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Case Report

Hemophagocytic lymphohistiocytosis associated with oxcarbazepine

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Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening multisystem disorder. Reports of the disorder as a side effect of drugs are extremely rare. We report the case of a 3-year-old boy with a history of epileptic seizures in which oxcarbazepine was added to treatment for the last 35 days and dose had been increased. For 10 days he had a fever, hepatosplenomegaly, rash, edema and other systemic symptoms. He was diagnosed with HLH after bone marrow examination. Oxcarbazepine treatment was terminated after the intravenous immunoglobulin treatment. The next day, clinical and laboratory results had improved. This is the first HLH report of an association with oxcarbazepine. Bone marrow aspiration may be indicated to confirm the diagnosis when facing a patient with systemic symptoms after newly added antiepileptic drug treatment.

Key words: epilepsy, hemophagocytic lymphohistiocytosis, oxcarbazepine.

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon life-threatening multisystem disorder that is more often seen in children. The disease may emerge in primary form with genetic impairment, or it may be triggered secondarily by immune system activation due to an underlying infection, malignancy, drug use, or immune failure.[1] The underlying causes are extremely variable, and the inappropriate stimulation and proliferation of cytotoxic lymphocytes and macrophages can trigger blood cell phagocytosis, damage multiple organs and there is a high risk of mortality.[1,2] Treatment includes the use of immunosuppressive, immunomodulatory, and cytostatic drugs and is focused on the underlying cause. Therefore, to increase the survival rates of affected patients, rapid diagnosis and treatment initiation are of great importance. Reports on HLH as a side effect of drugs are rare, and this is the first report of an association with oxcarbazepine.[2,3] Here, we report a patient diagnosed with HLH attributed to oxcarbazepine intake.

Case Report

A 3-year-old boy who had been followed for 1 year with a diagnosis of epilepsy presented to our clinic with a fever, vomiting, and listlessness. The patient was taking sodium valproate (Depakin) and clonazepam (Rivotril). His seizure frequency was 1-3 per week. For the previous 35 days, oxcarbazepine (Trileptal) had been added to the treatment, and for the last 16 days, the oxcarbazepine dose had been increased to 600 mg/day (40 mg/kg/day). For 10 days, the patient had had a temperature >38°C and persistent diarrhea. The patient had been given acetaminophen, but his complaints persisted, so he was brought to the Emergency Department. Physical examination revealed a temperature of 38.3°C, pale skin color, mild edema of the body, two bilateral submandibular palpable lymph nodes measuring approximately 2×1 cm, and hepatosplenomegaly. The blood test

results were hemoglobin 9.8 g/dl (10-14 g/d), WBC 4,620/mm^3 (3,390-8,860/mm^3), platelet count 103,000/mm^3 (171,000-388,000/mm^3), absolute neutrophil count 40/mm^3 (1,500-5,000/mm^3), eosinophil count 30/mm^3 (40-600/mm^3), C-reactive protein 12.7 mg/dl (1-15 mg/dl), aspartate aminotransferase (AST) 117 (normal 0–40) U/L, alanine aminotransferase (ALT) 54 (normal 0–35) U/L, and lactate dehydrogenase 664 (normal 120–246) U/L. Total and direct bilirubin levels were normal. Serum electrolyte levels were normal. Treatment was started with the existing anti-epileptics and intravenous ampicillin–sulbactam and amikacin. On the second day of hospitalization, a rash and widespread edema developed. The patient's total protein and albumin levels were normal. No proteinuria was seen. Viral serology tests for Epstein Barr virus, cytomegalovirus, influenza, rotavirus and adenovirus were negative, as were the results for Brucella and Salmonella. Anti-smooth muscle antibodies and antinuclear antibodies were negative and no arthritis was detected; therefore autoimmune conditions were not considered primary. There was no growth in blood or stool cultures. Erythrocyte sedimentation rate and immunoglobulin (Ig) levels were normal. The triglyceride level was 283 mg/dl (0–150) mg/dl, the fibrinogen level was 81.63 mg/dl (125-400), and ferritin was 971 (10–322) ng/ml. Natural killer (NK) activity and soluble IL 2 receptor values could not be measured in our laboratory. Based on the laboratory results and clinical findings, HLH was considered. On the 7th day of admission, a bone marrow aspiration showed hemophagocytic cells and no blasts were seen. (Fig. 1). Intravenous immunoglobulin 1 g/kg/day was administered for 2 days. As the patient's complaints continued, the oxcarbazepine treatment was terminated on the 10th day of hospitalization. The next day, the fever started to recover, and the AST and ALT levels started to decrease. On the 13th day, the edema resolved. Consequently, the patient was diagnosed with HLH related to oxcarbazepine.

Informed consent in this report was obtained from the patient's family.

Discussion

The diagnosis of HLH caused by erythrophagocytosis is based on the clinical, hematological, and bone marrow aspiration findings. As shown in Table I, the diagnostic criteria are fever, hepatomegaly and/or splenomegaly, pancytopenia/bicytopenia, high triglyceride level, low fibrinogen level, and hemophagocytosis seen in the bone marrow or lymph nodes.[1] The presence of five of these eight criteria is necessary.[1,2] Our patient had six of the criteria, with a severe clinical course accompanied by fever, bicytopenia, edema, and hepatosplenomegaly, with laboratory findings of hemophagocytosis, hypofibrinogenaemia, hypertriglyceridaemia, and a high ferritin level. There was no similar family history

Table I. Diagnostic Criteria for HLH.

1.	Fever
2.	Splenomegaly
3.	Cytopenia (cytopenia in at least two of the three cell lines)
	Hemoglobin (Hb) <9 g/dl; for neonates, Hb <2 g/dl
	Thrombocytes <100,000/mm^3
	Neutrophils <1,000/mm^3
4.	Hypertriglyceridaemia or hypofibrinogenaemia
	Fasting triglycerides >265 mg/dl
	Hypofibrinogenaemia <1.5 g/L
5.	No or reduced NK activity
6.	Ferritin ≥500 μg/L
7.	Soluble CD25 ≥2400 U/ml
8.	Hemophagocytosis observed in the bone marrow, lymph nodes, or spleen with no malignancy

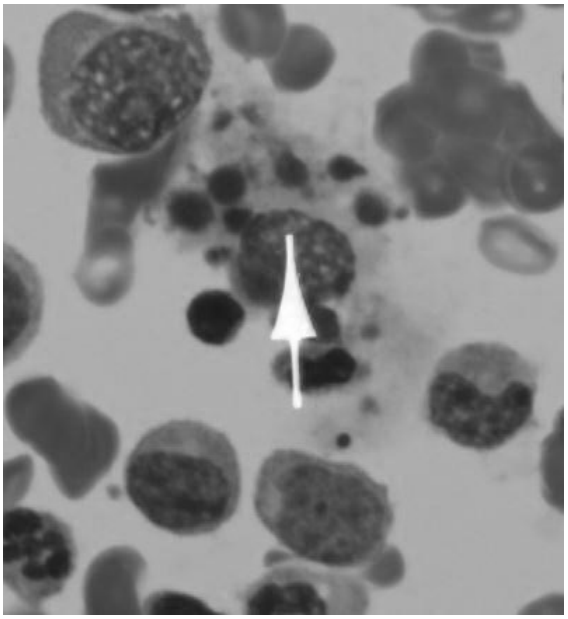

Fig. 1. Bone marrow aspirate contains phagocytic histiocytes (white arrow)

and no evidence of other diseases. Drug rash, eosinophil, and systemic symptoms (DRESS) syndrome is a life threatening, severe cutaneous adverse drug reaction characterized by hematological abnormalities, including fever, skin rash, eosinophils or atypical lymphocytes, and multi-organ involvement. DRESS syndrome is the condition most often confused with HLH. In our case, the findings of hypereosinophilia, fever, skin rash, and impaired liver function excluded DRESS syndrome. Furthermore, bicytopenia is not a usual feature of drug hypersensitivity syndrome [4]. Oxcarbazepine (OXC) is a 10-keto analogue of carbamazepine (CBZ), but there are important differences between the two drugs. While OXC is metabolized almost completely to the keto form, a pharmaceutically active monohydroxy derivative is also produced. This monohydroxy derivative undergoes glucuronidation via the action of 5'- diphospho-glucuronosyltransferase on uridine and is not affected by the cytochrome P450 system through any of the enzymatic pathways of OXC metabolism. OXC and most of its metabolites are excreted in urine. In comparison, most of the side effects of CBZ result from the oxidisation of 10,11-epoxide derivatives. Consequently, OXC is safer than CBZ and better tolerated. According to the Food and Drug Administration (FDA), in the normal population, side-effects related to severe systemic drug reactions induced by OXC occur in 0.5–6/1,000,000 people per year [3-5]. To our knowledge, this case is the first report of HLH due to OXC. IgA deficiency and an associated drug allergy are a possibility. Nevertheless, hypogammaglobulinaemia is often related to DRESS syndrome.[4,5] However, our patient had no history of recurrent infection or atopy, and the serum IgA level was within the normal range.

Secondary HLH is frequently associated with infections, autoimmune disorders, or malignancies. Secondary HLH may develop in various immunodeficiencies, including Chediak–Higashi syndrome (CHS), Griscelli syndrome (GS) type 2, Hermansky–Pudlak syndrome (HPS) type 2.[8] In our patient there was no history of recurrent infections and no dermatological findings such as oculocutaneous albinism and, immunodeficiencies were excluded. Juvenile idiopathic arthritis is another cause of secondary HLH.[8] In this case, there was no complaint from arthralgia and no clinical findings of arthritis. Bilirubin and electrolyte levels were normal, no soap bubble cell detected in bone marrow aspirate and rapidly improvement after the withdrawal of the OXC, metabolic conditions were excluded. Rapid improvement after the withdrawal of the OXC, no blasts in bone marrow aspirate and decreased size of lymph nodes after the treatment ensured that possible malignancies were excluded.

Similar to our case, there are two cases of HLH related to the anticonvulsant lamotrigine and one case related to phenobarbital.[6,7,9] In our patient, as in those three cases, clinical recovery followed termination of the drug. In conclusion, HLH associated with anti-epileptic drugs has rarely been reported. Awareness of this potentially life-threatening syndrome is extremely important so that clinicians can take life-saving measures. In this context, when HLH is suspected, anti-epileptics that could be causing this condition must be stopped rapidly. In this case, the most efficacious and rapid response was obtained by withdrawal of the OXC and there were significant improvements in his clinic findings. This report is of value because it is the first report of a patient who developed HLH associated with OXC.

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