to carbamazepine. Therefore, we are presenting a case of hemophagocytic lymphohistiocytosis secondary to DiHS/DRESS syndrome after using carbamazepine in a patient who carried the HLA-B*1301 gene. Our case report will provide a reference for clinical treatment of carbamazepine-induced DiHS/DRESS syndrome.

Abbreviations
DiHS: Drug-induced hypersensitivity syndrome; DRESS: drug reaction with eosinophilia and systemic symptoms; CT: Computed tomography; HHV: Human herpesvirus; PCR: Polymerase Chain Reaction; HLA: human leukocyte antigen; MPE: maculopapular exanthema; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; MHC: major histocompatibility complex; HLH: Hemophagocytic lymphohistiocytosis; sHLH: Secondary HLH; VAHS or IAHS: virus-(infection) associated hemophagocytic syndromes; PET: positron emission tomography.

2. Case presentation

The female patient was 66 years old with a weight of 51 kg, and she had no history of other diseases. She went to The First Affiliated Hospital of Anhui Medical University with the symptoms of a rash, which initially appeared in the abdomen and then spread all over the body. She had a fever of 39 °C and itches for 12 days. Due to tinnitus, she had taken carbamazepine for 20 days until skin symptoms developed. The study was approved by The First Affiliated Hospital of Anhui Medical University. Informed consent was obtained.

The physical examination at day 1 of hospitalization showed a temperature of 39.2 °C, heart rate of 120 beats/min, respiratory rate of 20 breaths/min, blood pressure of 128/78 mmHg, and PO_2 content of 72.6 mmHg, PCO_2 content of 21.5 mmHg. There were patches and plaques with uncertain boundaries that tended to merge and were non-bleachable on the widespread erythematous layer. Moreover, facial edema and lymphadenopathy were noted in the physical examination. Laboratory tests revealed increased white blood cells, decreased eosinophils, and liver damage (Table 1). A computer tomography (CT) scan demonstrated pulmonary infections. Therefore, the patient received the systemic glucocorticoid methylprednisolone, gamma globulin, and antibiotics by intravenous injection.

Interestingly, we observed three peaks of skin lesions in this patient. On the first peak of skin lesion (day 7), fever, rashes, and liver symptoms had almost disappeared (Table 1), On the second peak, fever and rashes reappeared in the second week (Fig. 1A), accompanied by apparently increased liver enzymes and significant decreases of red blood cell count, white blood cell count, platelets, and even fibrinogen (Table 1). Abdominal skin biopsy revealed lymphocytic infiltration, keratinocyte apoptosis, dyskeratosis, extravasation of erythrocytes, and rare eosinophils at the dermoepidermal junction (Fig. 1B). Bone marrow biopsy found hemophagocytosis in bone marrow (Fig. 1C). Soluble CD25 in peripheral blood was increased up to 3029 U/mL on day 15. In the fourth week, we did not change the dose of glucocorticoid or any other medicine, while patches and plaques raised again from legs for the third time. After that, they spread to the whole body within

Table 1: Laboratory tests

Tests	Values (Day 1)	Values (Day 13)	Values (Day 24)	Values (Day 29)	Values (Day 39)	Reference values
Red blood cell count ($\times10^{12}$/L)	4.58	2.74	3.29	2.66	2.83	3.80-5.10
Hemoglobin (g/L)	132	93	108	91	89	115-150
White blood cell count ($\times10^{9}$/L)	28.58	7.75	5.33	4.03	5.23	3.50-9.50
Neutrophils ($\times10^{9}$/L)	17.97	3.96	4.28	3.09	4.33	1.80-6.30
Lymphocytes (%)	32.64	37.34	14.44	21.64	15.14	20.00-50.00
Monocytes (%)	3.44	10.14	2.84	1.54	1.74	3.00-10.00
Eosinophils ($\times10^{9}$/L)	0.00	0.03	0.12	0.00	0.02	0.02-0.52
Platelets ($\times10^{9}$/L)	282	42	141	64	104	125-350
C-reactive protein (mg/L)	43.75	5.40	-	4.6	19.3	0.00-10.00
Aspartate aminotransferase (U/L)	134	897	-	48	40	14-36
Alanine aminotransferase (U/L)	168	730	-	51	50	9-52
γ-glutamyl transferase (U/L)	717	612	-	486	1805	12-43
Lactate dehydrogenase (mmol/L)	>2150	1332	-	450	433	313-618
Urea (μmol/L)	5.1	4.28	-	8.85	3.22	3.10-8.80
Creatinine (U/L)	74.1	48.0	-	43.0	35.0	41.0-81.0
Creatine kinase (U/L)	31	-	-	-	-	30-135
Creatine kinase isoenzyme (U/L)	18	-	-	-	-	0-26
Blood glucose (mmol/L)	4.37	6.05	-	3.96	3.88	3.89-6.11
Procalcitonin (ng/ml)	0.632	0.306	0.113	0.262	0.263	0.000-0.046
Interleukin- 6 (pg/ml)	25.80	4.76	26.51	6.56	34.26	0.00-7.00
Prothrombin time (s)	14.6	15.1	11.6	11.2	12.8	11.0-16.0
Prothrombin time activity (%)	78.00	55.3	95	104.40	73.90	70.00-120.00
Fibrinogen (g/L)	3.06	0.74	1.36	1.52	1.88	2.00-4.00

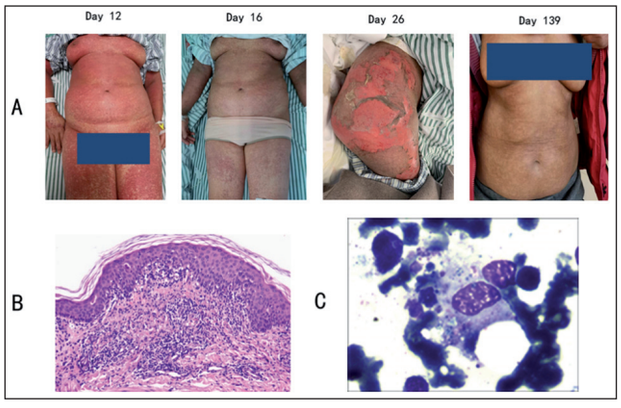

Fig. 1: Images of the patient. (A) The skin lesions in different stages. (B) Skin biopsy showed infiltration of lymphocytes in the dermoepidermal (Hematoxylin eosin stain, original magnification:×200). (C) Bone marrow biopsy found hemophagocytosis (Bone marrow smear, original magnification: ×1000).

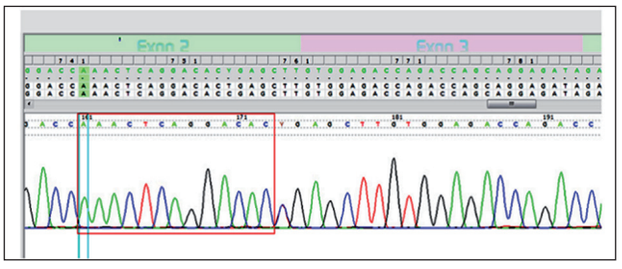

Fig. 2: Gene sequencing results of the patient.

the next six days, even blister and skin loosening appeared in the buttocks area (Fig. 1A). The decrease of platelet amount and fever of 38.8 °C was observed again at the same time, but liver enzymes were always at a normal level (Table 2).

During the whole treatment, the patient always received systemic glucocorticoid methylprednisolone, antibiotics, and ganciclovir that was used to prevent the activation of the herpes virus. She also got support from plasma, gamma globulin, and exogenous fibrinogen. Human herpesvirus (HHV)-6 determined by Polymerase Chain Reaction (PCR) was negative on Day 15 and 29. We further sent her blood sample for the human leukocyte antigen (HLA) genotype test, and the results showed that she carried the HLA-B*1301 gene (Fig. 2).

Overall, the patient was diagnosed as carbamazepine-induced DiHS/DRESS syndrome leading to hemophagocytic lymphohistiocytosis based on her medical history, physical examination, and a histopathological examination (Tables 2 and 3). This patient was cured after the use of systemic glucocorticoid, gamma globulin, plasma, and antibiotics.

3. Discussion

Carbamazepine is one of the most common antiepileptic drugs. Approximately 5 to 10% of patients who used carbamazepine would develop carbamazepine-induced cutaneous reactions (Hirsch et al. 2008). Although most were considered mild, such as maculopapular exanthema (MPE) and Erythema multiforme, these cutaneous reactions can cause considerable discomfort to the patient and often lead to the discontinuation of carbamazepine treatment (Yang et al. 2015; Pavlos et al. 2015; Amstutz et al. 2014).

Stevens-Johnson syndrome (SJS) and the more severe form, toxic epidermal necrolysis (TEN), are two allergic reactions induced by carbamazepine therapy. Another severe and potentially life-threatening hypersensitivity reaction induced by carbamaze-

Table 2: Diagnostic criteria for DiHS/DRESS syndrome

RegiSCAR study group		Japanese consensus group	
Haematological abnormalities; eosinophilia > 1.5 × 10^9/L(or) atypical lymphocytes		Typical DRESS (presence of all 7 criteria): atypical DIHS (all criteria present except lymphadenopathy and HHV-6 reactivation)	
1. Hospitalization	Yes	1. HHV-6 reactivation	
2. Reaction suspected to be drug related	Yes	2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug	Yes
3. Acute rash	Yes	3. Maculopapular rash developing > 3 weeks after starting drug	Yes
4. Fever above 38°C	Yes	4. Fever above 38°C	Yes
5. Enlarged lymph nodes involving at least two sites	Yes	5. Lymphadenopathy	Yes
6. Involvement of at least one internal organ	Yes	6. ALT > 100 U/L or other organ involvement	Yes
7. Blood count abnormalities Lymphocytes above or below laboratory limits Eosinophils above laboratory limits (in percentage or absolute count) Platelets below laboratory limits	Yes	7. Leukocyte abnormalities (at least one) Leucocytosis (> 11 × 10^9/L) Atypical lymphocytosis (> 5%) Eosinophilia (1.5 × 10^9/L)	Yes

DRESS, drug rash with eosinophilia and systemic symptoms; RegiSCAR, European registry of severe cutaneous adverse reactions, DiHS, drug-induced hypersensitivity syndrome; HHV-6, human herpesvirus 6; ALT, alanine aminotransferase.

Table 3: Histiocyte Society HLH-2004 diagnostic criteria

The diagnosis HLH requires that either 1 or 2 below are fulfilled: (1) A molecular diagnosis consistent with HLH; (2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)	
(A) Initial diagnostic criteria	
Fever	Yes
Splenomegaly	
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):	
Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L)	Yes
Platelets < 100 × 10^9/L	Yes
Neutrophils < 1.0 × 10^9/L	
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥265 mg/dL)	
Fibrinogen ≤ 1.5 g/L	Yes
Hemophagocytosis in bone marrow or spleen or lymph nodes	Yes
(B) New diagnostic criteria	
Low or absent NK-cell activity	
Ferritin ≥ 500 mg/L	
Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2400 U/mL	Yes

pine is known as a drug reaction with eosinophilia and systemic symptoms. The underlying mechanism of this hypersensitivity is unclear, but it is believed to involve the interaction between drugs or drug-derived molecules and major histocompatibility complex (MHC) expressed on the cell surface to stimulate the immune system, especially T cells and eosinophils (Pavlos et al. 2015; Amstutz et al. 2014).

For this patient, the diagnosis of DiHS/DRESS was all established according to the RegiSCAR criterion and the Japanese consensus group DRESS criteria (Shiohara et al. 2007; Kardaun et al. 2007). To meet the DRESS definition, patients must have three of the four main RegiSCAR criteria shown in Table 2. The Japanese consensus group developed another diagnostic criterion. According to these criteria, seven of the criteria in Table 2 or all of the first five criteria must be present for the diagnosis. Although the first criterion of the Japanese consensus group, HHV-6 test result, was negative, the patient in our case report met all of the other criteria. In addition, her symptoms met all of the RegiSCAR study group scoring system criteria. As a result, she was diagnosed as DiHS/DRESS syndrome.

There were usually two peaks of skin lesions in typical DiHS/DRESS (Morito et al. 2014). In most cases, the second peak, caused by HHV-6 infection, is known as activation. However, in our case, the patient received the HHV-6 tests twice in different stages and both of the results were negative. There might be a correlation between the appropriate use of systemic glucocorticoids and the anti-virus drug, ganciclovir (Chee and Jap 2011). The three peaks of skin lesions were uncommon in patients with DiHS/DRESS, which may be caused by the delayed reaction of carbamazepine or the multiple reactions of carbamazepine with other antibiotics for treating pulmonary infection. Notably, we also found another special phenomenon in which the eosinophils in peripheral blood were always at a low level, even without eosinophil count. Eosinophilia did definitely not appear in drug eruptions in a previous evaluation of inpatient adverse cutaneous drug eruptions (Romagosa et al. 2001), in which only 18% had peripheral eosinophilia (>700 eosinophils/µl) with tissue eosinophilia in 24%. Similarly, histopathologic examination of 108 drug-induced cutaneous eruptions noted eosinophilic infiltration in only 50% cases (Gerson et al. 2008). Interestingly, increased eosinophilia count was observed around 120 days in the follow-up after discharge. After increasing the dose of glucocorticoid, this phenomenon was controlled.

Hemophagocytic lymphohistiocytosis (HLH) is a disease that is difficult to diagnose and treat. HLH comprises two different conditions that might be difficult to distinguish from one to another, including primary and secondary forms (Esteban et al. 2017; Janka et al. 1998). Secondary HLH (sHLH) may occur due to the strong immunological activation of the immune system. sHLH

has been described in immunocompromised hosts in association with viral infections and virus-(infection) associated hemophagocytic syndromes (VAHS or IAHS) (Janka et al. 1998; Risdall et al. 1979). Diagnosis of HLH was all established according to the Histiocyte Society HLH-2004 diagnostic criteria (Henter et al. 2007), and 6 out of the 8 criteria for sHLH were fulfilled. sHLH may also develop during malignancies or may develop during the treatment of known malignancies (Janka et al. 1998). For the patient, we have done positron emission tomography (PET)-CT to exclude the exhibition of tumors. What's more, we also observed that sHLH was accompanied by the regeneration of skin lesions. After the skin lesion was controlled, blood cell lines also returned to a normal level. Therefore, we considered that sHLH was caused by a drug reaction induced by carbamazepine.

Recently, HLA variants have been associated with an increasing number of drug hypersensitivities (Type B adverse drug reactions). The strongest HLA-associated drug responses are HLA-B*15:02 and carbamazepine-induced SJS/TEN in Asian populations, HLA-B*57:01 and abacavir hypersensitivity syndrome in the Caucasian population, and HLA-B*58:01 in allopurinol hypersensitivity syndrome and SJS/TEN (Michels and Ostrov 2015).

However, our patient carried the HLA-B*1301 gene. The HLA-B*1301 gene was reported to be correlated with occupational trichloroethylene hypersensitivity syndrome (Wang et al. 2019), dapsone hypersensitivity syndrome in patients with leprosy (Liu et al. 2019) and phenytoin-SJS/TEN (Hung et al. 2010), and it may be correlated with hypersensitivity to a drug reaction. Moreover, since OXC, PHT, and LTG, which possess an aromatic ring just as CBZ does, the HLA-B*1301 gene may be the genetic reason for DiHS/DRESS in this patient.

To our knowledge, this is the first case report in the English-language literature that carbamazepine-induced DiHS/DRESS syndrome led to the development of hemophagocytic lymphohistiocytosis in a woman carrying the HLA-B*1301 gene. The patient showed improvement after treatment and recovered. We hope our experience can help others to understand DiHS/DRESS syndrome better in the clinical manifestations, treatment, and genetic labels.

Ethics approval and consent to participate: The study was approved by The First Affiliated Hospital of Anhui Medical University. Informed consent was obtained.

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Competing interests: There are no potential conflicts of interest to disclose.

Author Contributions: Ze Guo was responsible for the clinical studies, experimental studies, manuscript preparation; JinPing Gao was responsible for the data acquisition; Xing Fan and AnPing Zhang were responsible for the definition of intellectual content; ZaiXing Wang was responsible for the literature research; XianFa Tang was responsible for the data analysis; Yue Chen was responsible for the statistical analysis; HuaYang Tang was responsible for the study design, manuscript editing; Hui Li was responsible for the guarantor of integrity of the entire study, manuscript review. All authors read and approved the final manuscript.

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