

CASE REPORT

A case of macrophage activation syndrome in a patient with anti-synthetase syndrome

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Abstract

Anti-synthetase syndrome (ASS) is an autoimmune disease characterized by autoantibodies against an aminoacyl transfer RNA synthetase with clinical features including interstitial lung disease, non-erosive arthritis, myositis, Raynaud's phenomenon, unexplained fever and/or mechanic's hands. Macrophage activation syndrome (MAS) is a potentially fatal hyper-inflammatory syndrome that can occur as a complication of systemic rheumatic diseases. However, the association of MAS and ASS has rarely been reported in the literature. Here, we report this association in a patient with overlap ASS and anti-CCP positive rheumatoid arthritis. First line management with steroids was complicated by diabetic ketoacidosis, hence requiring use of anti-IL1 therapy (anakinra) for disease control.

INTRODUCTION

Anti-synthetase syndrome (ASS) is an autoimmune disease characterized by autoantibodies against an aminoacyl transfer RNA (tRNA) synthetase with clinical features that may include interstitial lung disease (ILD), non-erosive arthritis, myositis, Raynaud's phenomenon, unexplained fever and/or mechanic's hands [1]. Macrophage activation syndrome (MAS) can be a fatal complication of rheumatic disorders. It has rarely been reported in patients with ASS. Here, we describe this association in an adult patient.

CASE REPORT

We present a case of 65-year-old Nepalese female with an overlap of ASS and anti-cyclic citrullinated peptide (CCP) antibody positive rheumatoid arthritis (RA) who developed MAS which was successfully treated with anakinra. She was diagnosed with ASS based on the presence of arthritis, ILD, anti-Jo1 and antiRo52 autoantibodies. She was maintained on 6-monthly Rituximab cycles (one 1gm infusion repeated 15 days after the first for each cycle), completed two cycles, last given 6 months prior

to her presentation. In view of the coronavirus disease 2019 (COVID-19) pandemic the third cycle was withheld and Azathioprine was commenced which she took for 2 weeks. Two weeks prior to her admission Azathioprine was switched to an up titrating dose of Mycophenolate due to nonspecific symptoms of headache and dizziness attributed to possible medication intolerance. She was admitted with fever, abdominal pain and headaches. Clinical examination revealed pyrexia (38.3°C), hypotension (109/70 mmHg), tachycardia (HR 94 bpm) and palmar maculopapular rash. Laboratory investigations showed pancytopenia, Hb 100 (115–165 g/L), WCC 2.40 ($4\text{--}11 \times 10^9/\text{L}$), Platelets 61 ($150\text{--}450 \times 10^9/\text{L}$), Neutrophils 1.75 ($2\text{--}7 \times 10^9/\text{L}$), lymphocytes 0.50 ($1\text{--}4 \times 10^9/\text{L}$), Ferritin of $>55\,000$ (15–300 ug/L), Triglycerides 4.3 (1.8 mmol/L), LDH 1200 (135–214 IU/L), Fibrinogen 2.8 g/l (normal), ALT 108 (<34 IU/L), CRP 141 (0–6 mg/L) and ESR 24 mm/hr.

A septic screen for common bacterial and viral pathogens including parvovirus, Epstein-Barr virus, Cytomegalovirus, human immunodeficiency virus and hepatitis was negative. Multiple covid-19 swabs were negative. Computed tomography of chest, abdomen and pelvis showed no evidence of hepatosplenomegaly or an underlying malignancy. Lack of

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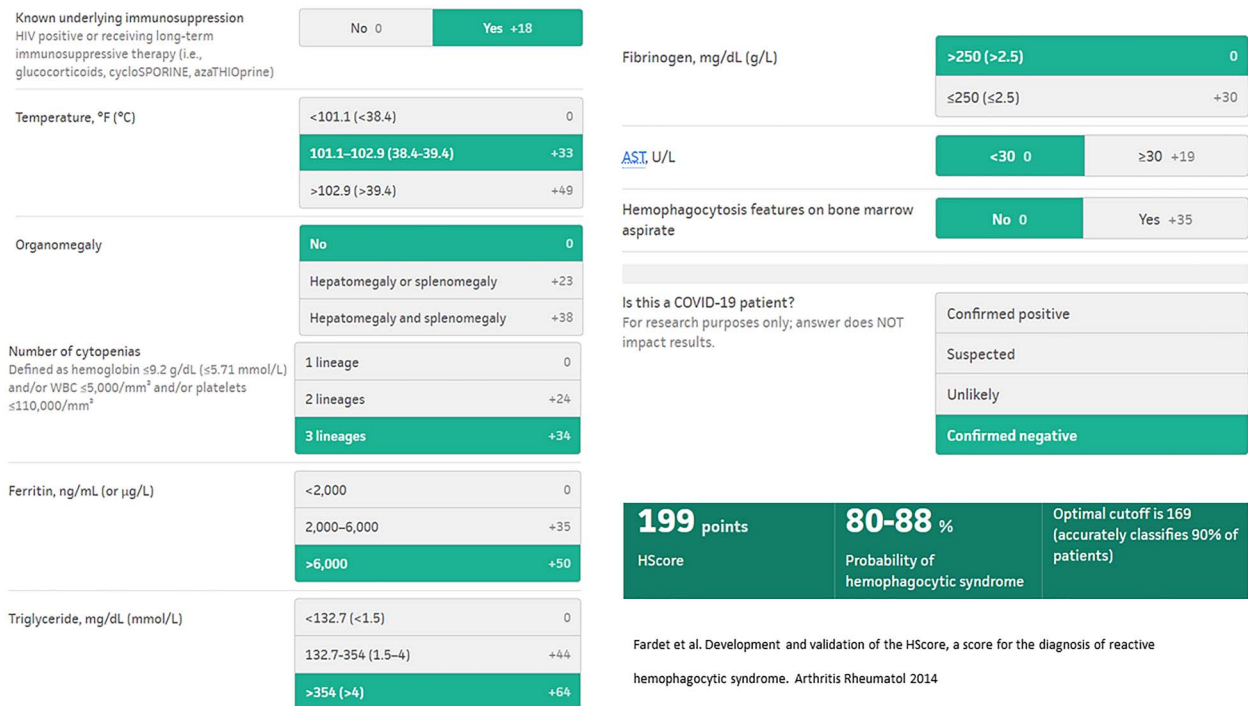


Figure 1: H score.

improvement with broad-spectrum antimicrobials, evolving pancytopenia, elevated ferritin and persistent fever with patient's background history of autoimmune disease raised concerns about MAS. She fulfilled the 2014 HScore by Fardet et al. [2] with a score of 199 (cut off 169), (Fig 1). Treatment with IV methylprednisolone 15 mg/kg/day for 3 days was initiated followed by oral prednisolone, 60 mg along with ciclosporin 2 mg/kg/d. She had a history of type 2 diabetes, was on oral hypoglycaemic medications but developed hyperglycaemia and ketosis secondary to steroid and required insulin therapy. Anakinra 100 mg once daily subcutaneously was added after Multidisciplinary team discussion to reduce steroid toxicity and facilitate a rapid steroid taper, whilst providing optimal disease control. Immediate clinical improvement was noted with normalization of fevers and gradual normalization of laboratory abnormalities including ferritin, cell counts (Fig 2) and inflammatory markers. We believe an underlying rheumatic immune disorder was the likely predisposing factor for the development of MAS in our patient, as she was not maintained on biologic/immunomodulatory therapy due to paused Rituximab in view of COVID-19 pandemic and possible intolerance to various agents.

DISCUSSION

Haemophagocytic lymphohistiocytosis (HLH) is characterized by an unregulated inflammatory response with cytokine storm leading to multisystem organ failure and can be fatal if not recognized and treated promptly. HLH can be familial (primary) or acquired (secondary to infection, malignancy or active autoinflammation). Secondary HLH (sHLH) in association with rheumatologic autoimmune diseases including systemic lupus erythematosus, adult-onset Still disease, and systemic juvenile idiopathic arthritis is known as MAS [3]. However, it is rarely seen in patients with ASS and has been described only in case reports where most patients reportedly suffered from dermatomyositis.

Anti-Jo-1, anti-Mi-2 and anti-MDA-5 autoantibodies have been found in cases of idiopathic inflammatory myositis complicated by MAS [4]. Early diagnosis is often challenging due to clinical manifestations mimicking sepsis, active autoimmune diseases and lack of widely accepted diagnostic criteria. Various tools have been developed which use clinical symptoms and laboratory abnormalities to risk-stratify patients but have limitations. The H-score by Fardet et al. [2] has been validated for the diagnosis of reactive HLH and subsequently showed good diagnostic accuracy in an observational study by Knaak et al. [5]. However, clinical judgement and awareness of the condition remains paramount in diagnosis. Timely diagnosis and treatment to reduce systemic inflammation is imperative to reduce high mortality. High-dose glucocorticoid monotherapy is usually the first line treatment with subsequent addition of immunomodulatory agents in refractory cases [6]. Over recent years, various biologics and immunotherapies have been used successfully for MAS treatment. This also includes Anakinra, a recombinant interleukin-1 (IL-1) receptor antagonist used in various autoinflammatory diseases. Although limited, there are now case reports and series showing favourable response to anakinra, both subcutaneously and intravenously in sHLH subtypes [7]. Its use is also appealing due to relatively short half-life that permits its discontinuation if an adverse effect occurs or concern for worsening infection arises.

Our case was challenging as patient initially manifested joint symptoms with positive immunology for RA and later developed ILD with positive ASS immune profile in the absence of clinical myositis, typical skin rash and normal CK levels. Aminoacyl tRNA positivity has been described in patients who fulfilled RA diagnostic criteria in the literature and hence ASS is an important clinical condition in the differential diagnosis of early RA. It has been reported that development of myositis can take years after onset of arthritis and ILD, which are also not rarely seen before myositis and in some myositis never occurs [8]. The most common arthritis pattern seen in ASS is small joint

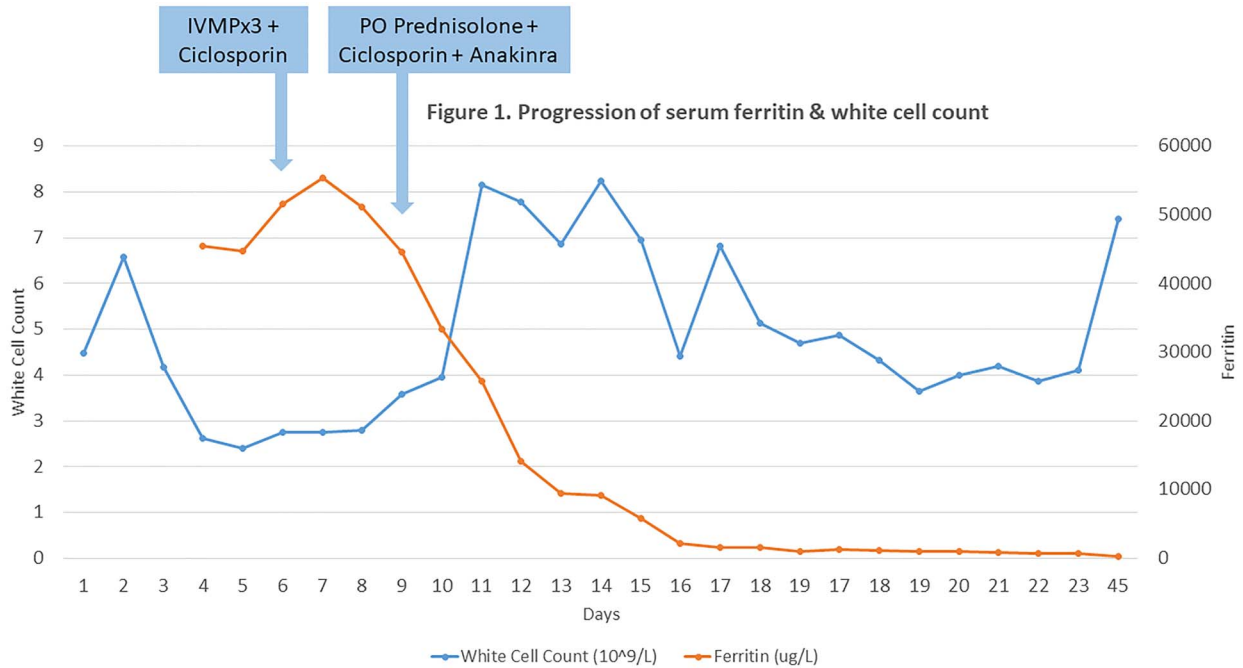


Figure 1. Progression of serum ferritin & white cell count

Figure 2: Progression of serum ferritin and white cell count.

symmetrical polyarthritis quite similar what seen in RA. AntiCCP and rheumatoid factor positivity can be observed in ASS and lead to false RA diagnosis [9]. On the other hand, established knowledge that ASS is seen in cases with classical RA is quite limited. Current literature regarding the use of anakinra in cases of adult MAS is limited, further information regarding its effectiveness and potential clinical benefits and risks is needed [10]. In this case, however, we had a successful response and outcome in resistant MAS associated with ASS using anakinra.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

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ETHICAL APPROVAL

Not applicable.

CONSENT

An informed consent for publication has been obtained, Identifying details of the.

Patient have not been used in this case report.

GUARANTOR

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REFERENCES

- Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest* 2010;**138**:1464–74.
- Fardet, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–20.
- Tristano AG. Macrophage activation syndrome: a frequent but under-diagnosed complication associated with rheumatic diseases. *Med Sci Monit* 2008;**14**:RA27–36.
- Bazan-Socha S, Zolcinski M, Szostek M, 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* 2017;**20**:2171–74.
- Knaak C, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. *Crit Care* 2020;**24**:244. doi: 10.1186/s13054-020-02941-3.
- Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. *Annu Rev Med* 2015;**66**:145–59.
- Halyabar O, Chang MH, Schoettler ML, Schwartz MA, Baris EH, Benson LA, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatr Rheumatol Online J* 2019;**17**:7.
- Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. *Curr Rheumatol Rep* 2011;**13**:175–81.
- Mumm GE, McKown KM, Bell CL. Antisynthetase syndrome presenting as rheumatoid-like polyarthritis. *J Clin Rheumatol* 2010;**16**:307–12.
- Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015;**125**:2908–14.