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Yile Ren *

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Case Report

Macrophage Activation Syndrome Originating from Primary Biliary Cholangitis: A Case Report

Jiayi Liu [1], Zhenzhen Miao [1], Liyong Gao [2], Jianfen Meng [1], Yile Ren [1]*

[1] Department of Rheumatology and Immunology, Xuzhou Municipal Hospital Affiliated to Xuzhou Medical University, Xuzhou, China.

[2] Department of Pathology, Xuzhou Municipal Hospital Affiliated to Xuzhou Medical University, Xuzhou, China.

***Corresponding Author:** Yile Ren., Department of Rheumatology and Immunology, Xuzhou Municipal Hospital Affiliated to Xuzhou Medical University, Xuzhou, China.

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Abstract:

Background: Macrophage activation syndrome is a rare and potentially life-threatening complication of systemic inflammatory disorders, which is rarely detected in primary biliary cholangitis.

Case summary: We describe a 49-year-old female who at the time of admission had a history of intermittent fever for one year. Laboratory tests showed hypohepatia, anaemia, thrombocytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, elevated sCD25 and evidence of hemophagocytosis in bone marrow aspirate. Meanwhile, the patient tested positive for AMA-M2 antibodies. Liver pathology further cleared that the primary disease was primary biliary cholangitis. Our patient was initially treated with a combination of intravenous glucocorticoid pulse therapy and intravenous immunoglobulin therapy (IVIG), which was followed by intravenous etoposide. On discharge, she received oral ursodesoxycholic acids (13 mg·kg-1·d-1), cyclosporine (150mg·d-1) and methylprednisolone (40mg·d-1). Ultimately, the patient's clinical symptoms and laboratory indicators improved.

Conclusion: To our knowledge, this is the first report of primary biliary cholangitis complicated by macrophage activation syndrome. There is no consensus on therapeutic treatment. Our case demonstrates that glucocorticoid, IVIG, etoposide, ursodesoxycholic acids and cyclosporin can be successful treatments.

Key words: primary biliary cholangitis; macrophage activation syndrome; case report

Introduction

A 49-year-old female had intermittent fever for one year, with maximum recorded temperature of 39.0℃, accompanied by itchy skin, no joint swelling and pain, ineffective in antibiotic treatment, and responding well to non-steroidal anti-inflammatory drugs (NSAIDs). Patchy rash appeared on the trunk during fever, which faded away when the fever subsided. One month ago, she developed hyperpyrexia again, complicated by anorexia.

Pertinent laboratory findings were as follows: hemoglobin, 98 g/L; aspartate aminotransferase (AST), 806 U/L; alanine aminotransferase (ALT), 644 U/L; alkaline phosphatase (ALP), 279 U/L; gamma-glutamyl transferase (GGT), 115U/L; C-reactive protein, 77.04 mg/L; erythrocyte sedimentation rate (ESR), 58mm/h; ferritin, 6415 ng/mL; anti-nuclear Ab (ANA), speckled pattern, 320(+); anti-M2 Ab (AMA-M2), 41.27 units (+). Infection and tumor screening showed no obvious abnormality. The patient was treated with methylprednisolone (40mg daily), indomethacin suppository for antipyretic and liver-protecting treatment. The invalid had poor temperature control, with a maximum temperature of 42.0℃, accompanied by headache, dizziness, and severe muscle soreness.

At admission, she had a temperature of 37.5℃, heart rate of 95 beats/minute, blood pressure of 152/96 mmHg, and breathing rate of 22 cycles/minute. Physical examination revealed listlessness, hot face, pharyngeal ulcer, diffuse red rashes on the face, trunk and limbs, scleral icterus, positive Murphy's sign. Comprehensive analysis of the patient's condition: the diagnosis of primary biliary cholangitis (PBC) or adult-onset Still's disease (AOSD) was controversial, lymphoma and infection needed further investigation.

The laboratory tests showed hypohemia, thrombocytopenia and liver dysfunction (Table 1). ALP was 3 times higher than the upper limit of normal (ULN), GGT 10 times higher than the ULN. At the same time, AST and ALT increased significantly (AST: 4510U/L; ALT: 1438U/L). Further workup showed that she had marked elevated d-dimer, ferritin(>100,000ng/ml), lactate dehydrogenase (LDH), and triglycerides. Soluble interleukin-2 receptor alpha chain (sCD25) was 116365pg/ml.

Hemophagocytic macrophages were seen in the bone marrow aspiration performed in the prediagnosis of MAS (Figure 1). Screening for infections: blood cultures, Widal's test, EBV and CMV polymerase chain reaction (PCR), HIV, virus hepatitis serology was all negative. A fine needle aspiration biopsy of the liver parenchyma was performed. diagnostic criteria, a diagnosis of MAS secondary to PBC was made. Inflammatory cells in the portal area were found (Figure 2). Immunohistochemical results showed cholangitis, CK7+, CK19+ (Figure 3). Based on the clinical and laboratory findings in accordance with the HLH

	Reference range	Admission	7th day	12th day	16th day
White blood cell count (10^9/L)	3.5-9.5	16.12	9.76	1.15	5.16
Hemoglobin (g/L)	115-150	98	71	69	72
Platelets (10^9/L)	120-350	94	52	71	163
Aspartate aminotransferase(U/L)	13-35	4510	68	18	18
Alanine aminotransferase(U/L)	7-40	1438	404	95	39
Alkaline phosphatase(U/L)	35-100	355	239	153	109
Gama-glutamyl transferase(U/L)	7-45	454	351	196	127
Lactate dehydrogenase(U/L)	120-250	11746	1042	-	329
Triglyceride (mmol/L)	0.4-1.7	3.05	1.95	-	-
Ferritin (ng/mL)	13-150	>100,000	10932	1740	-
Fibrinogen(g/L)	2.38-4.98	1.27	1.44	-	-
NK cell activity (%)	≥15.11	21.18	-	-	-
sCD25(pg/ml)	<6400	116365	-	-	-

Table 1: Laboratory tests upon admission, during the treatment.

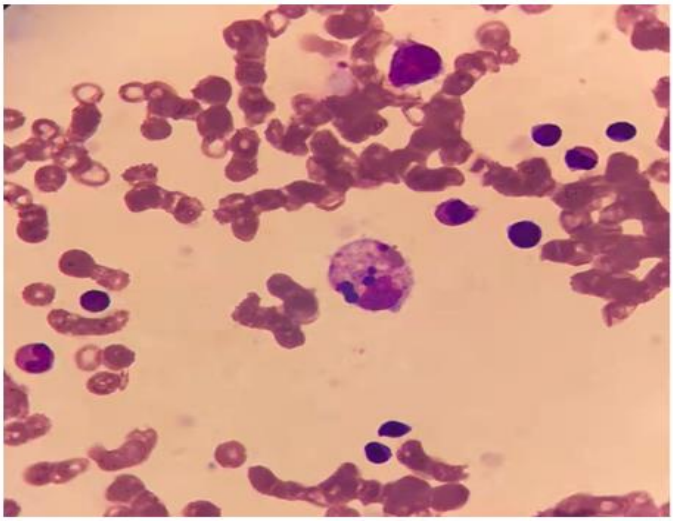

Figure 1: Hemophagocytosis in the bone marrow.

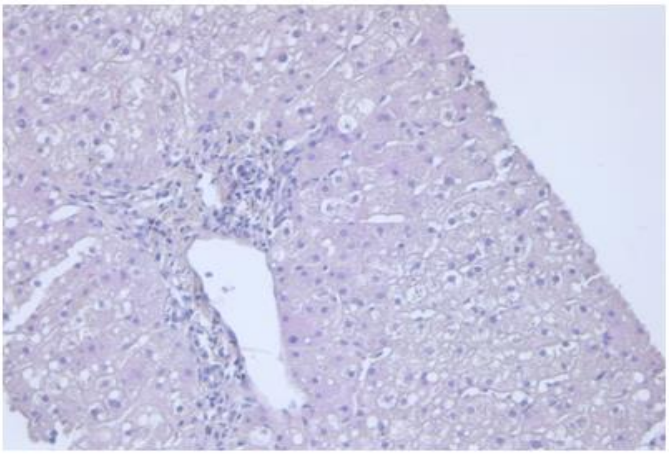

Figure 2: Inflammatory cells infiltrate the portal area (Hematoxylin and Eosin staining, original magnification×400).

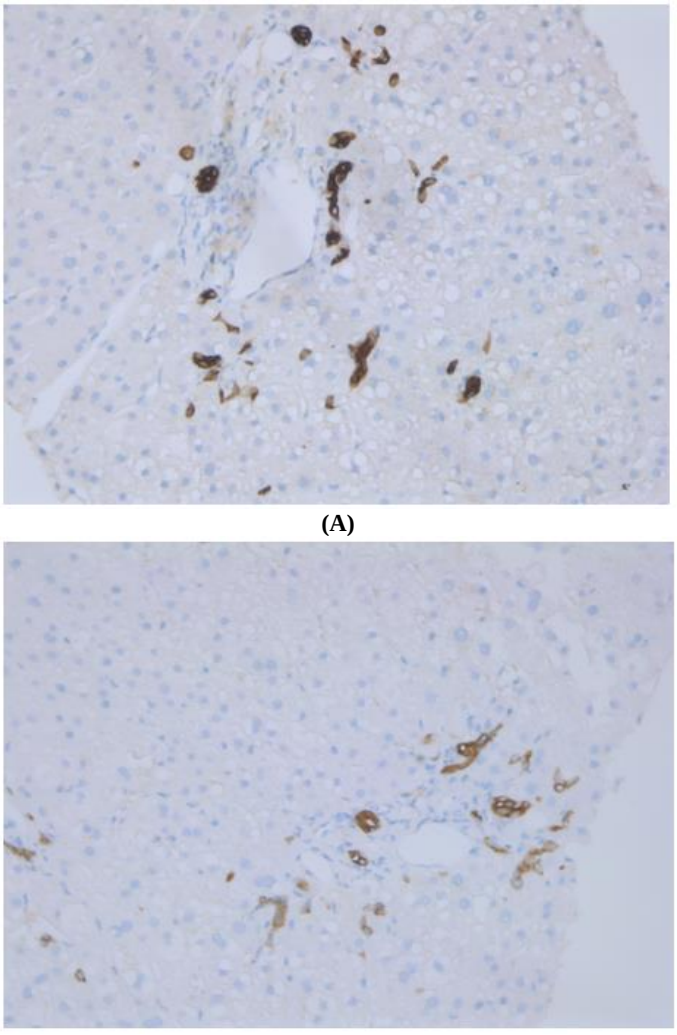

Figure 3: (A): CK7 positive liver cells; **(B):** CK19 positive liver cells.

Initial treatment was based on dexamethasone therapy to 20mg twice daily for 3 days with blood transfusion (cryoprecipitate and platelets). Etoposide treatment was 100mg in a single intravenous injection, twice a week. Intravenous immunoglobulin therapy (IVIG), liver-protecting given concurrently with steroid. Subsequently, dexamethasone was reduced to 10mg twice daily. After 5 days of treatment, the patient had normal temperature and laboratory indicators improved, but fever rose again on day 7. On the 8th day, the patient developed herpe around the lip. Dexamethasone was reduced, etoposide was stopped, and antiviral drugs were used for treatment. The patient's body temperature returned to normal. On the 12th day, the patient herpe lip improved, but developed fever again and white blood cells continued to decline. Dexamethasone increased to 20mg twice daily again. The patient's body temperature was normalized again. On the 15th day, the patient had a temperature of 39.6℃, accompanied by cough, expectoration. Thoracic computed tomography showed pulmonary infection. Cytobacteriological examination of sputum examination confirmed multiple infections such as Legionella and Aspergillus. With anti-infection treatment, dexamethasone decreased to 10mg per day. The patient's body temperature returned to normal again, and the laboratory indicators gradually improved. On discharge, she was switched to ursodesoxycholic acids (13 $mg \cdot kg^{-1} \cdot d^{-1}$), ciclosporin (150$mg \cdot d^{-1}$) and methylprednisolone (40$mg \cdot d^{-1}$). After discharge with regular follow-up, methylprednisolone was gradually reduced. The patient is competent for daily housework now.

Discussion

Macrophage activation syndrome (MAS), also known as secondary or reactive hemophagocytic Lymphohistiocytosis (HLH), is a clinical syndrome caused by excessive immune activation leading to cytokine storm in the body [1]. Previous MAS is noted in pediatric patients with systemic juvenile idiopathic arthritis (sJIA) and systemic lupus erythematous (SLE) [2]. The MAS in adult rheumatic diseases most commonly develops with AOSD and SLE [3]. In this paper, we are the first to report a patient with MAS originating from PBC.

PBC is a chronic, seropositive and female-predominant inflammatory and cholestatic liver disease. It is histologically characterized by intralobular nonpurulent bile duct injury caused by lymphocytic cholangitis. Approximately 50% of patients are asymptomatic at diagnosis but rather due to abnormal biochemical indicators found during physical examination. PBC can be diagnosed if two of the following three criteria are met: Elevated ALP and other serum biochemistry reflecting cholestasis evidence; Serum AMA/AMA-M2 or anti sp100 antibody, anti gp210 antibody is positive; Histological features of non-suppurative destructive cholangitis and interlobular bile duct injury. PBC characteristic pathological manifestations of chronic non-suppurative

destructive cholangitis. In addition to routine HE staining, immunohistochemical staining can also be used to assist the examination of liver pathology. When lymphocyte aggregation in the portal area or bile duct injury is obvious, it is often difficult to identify the bile duct structure. Specific bile duct markers CK7 or CK19 can be used to identify and evaluate the degree of bile duct injury.

There are very few cases of MAS occurring in autoimmune hepatitis (AH). The first case report is a 15-year-old female with MAS originating from acute-onset AH who demonstrated clinical remission after treatment with prednisolone and cyclosporine A [4]. After five years of treatment, no disease recurrence was detected. In addition, Colin Casault et al report a 34-year-old male with a prior history of biopsy-proven AH and MAS who responded to treatment with dexamethasone and etoposide [5].

The 2004 proposed diagnostic criteria for HLH serve as a useful diagnostic tool. Patients fulfilling at least five main criteria can be diagnosed with HLH [6]. Our case was presented with unremitting fever, anaemia, thrombocytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated sCD25 and evidence of hemophagocytosis in bone marrow aspirate, fulfilling 6 of the 2004 HLH criteria.

MAS treatment mainly consists of inhibiting inflammation and cell proliferation to relieve patient of symptoms and rescue organ function. Adult patients with MAS should be treated with individualized therapy. Glucocorticoids used as first-line therapy are initially high-dose. with the addition of cyclosporine and biologics when response is poor. If the condition is serious and the condition is still not controlled after the above treatment, a reduced etoposide frequency should be considered [7]. In addition, IVIG may be useful in treatment [8]. Our reported case was effectively controlled with MAS after high-dose glucocorticoid, IVIG, and etoposide treatment. But in the course of treatment, this case appeared the viral infection, bacterial infection. How to balance the treatment between MAS and infections is challenging. Fortunately, although this case fluctuated in MAS in the course of anti-infection, it finally achieved a good prognosis.

Conclusion

In conclusion, this is the first report of a case of MAS originating from PBC with a successful response to therapy. Early diagnosis and treatment are important. The patient was followed up for a long period after treatment, and no disease recurrence was detected.

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Disclosure statement:

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