

Case study of tocilizumab in the treatment of macrophage activation syndrome secondary to systemic lupus erythematosus

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Abstract: Macrophage activation syndrome (MAS) is a serious complication of autoimmune diseases, with a potentially fatal risk, belonging to secondary hemophagocytic lymphohistiocytosis (HLH), often secondary to juvenile idiopathic arthritis (sJIA), adult still disease (ASOD), and can also be secondary to systemic lupus erythematosus (SLE), etc., SLE combined with MAS has a very high mortality rate, and the clinical manifestations are not easy to control high fever, pancytopenia, hepatosplenic lymphadenopathy, coagulation dysfunction, etc. Because SLE patients can have a variety of clinical manifestations, MAS is often difficult to identify, some patients are critically ill, and traditional glucocorticoids, immunosuppressants and other treatments are often difficult to control the disease, and the treatment of cytokines is gradually tried. This article reports a case of refractory SLE complicated with MAS successfully controlled by tocilizumab, and summarizes and analyzes the literature to explore the diagnosis and treatment experience of SLE complicated with MAS.

Keywords: Tocilizumab; systemic lupus erythematosus; macrophage activation syndrome

1. Introduction

Macrophage activation syndrome (MAS) is a common fatal complication of secondary hemophagocytic lymphohistiocytosis and a common fatal complication of a variety of inflammatory diseases. These include a variety of rheumatic diseases, such as adult Still's disease, juvenile idiopathic arthritis, and systemic lupus erythematosus (SLE), but SLE is relatively rare [1]. In SLE patients, the incidence of MAS is 0.9%~4.6% [2], and the pathogenesis may be due to the high activity of SLE, secondary overactivation of T lymphocytes and macrophages, phagocytosis of blood cells, and multi-tissue organ damage. The clinical manifestations are uncontrollable high fever, pancytopenia, hepatosplenic and lymphadenopathy, abnormal liver function, coagulation dysfunction, hypofibrinogenemia, high triglycerides, elevated ferritin levels, and even neurological damage [3]. MAS secondary to SLE is often difficult to identify, and statistics suggest that the onset of SLE itself, as well as the timing of onset and high systemic lupus erythematosus disease activity index (SLEDAI) scores, are major risk factors for the development of MAS. Infection, underlying malignancy, and pregnancy were other potential triggers identified. Unexplained fever, splenomegaly, lymphadenopathy, severe cytopenias, ferritinemia, hypertriglyceridemia, high SLEDAI, and H-score should increase the likelihood of diagnosing MAS in patients with SLE [4]. To predict the risk of MAS in childhood SLE, a retrospective cohort study showed ferritin ≥ 1107 micrograms/L to be the best differentiator of MAS, followed by lymphocytes $< 0.72 \times 10^3/\text{mm}^3$. In patients with febrile manifestations of SLE, testing is appropriate to detect the propensity for early detection of MAS [5]. With a better understanding of the pathophysiology of MAS and the advent of new therapies, targeted cytokine therapies have emerged, including drugs that block interleukin-1 (IL-1), IL-6, IL-18, interferon- γ , and Janus kinase inhibitors [6,7]. Increasing early recognition of multiple MAS in inflammatory diseases, along with the use of effective and less toxic cytokine-targeted therapies, should reduce mortality from this fatal disease. In this article, we report a case of MAS secondary to refractory SLE successfully controlled by tocilizumab, and summarize and analyze the literature to explore the diagnosis and treatment experience of SLE complicated with MAS.

2. Case data

2.1 Case Profile

On March 19, 2020, a 15-year-old female patient was admitted to the Department of Rheumatology and Immunology of the Affiliated Hospital of Hebei University due to intermittent fever for 13 days and cough for 4 days. The patient developed fever after a cold in early March 2020, with a body temperature of up to 40 °C, accompanied by chills, chest tightness, bilateral thigh muscle pain, no joint swelling and pain, rash, etc., and was given "azithromycin" for 6 days, but the effect was not good. On March 15, 2020, he developed cough and sputum production, Routine blood examination in the outer hospital: WBC $3.05 \times 10^9/L$, HGB 110g/L, PLT $96 \times 10^9/L$, NEUT 62.30%; ANA positive (titer >3200), nuclear homogeneous. The diagnosis of "systemic lupus erythematosus is not excluded", and he was treated with piperacillin sodium, tazobactam sodium, methylprednisolone and other treatments (specifics unknown), but he still had recurrent fever, and the blood routine was rechecked on March 18, 2020: WBC $0.88 \times 10^9/L$, N $0.44 \times 10^9/L$, HGB 104g/L, PLT $63 \times 10^9/L$. Previous health. Physical examination: T 38.7°C, P 100 times/min, R 20 times/min, BP 135/94mmHg There is no yellow staining, rash and hemorrhage on the skin and mucous membranes of the whole body, coarse breath sounds in both lungs, no dry and wet rales are heard, cardiac examination (-), the abdomen is flat and soft, there is no tenderness, rebound tenderness and muscle tension, the liver is palpable 3 cm below the cost, and the spleen is not palpable under the costals. Bilateral thigh muscle tenderness, no edema in both lower extremities. The results of laboratory tests showed on admission: Complete blood count :WBC $0.79 \times 10^9/L$, NE $0.21 \times 10^9/L$, HGB 99g/L, PLT $88 \times 10^9/L$; Urinalysis: urine occult blood 3+, urine protein 3+; 24-hour urine protein 3.56g/24h; TG 5.37mmol/L, LDH 581U/L, AST 84U/L, ALB 21g/L, Creatinine 82umol/L, Ferritin 3000ng/ml, Soluble CD25/IL-2Ra 2344.91pg/ml; NK cell viability (%): 19.56%; ESR 9mm/h; CRP 7.2mg/L; C3 0.04g/L, C4 0.01g/L; ANA spectrum: positive for ANA, nuclear homogeneous type 1:32000, positive for anti-dsDNA antibody 1:32, positive for anti-nucleosome antibody, positive for anti-ribosomal P antibody; Negative for ACL, anti-CCP antibody, ANCA; FIB 0.78g/L, D-dimer 5715ng/ml; PCT 0.47ng/ml; Serum amylase, total poverty lysis, and immunoglobulin were normal; Hepatitis B and C syphilis antibodies, fungal G, Epstein-Barr virus DNA, TORCH, TB-Spot, new coronavirus IgM, IgG antibodies, sputum cultures, blood cultures, etc. (-); Color ultrasound: left atrium enlargement, small amount of mitral regurgitation. Hepatomegaly, splenomegaly, slightly increased echogenicity of the parenchyma of both kidneys, and abdominopelvic effusion. Chest CT: (1) Twin pneumonia, (2) Bilateral pleural effusion, poor local lung distension in both lower lobes, (3) Small amount of pericardial effusion, (4) Multiple slightly larger lymph nodes in both axillas, (5) Decreased density of large blood vessels in the heart chambers, anemia should be considered, (6) Subcutaneous edema of the chest and abdominal wall. CT abdomen: (1) A small amount of fluid in the abdominal cavity, (2) Full pancreatic morphology. Bone marrow smear: Bone marrow smear occasionally shows histiocytes phagocytosis. Consider diagnosing (1) Systemic lupus erythematosus Lupus nephritis Lupus hematologic involvement Polyserosal effusion Lupus pneumonia? Lupus gastrointestinal and intestinal involvement? (2) Macrophage activation syndrome (3) Coagulopathy (4) Lung infection.

2.2 Treatment and prognosis

The specific treatment process is as follows: After admission, methylprednisolone (MP) 80mg was given intravenous infusion twice a day, and the body temperature returned to normal the next day, and gamma globulin 20g was given once a day infusion (Use for 3 days). After 3 days, the fever reappeared, adjusted to MP 480 mg once a day infusion (for 3 consecutive days), the body temperature control was acceptable after high-dose hormone therapy, and then the MP was adjusted to 80 mg once a day (for 2 consecutive days), and then the fever again, the body temperature reached the peak (40.3°C), and cyclosporine 75 mg was given orally twice a day, MP infusion was discontinued and dexamethasone was adjusted (20 mg once daily for 13 days, 15 mg once daily for 3 days), At the same time, he was treated with cryoprecipitate, human blood albumin, colony-stimulating factor, low molecular weight heparin, etc., and the body temperature decreased, but the fever still recurred (up to 39.5 °C), accompanied by chills, chest tightness, cough, And gradually appear edema of both lower limbs and face, increased blood pressure, vaginal bleeding, multiple nosebleeds, hematuria, poor appetite, nausea, abdominal distention, epigastric pain, Nausea was severe after oral cyclosporine, and the ferritin was elevated during the period, and cyclosporine was discontinued. After general discussion, tocilizumab 400mg (8mg/kg) infusion was given on April 8, 2020, The body temperature returned to normal the next day, the spirit and appetite improved, the cough decreased, no bleeding again, the urine color became light to normal, the symptoms of abdominal distention and abdominal pain disappeared, the laboratory ferritin decreased, the blood

trilineage improved, and the fibrinogen tended to be stable (Figure 1). On April 12, 2020, the hormone was adjusted to methylprednisolone 48mg orally once a day, and tacrolimus 1mg was given orally twice a day the next day, with no adverse reactions. The patient's condition was stable since the last discharge, and the dose of methylprednisolone was gradually reduced from 48 mg once a day to 8 mg once a day, and oral tacrolimus 1 mg twice a day was continued. On September 4, 2020, the outpatient clinic re-examined that the urine protein turned negative, and the blood trilineage, creatinine, complement, and inflammatory indexes were normal. The patient was readmitted to the hospital after 1 year due to fever, creatinine was progressively elevated, considering the disease activity, recurrent infections occurred during the active control of the disease through cyclophosphamide, and blood in the stool appeared, and the creatinine rose to 855umol/L, and was transferred to the Department of Nephrology for renal replacement therapy. The patient's family was automatically discharged from the hospital on August 5, 2021 due to the heavy financial burden.

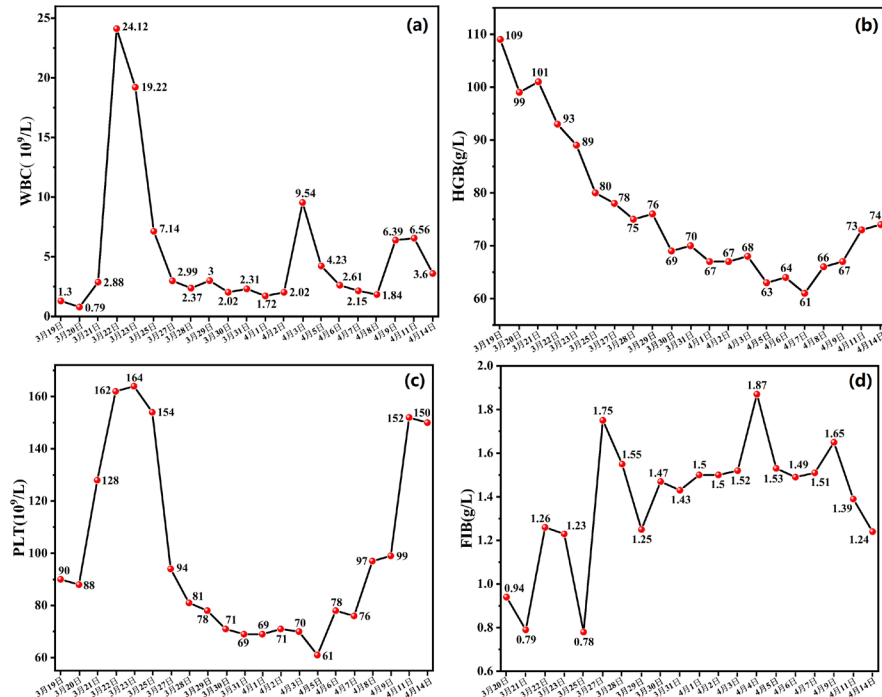


Figure 1: Trends in WBC (a), HGB (b), PLT (c) and FIB (d).

3. Discussion

Systemic lupus erythematosus is an autoimmune disease characterized by multi-organ and multi-system damage, and there are a variety of pathogenic autoantibodies in the serum, which are highly heterogeneous, and the cause of the disease is not clear, which may be related to genetics, infection, and environment. The manifestations of systemic lupus erythematosus are complex and diverse, and the prognosis is poor when important organs such as the kidneys and nervous system are involved. This patient was an adolescent female, with fever, cough, abdominal distension, abdominal pain, bleeding tendency, and examination showed that the blood trilineage was reduced, massive proteinuria, hematuria, polyserous effusion, double pneumonia, decreased complement, positive ANA high titer, positive anti-ds-DNA antibody, meeting the ACR classification criteria for systemic lupus erythematosus modified by SLICC in 2012, SLEDAI score of 28 points, and the condition was critical. However, the patient also has hypofibrinemia, coagulation disorders, obvious bleeding tendency, high triglycerides, and significantly elevated ferritin, which cannot be explained by monism alone, according to the 2004 revised diagnostic criteria for hemophagocytic syndrome (HPS) [8], Patients with fever, cytopenias, high TG, hemophagocytes in the bone marrow, and elevated serum ferritin support the diagnosis of HPS, HPS can be divided into "primary" and "secondary", and primary HPS is genetically related and is caused by hereditary impaired lymphocyte toxicity or defects in genes related to inflammatory activity. According to the characteristics of gene defects, primary HPS can be divided into familial HPS, immunodeficiency syndrome-related HPS, X-linked lymphoproliferative disorders, and EBV-driven HPS. However, secondary HPS is mostly caused by tumors, rheumatic immune diseases, infections and other triggers of severe inflammatory syndrome, and it is believed that many secondary HPS also have a certain genetic

background. Systemic lupus erythematosus is a relatively common connective tissue disease. HPS secondary to connective tissue disease is also known as MAS. In cases of SLE, high activity (high SLEDAI score), secondary infections (particularly Epstein-Barr virus, CMV infection), drug factors, pregnancy, and underlying malignancy may predispose to MAS^[9], and high serum ferritin can help distinguish the presence of concomitant MAS^[10]. Serum ferritin is markedly elevated in this patient, which is a high warning of the presence of MAS.

For SLE, an individualized treatment plan is advocated, and the treatment plan is determined according to the activity of the disease, the severity of organ injury and the patient's tolerance, and the treatment is generally treated with glucocorticoids and immunosuppressants, and for patients with refractory SLE and glucocorticoids who have difficulty in reducing the dose, biological agents and immunoadsorption can also be used. There are two main stages of MAS treatment, first, induction remission therapy mainly targets the excessive inflammatory state to control the progression of macrophage activation, and second, the etiological treatment focuses on correcting the immune deficiency and controlling the primary disease to prevent the occurrence of macrophage overactivation. The commonly used drugs at home and abroad include glucocorticoids (GC), high-dose gamma globulin (IVIG), immunosuppressants, chemotherapy drugs (such as etoposide) and biological agents. Intravenous GC is often the drug of choice, and high-dose corticosteroids alone can be used early in the course of the disease to bring some patients into remission, while high-dose IVIG can help control disease activity, control infection, and shorten the course of the disease. The patient was treated with high-dose MP and IVIG in the early stages of the disease, and the body temperature dropped briefly and then recurred. In terms of immunosuppressants, the calcineurin inhibitor cyclosporine A (CsA) can be used as a first-line treatment for MAS, which has a certain effect on reducing the use of corticosteroids and reducing the mortality rate in the early stage. In addition, there is literature^[11,12] supporting the advantages of dexamethasone in the treatment of MAS, because of its better anti-inflammatory effect, the body temperature of this patient decreased after the addition of oral CsA and adjustment to dexamethasone infusion, but there were still recurrences, frequent nausea, vomiting, and abdominal distension, and the use of CsA was considered intolerable, so the use of CsA was not tolerated, so the use of CsA was discontinued. Etoposide, the first-line treatment for primary HPS, can rapidly control inflammation, and is widely used in hematology, especially in patients with MAS who do not respond well to glucocorticoids and CsA, and is rarely used by rheumatologists due to its large adverse effects^[13]. Other supportive care, such as control and prevention of infections including fungi and *Pneumocystis carinii*, is also important. Patients with MAS are often at high risk of spontaneous bleeding due to thrombocytopenia and abnormal coagulation function. Patients with bleeding can be treated with symptomatic platelets, fresh frozen plasma, and activated factor VII supplementation if necessary. In terms of organ function, due to MAS inflammatory response and drug toxicity, multiple organ insufficiency can be caused, and it is necessary to closely monitor organ function during treatment and symptomatic supportive treatment.

According to the literature^[14], the pathophysiology of MAS is ultimately attributed to a "cytokine storm", in which elevated cytokines including interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor (TNF) α , and interferon- γ (IFN- γ) can be detected in these patients. High levels of circulating cytokines (IL-1, IL-6, interferon INF- γ , TNF- α) not only enhance the aberrant activation of macrophages, but also lead to a strong systemic inflammatory response. MAS can be trialed as second-line therapy, such as biologic agents such as interleukin-1 (IL-1) receptor antagonists (anakinra), anti-CD20 monoclonal antibodies, IL-6 receptor antagonists (tocilizumab), and Jak inhibitors (tofacitinib)^[14-17]. Among them, tocilizumab is an IL-6 receptor antagonist, which is widely used in clinical practice in addition to rheumatoid arthritis, sJIA, Takayasu's arteritis, etc., and is also used in the inflammatory storm caused by a variety of diseases, such as MAS caused by adult Still disease, especially in the inflammatory storm caused by new crown pneumonia^[18], and significant efficacy in refractory SLE has also been reported^[19], while it is rarely reported in MAS caused by SLE. In this case, after the application of tocilizumab, the body temperature returned to normal the next day, the symptoms of abdominal distention, abdominal pain, and chest tightness were significantly reduced, and the clinical indicators gradually recovered, and it was considered that IL-6 may play an important role in the activity of SLE, the vicious circle of inflammatory response, and the combination of MAS. In the clinical course of this patient, there are at least some cases of SLE and MAS, and blocking inflammatory cytokines is beneficial for recovery, even if only when used for induction therapy.

The progression of SLE-related MAS is dangerous and the prognosis is poor. The patient's disease was controlled after active treatment, but the final outcome was poor, which may be related to secondary infection, which is easy to induce disease activity, and immunodeficiency and secondary infection are easy to develop in the process of controlling the disease with immunosuppressants, forming a vicious

circle. In addition, the early age of onset and severe disease of the patient, and literature review [20] cannot rule out the possibility of susceptibility genes. Mutations in multiple pathways have been identified in patients with MAS. Many of the pathways that are genetically disrupted lead to similar cytokine storm syndromes [21], which can be broadly categorized into impaired viral control (e.g., SH2P1A), dysregulated inflammasome activity (e.g., NLRC4), other immunodeficiencies (IKBK), and metabolic dysregulation (LIPA). These genetic defects lead to recurrent disease activity and cytokine storms. Testing for genetic mutations is recommended in patients with multiple episodes of MAS.

It is particularly important for the early clinical diagnosis and treatment of MAS, due to the lack of specific clinical manifestations, it is easy to misdiagnose and miss the diagnosis, and due to the variety of potential causes of MAS, there are relatively many departments for the first diagnosis, which often requires multidisciplinary diagnosis and treatment. In particular, the diagnosis of MAS in patients with SLE is often challenging, and continuous monitoring of relative changes in patient parameters may be the best way to identify and diagnose MAS at an early stage, especially because of the scattered initial diagnosis and overlapping clinical manifestations with MAS, such as fever, cytopenias, and liver enzyme abnormalities [22].

4. Conclusions

The clinical manifestations and pathogenesis of SLE complicated with MAS are highly heterogeneous, and clinicians need to closely observe the changes in the condition and detect the combination of MAS as soon as possible, and it is recommended that for refractory and hyperinflammatory MAS cases, in addition to traditional treatment, cytokine targeted drug therapy (such as IL-1, IL-6, etc.) can be tried. At present, there is a lack of in-depth mechanistic studies and further clinical validation of tocilizumab in the application of macrophage activation syndrome, and it is urgent to look forward to further studies to provide high-level evidence support for clinical treatment.

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