LETTER TO THE EDITOR
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Clinical Analysis of Two Cases of Histiocytic Necrotizing Lymphadenitis Complicated with Macrophage Activation Syndrome

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Dear Editor,

Histiocytic necrotizing lymphadenitis (HNL), a benign and systemic disease with self-limiting properties, is also known as Kikuchi-Fujimoto disease (KFD) or subacute necrotizing lymphadenitis (SNL).[1] It was first reported by Masahiro Kikuchi and Yoshishige Fujimoto in 1972 and is more common in adults. It typically presents with fever and tender superficial lymphadenopathy, often accompanied by non-specific symptoms such as rash, vomiting, abdominal pain, weight loss, fatigue, and joint pain.[2-4] Macrophage activation syndrome (MAS) is a severe complication of HNL and a major cause of death in HNL patients.[5] By retrospectively analyzing the clinical data of two children with HNL complicated by MAS, this study aims to enhance clinicians' understanding of HNL complicated by MAS, facilitating timely diagnosis and treatment and improving prognosis.

Case 1 was a 12-year and 9-month-old boy who was admitted to Anhui Provincial Children's Hospital due to a continuous fever lasting half a month. His main symptoms were recurrent high fever, initially accompanied by cough and runny nose, and occasional soreness in both knees, but without other symptoms such as rash or photosensitivity. Antibiotic treatment in other hospitals was ineffective. Physical examination upon admission showed a body temperature of 38.0°C, a heart rate of 110 beats per minute, respiratory rate of 22 breaths per minute, and a body weight of 40.0 kg. The physical examination revealed multiple enlarged lymph nodes, but no other obvious abnormalities.

Laboratory tests revealed decreased white blood cells and neutrophils, slightly low hemoglobin and platelets, elevated erythrocyte sedimentation rate, and a significant increase in lactate dehydrogenase and ferritin (Table 1). No abnormalities were found in pathogen tests, autoantibody profiles, tumor markers, etc. Imaging studies showed multiple enlarged lymph nodes and mild splenomegaly. Positron Emission Tomography-Computed Tomography (PET-CT) demonstrated abnormally increased Fludeoxyglucose (FDG) metabolism. Bone marrow cytology showed active bone marrow hyperplasia with decreased granulocyte proliferation and numerous phagocytes (Figure 1). Lymph node biopsy revealed the disappearance of most lymph node structures, with extensive histiocyte proliferation and nuclear debris (Figure 2).

The final diagnosis was HNL combined with MAS. In terms of treatment, cefoperazone sulbactam was initially used for anti-infection. cefoperazone-sulbactam was administered at a dose of 60 mg/kg/day (2.4 g/day based on the child's weight of 40 kg) in 2 intravenous infusions every 12 hours for 7 days. Immunoglobulin and methylprednisolone sodium succinate were subsequently administered to rapidly normalize the body temperature. Intravenous immunoglobulin 1 g/kg/day for 2 consecutive days; The initial dose of methylprednisolone sodium succinate was 2 mg/kg/day (80 mg daily) and was reduced to 1 mg/kg/day (40 mg daily) after 3 days. On day 13, oral prednisone acetate tablets (1 mg/kg/day, 40 mg/ day) were started, and the dose was reduced by 20% every 2 weeks. The total course of treatment was 12 weeks. There was no recurrence during the 5-year follow-up.

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Table 1. Laboratory indicators of two cases

Indicators	Case 1 (12 years and 9 months old)	Case 2 (12 years and 11 months old)
Blood Routine		
White Blood Cell (×10⁹/L)	1.17	1.5
Neutrophil (×10⁹/L)	0.45	0.9
Hemoglobin (g/L)	111	112
Platelet (×10⁹/L)	108	124
High-sensitivity C-reactive Protein (mg/L)	1.2	8.9
Erythrocyte Sedimentation Rate (mm/h)	40	16
Fibrinogen (g/L)	2.861	1.47
Biochemical Indicators		
Lactate Dehydrogenase (IU/L)	863	802
Ferritin (ng/mL)	1276.5	992.3
Triglyceride (mmol/L)	1.03	0.95
Etiological examination	Blood culture, stool culture, urine culture, EBV, CMV, etc. were all negative.	Blood culture, EBV, CMV, tuberculosis, etc. were all negative.
Imaging examination	No abnormalities were found in the Abdominal ultrasound, chest CT and echocardiography.	No abnormalities were found in the chest CT, abdominal ultrasound, cranial MRI, and echocardiogram.
Bone Marrow Cytology	Bone marrow was hyperactive, with decreased granulocyte proliferation and numerous phagocytes visible.	The bone marrow showed active hyperplasia with vigorous proliferation of granulocytes, erythrocytes, and megakaryocytes, and phagocytes were observed.
Lymph Node Pathology	The structure of most lymph nodes was lost, presenting with patchy necrosis and extensive histiocyte proliferation.	The lymph node structure was partially disrupted, with histiocyte hyperplasia, necrosis, and nuclear debris visible.
Immunohistochemistry		
CD68	+(Residual follicular spaces and necrotic areas)	+(Lesion area)
CD3	+(Residual follicular spaces and necrotic areas)	+(T-CELL area)
CD7	+(Residual follicular spaces and necrotic areas)	+(T-CELL area)
CD20	+(Residual follicles)	+(Residual follicles)
PAX5	+(Residual follicles)	+(Residual follicles)
CD21	+(Residual Follicular Dendritic Cell (FDC))	+(Residual FDC)
CD15	++(Residual follicular spaces and necrotic areas)	+ (Lesion area)
Ki67	+(Approximately 30%) -	+(60% hot spot area)
CD30	-	-

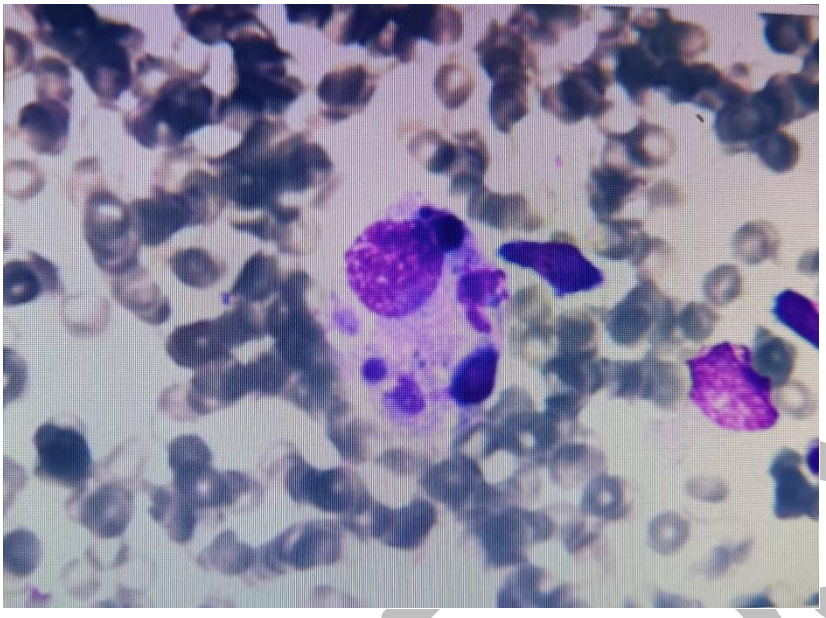

Figure 1. Bone marrow cytology of Case 1 (Swiss-Giemsa staining, 1000×).

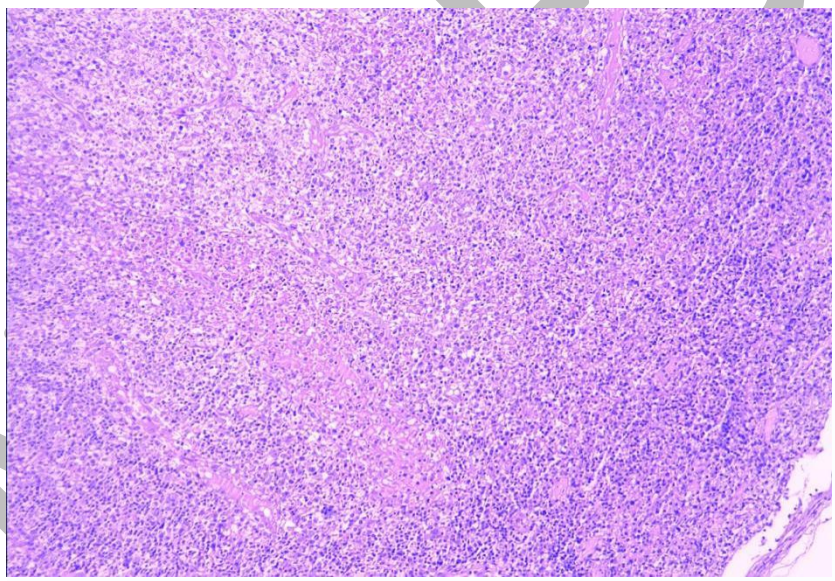

Figure 2. Hematoxylin-eosin staining images of lymph nodes of Case 1 (100×).

Case 2 involved a 12-year and 11-month-old male patient who was admitted to Anhui Provincial Children's Hospital due to recurrent cervical lymphadenopathy accompanied by fever lasting for one year. One year ago, he was hospitalized for similar symptoms and diagnosed with HNL. After 3 months of prednisone treatment, his symptoms were relieved. Nine months after discontinuation of the medication, he was readmitted due to cervical lymphadenopathy with fever for 12 days, along with a rash. Physical examination on admission showed a body temperature of 36.2°C, heart rate of 88 beats per minute, respiratory rate of 20 breaths per minute, and body weight of 45.0 kg. The physical examination revealed scattered red rashes on the trunk and limbs, and multiple enlarged lymph nodes could be palpated in the bilateral cervical and axillary regions, with the largest being approximately 1.5×1.5 cm and tender to touch.

Laboratory tests revealed decreased white blood cells and neutrophils, slightly low hemoglobin and platelets, elevated C-reactive protein and D-dimer, decreased fibrinogen, and a significantly elevated lactate

dehydrogenase and ferritin. No abnormalities were found in pathogen tests, autoantibody profiles, tumor markers, etc. Imaging studies showed multiple enlarged lymph nodes in both axillae, and ultrasound of the cervical lymph nodes indicated partial lymph node enlargement, with the largest being approximately 3.6×0.8 cm (Table 1). Bone marrow cytology showed active bone marrow hyperplasia with visible phagocytes. Lymph node biopsy revealed partial destruction of lymph node structure, with histiocyte proliferation and necrosis (Figure 3).

The final diagnosis was HNL combined with macrophage activation syndrome (MAS). In terms of treatment, methylprednisolone sodium succinate was administered at a bolus dose of 10 mg/kg/day (450 mg per day, based on body weight of 45 kg) by intravenous infusion for 3 days. Hydroxychloroquine was administered orally at a dose of 6 mg per kilogram of body weight per day (270 mg per day, based on a body weight of 45 kg). The body temperature returned to normal rapidly. After the shock treatment, methylprednisolone sodium succinate was given intravenously, and the blood picture and biochemical indicators improved significantly. The patient was discharged on the sixth day of admission. After discharge, prednisone tablets were taken orally at an initial dose of 2 mg/kg/day (90 mg daily), and the dose was reduced by 25% every 4 weeks for a total duration of 6 months. Hydroxychloroquine was used for two years. Follow-up for more than one year showed no recurrence of the disease. Due to the late enrollment time of case 2, the follow-up is still ongoing.

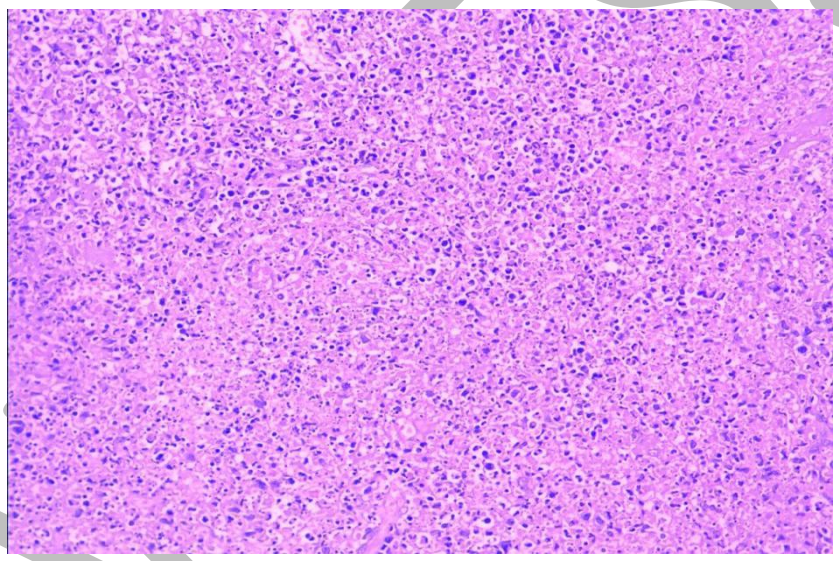

Figure 3. Hematoxylin-eosin staining images of lymph nodes of Case 2 (200×).

Case 1 had a relatively short history of continuous fever with mild symptoms. Case 2 had a longer history with recurrence and more complex symptoms, possibly due to insufficient glucocorticoid treatment duration. These two clinical cases suggest to clinical workers that in cases of unexplained fever accompanied by superficial lymph node enlargement and decreased white blood cells in the blood, when conventional anti-infection treatment is ineffective, the possibility of HNL should be considered and lymph node biopsy and pathological examination should be performed promptly to confirm the diagnosis. When HNL presents with prolonged high fever, monitoring several key indicators is crucial for early detection of MAS. Ferritin is a major marker of MAS; its significant elevation indicates excessive macrophage activation, and a decline often signals disease improvement. Platelets tend to decrease in MAS due to overactive inflammatory cytokines like IL-6 and TNF-α. A drop in platelet count may reflect disease severity, while the recovery suggests therapeutic response. Lactate dehydrogenase (LDH) elevation may indicate tissue necrosis and inflammation. Triglycerides can rise due to lipid metabolism disorders caused by the cytokine storm in MAS. Fibrinogen reduction may be indicative of consumption coagulopathy from hyperactive coagulation. Monitoring these indicators aids in diagnosing MAS, assessing disease severity, and evaluating treatment efficacy.

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In terms of treatment, it is mainly symptomatic therapy. For children with concurrent MAS, glucocorticoids or immunoglobulin treatment should be administered. MAS is triggered by an uncontrolled immune response causing a cytokine storm. Treatment involves suppressing excessive immune responses using glucocorticoids and immunoglobulin. The strategies in the two cases aligned with these principles.[1]

STATEMENT OF ETHICS

This study was approved by the ethics committee of Anhui Provincial Children's Hospital. Signed written informed consents were obtained from the patients and/or guardians. This study was conducted in accordance with the Declaration of Helsinki.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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