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

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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. Gancyclovir 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.

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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,
rheumatoid arthritis, and dermatomyositis, etc.\textsuperscript{(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, $1.2 \times 10^3 / \mu L$ (3.8-10.0 x $10^3 / \mu L$) with 70% neutrophils; hemoglobin, 10.5 g/dL (11.0-16.0 g/dL); platelets, $106 \times 10^3 / \mu L$ (140-450 x $10^3 / \mu L$)). 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. Gancyclovir 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.
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 *10^9/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 follow-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 anakinra (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

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