Macrophage Activation Syndrome in a Case of Myasthenia Gravis with Concurrent Cytomegalovirus Infection

Nai-Hsin Huang[1], Li-Ming Lien[1,2], Wen-Hung Chen[1,2]

Abstract

Objective: Macrophage activation syndrome (MAS) or reactive hemophagocytic lymphohistiocytosis (HLH) refers to a set of clinical symptoms caused by the excessive activation and proliferation of macrophages. It was linked with autoimmune disease such as systemic-onset juvenile rheumatoid arthritis, systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis, etc. Herein we report a case of myasthenia gravis (MG) with concurrent cytomegalovirus (CMV) infection developed MAS.

Case report: A 31-year-old female with history of MG for 2 years under stable control with azathioprine and prednisolone. She presented with persistent high fever for 2 weeks after an upper respiratory infection. Lab data revealed pancytopenia, elevated triglyceride, ferritin and C-reactive protein (CRP). A bone marrow aspiration confirmed hemophagocytosis. Investigation for occult infection revealed her plasma was positive for CMV IgG and IgM, and high for CMV viral load. She was then treated with 5 sessions of plasmapheresis and pulse steroid. Azathioprine was discontinued and replaced with cyclosporine. Gancylovir was given for her concurrent CMV infection. After 2 weeks of treatment, her fever gradually subsided, and her blood cell count, hepatobiliary enzymes, ferritin and CRP have returned to normal range. She was discharged in good recovery.

Conclusion: MAS is a rare complication of systemic autoimmune disease with poor prognosis, which may be precipitated by concurrent infection. Early recognition of this syndrome and prompt immune modulation therapy is crucial for successful treatment.

Keywords: Macrophage activation syndrome, hemophagocytic lymphohistiocytosis, myasthenia gravis, cytomegalovirus, myasthenia gravis, plasmpaheresis.

Acta Neurol Taiwan 2020;29:124-128

INTRODUCTION

Macrophage activation syndrome (MAS) or reactive hemophagocytic lymphohistiocytosis (HLH) refers to a set of clinical symptoms caused by the excessive activation and proliferation of macrophages [1,2,3]. It was linked with autoimmune disease such as systemic-onset juvenile rheumatoid arthritis, systemic lupus erythematosus,

From the [1]Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital; [2]Department of Medicine, School of Medicine, Taipei Medical University.
Received May 7, 2020. Revised May 18, 2020.
Accepted August 2, 2020.
Correspondence to: Wei-Hung Chen, Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
E-mail: M000735@ms.skh.org.tw

rheumatoid arthritis, and dermatomyositis, etc.[4]. Herein we report a case of myasthenia gravis (MG) with concurrent cytomegalovirus (CMV) infection developed MAS.

CASE REPORTS

A 31-year-old female with history of MG for 2 years under stable control with azathioprine and prednisolone. She presented with persistent high fever for 2 weeks after an upper respiratory infection, receiving clarithromycin treatment at other hospital. However, fever recurred after discharge with worsening muscle strength. Therefore, she visited our Neurology department and was admitted for management. Intermittent fever persisted (up to 39.7°C in first few days, then mostly around 38.1~38.5°C) despite broad-spectrum antibiotics. A thorough survey for fever of unknown origin showed no remarkable findings in sputum cultures, Influenza virus screening, blood cultures, urine cultures, various autoimmune antibodies, and tumor markers. Image study showed bilateral lung infiltration and splenomegaly. Lab data revealed pancytopenia (white blood cells, 1.2 x 10^3 /uL (3.8-10.0 x 10^3 /uL) with 70% neutrophils; hemoglobin, 10.5 g/dL (11.0-16.0 g/dL); platelets, 106 x 10^3 /uL (140-450 x 10^3 /uL)). Triglyceride 248 mg/dL (0~150 mg/dL)), ferritin 587 ng/mL (11~306 ng/mL) and CRP 11.76 mg/dL (0~1 mg/dL)) levels, as well as hepatobiliary enzymes including AST 152 U/L (5~35 U/L), ALT 126 U/L(10~50 U/L), D-Bilirubin 0.65 mg/dL (0.03~0.18 mg/dL), and LDH 499 U/L (140~271 U/L)) were elevated. A bone marrow aspiration was performed and confirmed hemophagocytosis (Figure 1). Investigation for occult infection revealed her plasma was positive for CMV IgG (64.6 AU/mL), IgM (7.10 AU/mL) and high for CMV viral load (10567 copy/ ml). She was then treated with 5 sessions of plasmapheresis and pulse steroid. Azathioprine was discontinued due to low white counts and elevated liver enzymes and was replaced with cyclosporine. Gancylovir was given for her concurrent CMV infection. After 2 weeks of treatment, her fever gradually subsided, and her blood cell count, hepatobiliary enzymes, ferritin and CRP have returned to normal range (Figure 2). She was discharged in good recovery.

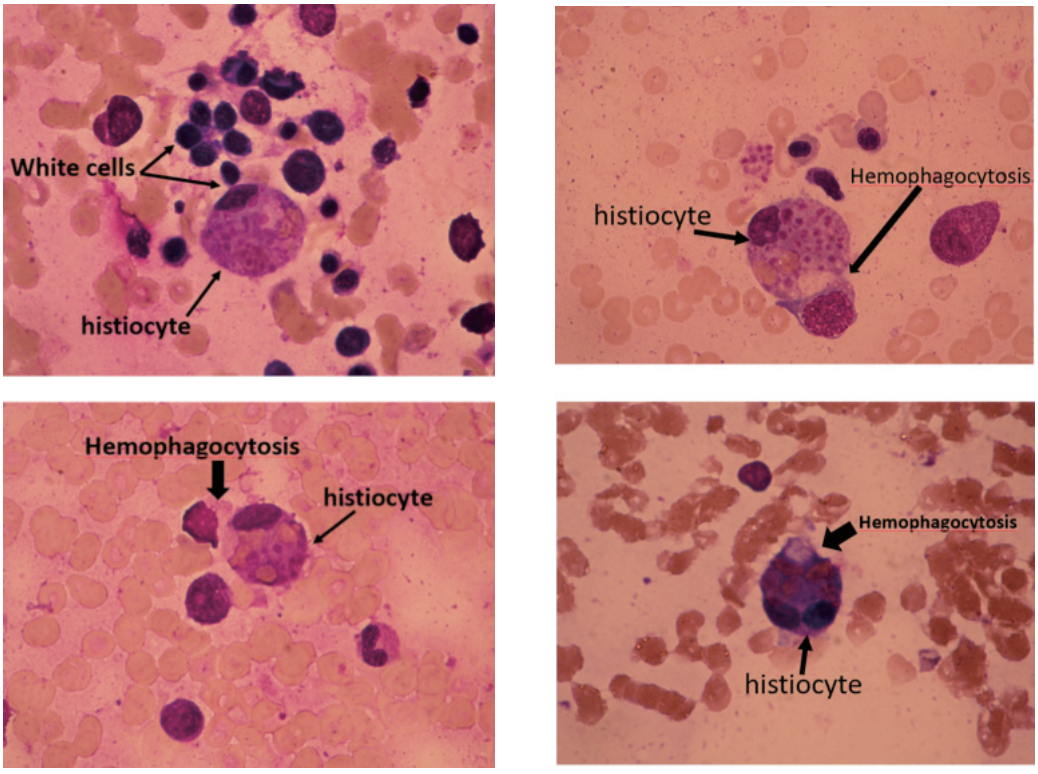

Figure 1. Bone marrow biopsy shows increased histiocytes with hemophagocytotic features.

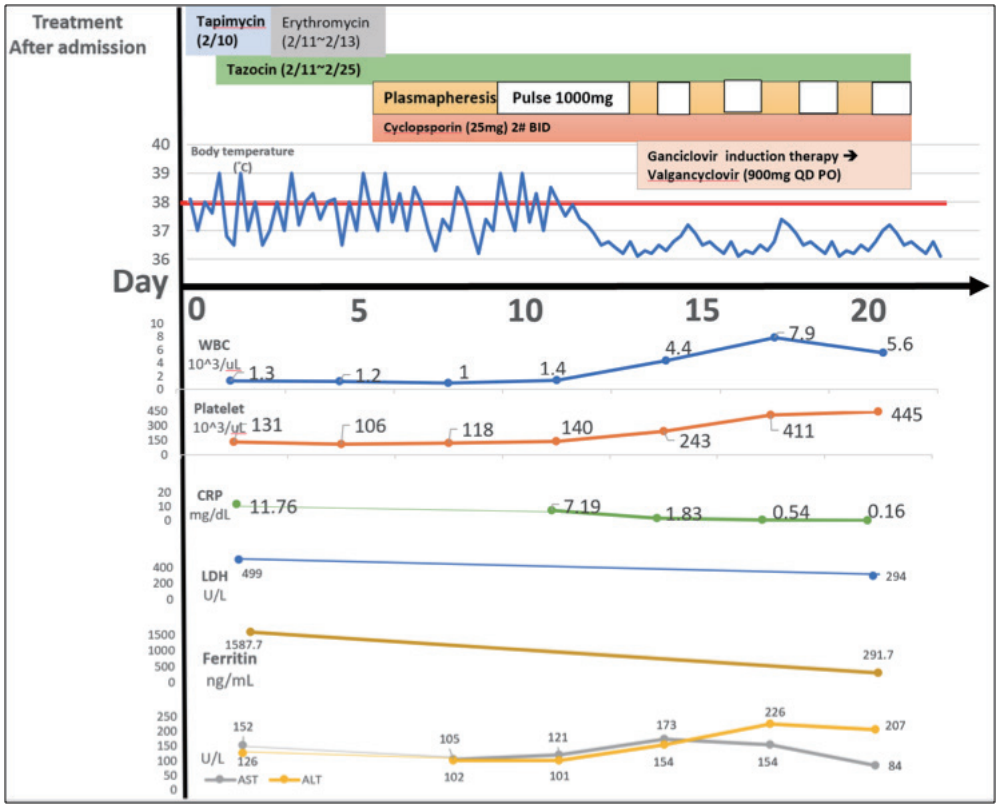

Figure 2. Summary of clinical course and relevant laboratory findings in response to treatment.

DISCUSSION

HLH is a histiocytic disorder with the feature of expansion of macrophages exhibiting hemophagocytic activity which would lead to cytokine storm and hyperinflammatory state. Common clinical presentation of HLH included fever, cytopenia, and splenomegaly.

At least 5 out of 8 clinical and laboratory criteria should be fulfilled to diagnose HLH in the patients without familial disease/known genetic defect, including (1) fever, (2) splenomegaly, (3) cytopenia ≥ 2 cell lines (hemoglobin < 90 g/L, platelets <100 *109/L, neutrophils <1*10^9/L), (4) hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥3 mmol/L, fibrinogen<1.5 g/L), (5) ferritin ≥ 500 g/L, (6) sCD 25≥ 2400 U/mL, (7) decreased or absent NK cell activity, (8) hemophagocytosis in bone marrow, cerebrospinal fluid, or lymph nodes. Our patient had clinical features of fever, splenomegaly, and laboratory data including severe neutropenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis revealed by bone marrow biopsy [5].

HLH is classified as primary (familial) and secondary (reactive). Reactive HLH may be caused by infection, malignancy, autoimmune diseases or immunosuppression status. If the HLH was related to autoimmune disorder, such as systemic-onset juvenile rheumatoid arthritis, systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis, it is then designated as MAS [6]. The causes of MAS in autoimmune diseases are still unknown; however, a concurrent infection like EBV, CMV, HIV, *Mycobacterium tuberculosis* have been suspected as triggers [7]. It may be difficult to differentiate MAS from concurrent severe infection, especially in critically ill or immunocompromised patients [9, 10]. Akenroye et al. reported 4 cases who were all initially treated as sepsis, then later were found fulfilling the criteria of HLH. The underlying etiologies included HIV infection, T cell lymphoma, histoplasmosis and juvenile rheumatoid

arthritis. Three cases were treated with chemotherapy, and all unfortunately died due to multiple organ dysfunction [8]. Chemotherapy toxicity including pancytopenia might worsen the outcome once the clinical condition progressed into critical illness. Therefore, early detection of HLH and underlying etiology is important for initiation of standard therapy with less side effects.

Fleischmann and Bohmerle reported a case with underlying SLE and combined with a MuSk type of MG, who developed severe pneumonia with septic shock during hospitalization. Though multidrug resistant bacterial infection was impressed; the lung infiltration showed resolution on followed-up image, the authors turned to survey other non-infectious inflammatory disorders which might mimic sepsis. The clinical features, lab data and bone marrow biopsy at last confirmed MAS-HLH. SLE-associated EBV infection was detected which might be the trigger factor. Patient presented with remarkable improvement after receiving intravenous immunoglobulins (IVIg) and intravenous corticosteroids [11]. Frederiksen et al. reported a similar case of MG with long term treatment by azathioprine, who was diagnosed as HLH and had a concurrent CMV infection. After treatment with etoposide, dexamethasone, and valganciclovir, the patient recovered [12].

Intravenous methylprednisolone pulse therapy and cyclosporine A are first-line treatments of MAS; etoposide could be considered if the above two show limited effect. Other options include ankinra (interleukin 1 receptor antagonist), TNF-alpha inhibitors, IVIg and rituximab (anti-CD20 antibody) [13]. For refractory condition, plasma exchange/plasmapheresis had been reported as salvage options [14]. There were several studies mentioning the effect of plasmapheresis in treating MAS, but most of the cases were children with rheumatic disorder including systemic juvenile idiopathic arthritis, and SLE [15, 16]. Kaieda.et al reported a dermatomyositis patient with MAS who was successfully treated, in addition to high dose steroid and cyclosporin, with combination of tacrolimus and plasma exchange [17]. In contrast to other therapies which suppress the activated immune system via different pathways, plasmapheresis was supposed to remove the pathogenic cytokines directly [7].

In our case, we initiated pulse steroid therapy and cyclosporine in accordance with the guidelines of treatment for MAS-HLH. Plasmapheresis was administered as the salvage treatment for acute exacerbation of MG; however, it probably contributed to the effective treatment of MAS. We also administered gancyclovir targeting at concurrent CMV infection. Our patient had prominent improvement after above treatments. Plasmapheresis may be a promising and effective salvage treatment in patients with refractory MAS, especially in patients with underlying antibody mediated autoimmune diseases, such as MG.

CONCLUSION

MAS is a rare complication of systemic autoimmune disease with poor prognosis, which may be precipitated by concurrent infection. Early recognition of this syndrome and prompt immune modulation therapy is crucial for successful treatment.

REFERENCES

1. Grom AA, Mellins ED. Macrophage activation syndrome: advances towards understanding pathogenesis. Curr Opin Rheumatol 2010;22:561-566.
2. Rosado FGN, Kim AS. Hemophagocytic Lymphohistiocytosis: an update on diagnosis and pathogenesis Am J Clin Pathol 2013;139:713-727.
3. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2013; 2013:605-611.
4. Lin HK. Macrophage activation syndrome and autoimmune disease. J Intern Med Taiwan 2014; 25: 195-198.
5. Janka GE, Lehmberg K. Hemophagocytic syndromes: an update. Blood Rev 2014;28:135-142.
6. Allen CE, McClain KL Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. Hematology Am Soc Hematol Educ Program 2015;2015:177-182.
7. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. Annu Rev Med 2015;66:145-159.
8. Akenroye AT, Madan N, Mohammadi F, Leider J. Hemophagocytic Lymphohistiocytosis mimics many common conditions: case series and review of

literature. Eur Ann Allergy Clin Immunol 2017;49:31-41.
9. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. J Intensive Care Med 2015;30:401-412.
10. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: Differential diagnosis of HLH and sepsis. Crit Rev Oncol Hematol 2017;114:1-12.
11. Fleischmann R, Böhmerle W, von Laffert M, Jöhrens K, Mengel A, Hotter B, Lindenberg R, Scheibe F, Köhnlein M, von Bahr Greenwood T, Henter JI, Meisel A. Adult hemophagocytic lymphohistiocytosis causing multiorgan dysfunction in a patient with multiple autoimmune disorders: when the immune system runs amok. Clinical Case Rep 2016;4:165-170.
12. Frederiksen JK, Ross CW. Cytomegalovirus-associated hemophagocytic lymphohistiocytosis in a patient with myasthenia gravis treated with azathioprine. Blood 2014:123:2290.
13. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, Kumar A, van Laar JAM, Lachmann G, Nichols KE, Ramanan AV, Wang Y, Wang Z, Janka G, Henter JI. Recommendations for the management of hemophagocytic lymphohistiocytosis in adult. Blood. 2019;133:2465-2477.
14. Bosnak M, Erdogan S, Aktekin EH, Bay A. Therapeutic plasma exchange in primary hemophagocytic lymphohistiocytosis: reports of two cases and a review of the literature. Transfus Apher Sci 2016;55:353-356.
15. Matsumoto Y, Naniwa D, Banno S, Sugiura Y. The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: two case reports. Ther Apher 1998;2:300-304.
16. Aytaç S, Batu ED, Ünal Ş, Bilginer Y, Çetin M, Tuncer M, Gümrük F, Özen S. Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatol Int 2016;36:1421-1429.
17. Kaieda S, Yoshida N, Yamashita F, Okamoto M, Ida H, Hoshino T, Fukuda T. Successful treatment of macrophage activation syndrome in a patient with dermatomyositis by combination with immunosuppressive therapy and plasmapheresis. Mod Rheumatol. 2015;25:962-966.