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# Fulminant macrophage activation syndrome in a patient with anti-synthetase syndrome

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## Key message

- Fulminant macrophage activation syndrome can occur in the context of anti-synthetase syndrome and can be treated with etoposide

## Conflicts of interest

The authors have no conflicts of interest to declare.

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Sir,

Macrophage activation syndrome (MAS) is a dreaded life-threatening complication of systemic rheumatic diseases [1]. MAS is closely associated with adult-onset Still's disease but as systemic lupus erythematosus (SLE) is more prevalent, the number of SLE-associated cases is higher [2]. MAS is extremely rare in patients with idiopathic inflammatory myopathy (IIM), especially in subtypes other than dermatomyositis.

We present a case of MAS in a 67-year old Caucasian male, previously diagnosed with anti-synthetase syndrome based on the presence of myositis, interstitial lung disease and the presence of anti-Jo-1 autoantibodies. After initial treatment with methylprednisolone 32 mg and azathioprine 50 mg, he was switched to maintenance treatment with azathioprine 100 mg. Over the last months, treatment had to be escalated due to active disease with rising creatine kinase levels and weight loss. Finally, he was admitted with fever, increased dyspnoea, muscle weakness, and general malaise. Physical examination was notable for tachycardia (101/min) and fever (38,9°C). Laboratory investigations on admission showed pancytopenia (haemoglobin 10,6 g/dl, reference range 14-18; leukocytes 760/µl, reference range 4.000-10.000; thrombocytes 37.000/µl, reference range 150.000-450.000), an extremely high ferritin level (> 100.000 µg/l, reference range 30-400), hypertriglyceridaemia (467 mg/dl, reference range ≤ 150), high transaminase levels (AST 162 U/l, ALT 77 U/l, reference range ≤ 37 and ≤ 41 respectively), elevated LDH (878 U/l, reference range 135-250), low fibrinogen levels (1,5 g/l, reference range 2-3.93) and elevated creatine kinase (1908 U/l, reference range ≤ 190). There was no hepatosplenomegaly on abdominal ultrasound. Shortly after admission, the patient developed haemodynamic instability and was transferred to the intensive care unit. Because of a high clinical suspicion of MAS, treatment with intravenous methylprednisolone 1 mg/kg was initiated. The presence of CD68 positive histiocytes on bone marrow biopsy confirmed the diagnosis of MAS. Central nervous system involvement was excluded by cerebrospinal fluid analysis. Underlying malignancy was excluded by PET-CT scan. Blood and urine cultures remained negative. Because of a positive polymerase chain reaction assay for cytomegalovirus (4,02 log IU/ml), ganciclovir (350 mg IV twice-daily) was associated.

After 4 days, the immunosuppressive treatment was changed to dexamethasone 16 mg/day and cyclosporine 3 mg/kg/day as there was no improvement of the clinical status or laboratory findings, with persistently elevated ferritin levels. After an initial 3-day decline, serum ferritin levels were once again increasing, which led to the initiation of etoposide (150 mg/m$^2$, 3 doses with 4-day intervals) for MAS and intravenous immunoglobulin (2 g/kg total dose in five consecutive daily doses) for the underlying anti-synthetase syndrome. Immediate clinical improvement was observed, while ferritin levels (figure 1) and other laboratory abnormalities gradually normalized. The period after treatment with etoposide was complicated by pneumonia, catheter-related bacteraemia and disseminated fusariosis with fungaemia and pulmonary involvement as evidenced by chest CT. He received appropriate antibiotics and voriconazole. Unfortunately, the patient died 3 weeks later of a massive intracranial bleeding following an accidental fall. Thrombocyte counts and clotting factors had returned to normal at that point, as such, this outcome was deemed unrelated to MAS.

MAS is extremely rare in patients with IIM. Most patients described in literature had dermatomyositis as subtype diagnosis [3]. However, many cases predate the description of the anti-synthetase syndrome as a distinct subtype. At least one fatal case could be retrospectively classified as anti-synthetase syndrome [4]. Of the myositis-specific autoantibodies, anti-Jo-1, anti-Mi-2 and anti-MDA5 autoantibodies have been found in cases of IIM complicated by MAS [4–6]. Besides an active underlying systemic rheumatic disease and immunosuppression as predisposing factors, infections are a frequent additional trigger [1,7] as was the case in our patient.

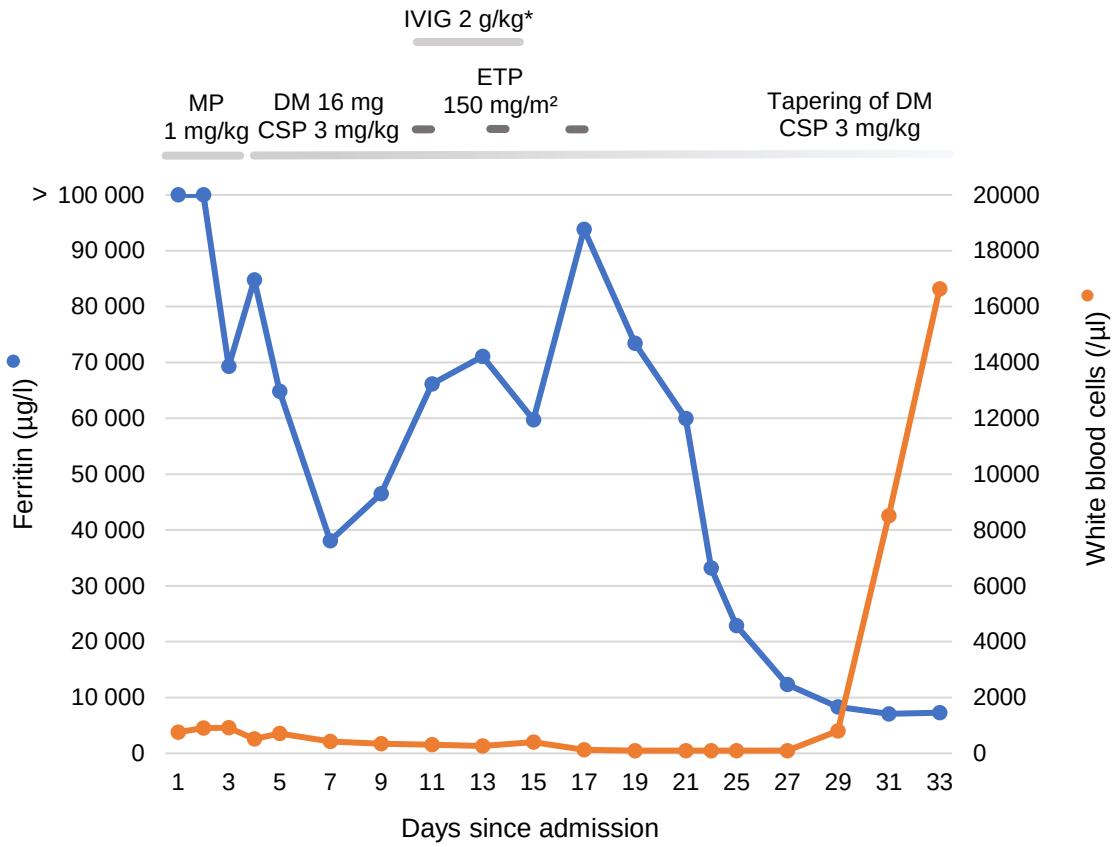
This patient had fulminant refractory MAS with extremely elevated ferritin levels, ultimately requiring etoposide. While many patients with MAS require a combination of immunosuppressive agents, etoposide is seldom needed in adult patients with MAS [1]. In this patient with anti-synthetase syndrome, treatment with etoposide proved successful with normalization of clinical and laboratory parameters. Early use of etoposide should be considered in refractory MAS, even more if an infectious trigger is suspected [1].

To conclude, fulminant MAS can complicate anti-synthetase syndrome and etoposide is a treatment option in these patients.

## References


1. Carter SJ, Tattersall RS, Ramanan A V. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology [Internet]. 2019 Jan 1;58(1):5–17. Available from: https://academic.oup.com/rheumatology/article/58/1/5/4898122
2. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet [Internet]. 2014 Apr [cited 2019 May 23];383(9927):1503–16. Available from: http://dx.doi.org/10.1016/
3. Yajima N, Wakabayashi K, Odai T, Isozaki T, Matsunawa M, Miwa Y, et al. Clinical features of hemophagocytic syndrome in patients with dermatomyositis. J Rheumatol [Internet]. 2008 Sep 1 [cited 2019 May 23];35(9):1838–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18634143
4. Bazan-Socha S, Zolcinski M, Szostek M, Jurczyszyn A, Rucinska M, Demczuk S, et al. A fatal case of acquired hemophagocytic lymphohistiocytosis (macrophage activation syndrome) in the initial course of dermatomyositis with anti-Jo-1 antibody. Int J Rheum Dis [Internet]. 2017 Dec;20(12):2171–4. Available from: http://doi.wiley.com/10.1111/1756-185X.12162
5. Madaule S, Porte L, Couret B, Arlet-Suau E. Fatal haemophagocytic syndrome in the course of dermatomyositis with anti-Mi2 antibodies [5]. Rheumatology [Internet]. 2000 Oct 1;39(10):1157–8. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/39.10.1157
6. Fujita Y, Fukui S, Suzuki T, Ishida M, Endo Y, Tsuji S, et al. Anti-MDA5 Antibody-positive Dermatomyositis Complicated by Autoimmune-associated Hemophagocytic Syndrome That Was Successfully Treated with Immunosuppressive Therapy and Plasmapheresis. Intern Med [Internet]. 2018 Dec 1;57(23):3473–8. Available from: https://www.jstage.jst.go.jp/article/internalmedicine/57/23/57_1121-18/_article
7. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. Rheumatology [Internet]. 2008 Aug 13;47(11):1686–91. Available from: https://academic.oup.com/rheumatology/article-abstract/47/11/1686/1789792

**Figure 1** Evolution of serum ferritin and white blood cell count




CSP cyclosporine, DM dexamethasone, ETP etoposide, IVIG intravenous immunoglobulin, MP methylprednisolone, * total dose