CASE REPORT

Fatal case of macrophage activation syndrome (MAS) in a patient with dermatomyositis and cytomegalovirus (CMV) viraemia

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SUMMARY

We describe a case of an adult with dermatomyositis (DM) who presents with a rash, high fevers, tachycardia and hypotension, initially concerning for an infectious aetiology or a DM flare. She was found to have cytomegalovirus viraemia which improved after starting valganciclovir. After extensive workup and lack of improvement with broad-spectrum antimicrobial therapy, intravenous immunoglobulin and steroids, the patient was diagnosed with macrophage activation syndrome after bone marrow biopsy and levels of soluble CD25 (soluble interleukin (IL)-2 receptor) and IL2 were obtained. Unfortunately, despite therapy with dexamethasone, anakinra and etoposide, the patient decompensated and the patient's family opted for comfort care. The patient subsequently expired in the intensive care unit.

BACKGROUND

The present case describes macrophage activation syndrome (MAS) associated with dermatomyositis (DM) and cytomegalovirus (CMV) viraemia. MAS is a rare condition of profound systemic but ineffective immune activation affecting multiple organs with high mortality. MAS is considered a subtype of haemophagocytic lymphohistiocytosis (HLH) associated with rheumatological disorders. HLH is split into two categories: familial, associated with inherited immunodeficiencies and secondary, associated with three categories of triggers in adults: (1) infectious, (2) autoimmune and (3) neoplastic. Among infectious triggers, viral infections are the most common. DM is one of the rare causes of MAS, which is more commonly associated with systemic juvenile idiopathic arthritis (sJIA) or systemic lupus erythematosus.¹ Up to one-third of adults with HLH have more than one trigger identified,² and in this case, it is possible that the CMV viraemia reactivated in the setting of the patient's DM and critical illness or was an independent trigger of MAS. CMV infection is known to occur in patients with DM,^{3,4} and CMV titres are known to increase in critically ill patients in the intensive care unit (ICU).⁵ Our patient was a schoolteacher and was likely exposed to CMV prior to her presentation. The significance of CMV reactivation in critically ill patients is unknown⁵; however, unfortunately in our patient, it likely had fatal consequences.

Viral infections are a known trigger of HLH, although in one review only 9% of cases triggered by viruses were due to CMV while most cases are associated with Epstein-Barr virus (43%).² Most patients diagnosed with CMV triggering HLH are immunosuppressed,⁶⁻⁸ and there are only a handful of case reports that describe CMV as the trigger for HLH in an immunocompetent host.⁹⁻¹¹ There are no other case reports in the literature that describe a patient with CMV viraemia in the setting of DM as a trigger for MAS.

MAS is known to have a high mortality, up to 20% in a study of 30 cases,¹² although in some reports mortality is even higher.^{13,14} Given the high mortality, the end-organ damage that can occur with severe immune activation and the benefit that early etoposide administration can afford patients,¹⁵ timely diagnosis of MAS is imperative. However, early diagnosis is often very challenging because systemic manifestations of MAS are not specific and often resemble those of infectious processes. Similar symptoms between MAS and sepsis, in particular tachycardia, fevers, hypotension and cytopenias make it difficult to distinguish these two diseases early in the course of illness. Unfortunately, as a result, the diagnosis is often delayed; Tseng *et al* note that the median time from symptom onset to the diagnosis of HLH was 34.5 days.¹⁶ Unfortunately, no guidelines exist for the diagnosis of MAS associated with DM.

Guidelines exist for the diagnosis of HLH and for MAS associated with sJIA. Criteria for the diagnosis of HLH include either (A) a molecular diagnosis of HLH (such as testing for *PRF*, *UNC13D* or *STX11* mutations) or (B) five of the following eight criteria: (1) fever, (2) splenomegaly, (3) cytopenias affecting ≥ 2 of 3 cell lines in peripheral blood, (4) hypertriglyceridaemia or hypofibrinogenaemia, (5) haemophagocytosis in bone marrow or spleen, (6) low or absent natural killer-cell activity (according to local lab reference), (7) ferritin $>500 \mu\text{g/L}$ and (8) soluble CD25 (soluble IL-2 receptor) $\geq 2400 \text{ U/mL}$.¹⁷ Guidelines for MAS are published only for sJIA. Preliminary guidelines proposed by clinicians were published first in 2004¹⁸ and were reviewed as a diagnostic tool compared with the HLH guidelines and found to be superior, with the addition of hyperferritinaemia to these preliminary guidelines improving the ability to distinguish MAS from systemic infection.¹⁹ More recently, new guidelines

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for MAS due to sJIA were published by the European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organization which are based on both expert consensus and a retrospective cohort of patients with JIA-associated MAS.²⁰ However, no study has been performed to see if these guidelines improve mortality in patients with sJIA.

Given the high mortality and known delay in diagnosis of HLH, guidelines are needed for the diagnosis of DM-associated MAS in order to aid in early diagnosis and administration of treatment. Unfortunately, these guidelines are difficult to write given the rarity of the disease and lack of clinical trial data.

CASE PRESENTATION

A middle-aged woman with recently diagnosed DM presented with fevers and diffuse arm and leg pain of 1 month duration. Five months prior to presentation, she developed a new onset rash and muscle aches and was diagnosed with DM. Records were unavailable but per clinical history, diagnosis was made by blood tests alone and no biopsy was performed. Therapy with methotrexate, prednisone and azathioprine was initiated and maintained. She took no other medications and her symptoms had gradually improved, until 1 month prior to presentation when she developed fevers, diffuse muscle pains and a rash on her face, arms and legs. She denied nausea, vomiting, weight loss, sick contacts, tobacco use, recreational drug use or recent travel.

INVESTIGATIONS

On admission, vitals were notable for fever up to 102.9°F, tachycardia to 125 beats/min, blood pressure 115/60 mm Hg, normal respiratory rate and her oxygen saturation on room air of 97%. Physical examination revealed heliotrope rash of eyelids, malar rash, eyelid oedema and diffuse erythematous rash on arms and legs, as well as significant musculoskeletal tenderness to palpation on upper and lower extremities and oral thrush. Cardiac, respiratory, gastrointestinal neurological examinations were unremarkable.

Routine labs were notable for hyponatremia (serum sodium 132 meq/L, reference 135–145 meq/L), preserved kidney function (serum creatinine of 0.39 mg/dL, reference 0.51–0.95 mg/dL), transaminitis (aspartate aminotransferase 60 units/L reference 10–35 units/L, alanine aminotransferase 71 units/L reference 10–35 units/L), elevated alkaline phosphatase (333 units/L, reference 35–104 units/L), normal total bilirubin, new leucopenia to 2.70 (reference $4.22\text{--}10.33 \times 10^9/\text{L}$) and ferritin elevated at 5665 ng/mL (reference 13–150 ng/mL). Autoimmune serologies obtained showed positive antinuclear antibodies (1:1280 with speckled pattern), extractable nuclear antigens (ENA) ribonucleoprotein (RNP) antibody positive (5.3 units, reference <1.0), ENA Anti-Sjogren's Syndrome A (Ro) antibody positive (>8.0 units, reference <1.0), ENA Anti-Sjogren's Syndrome B (La) antibody negative, ENA anti-histadyl-transfer RNA synthetase antibody (Jo-1) antibody negative, myositis MI-2 antibody weakly positive (reference negative), all other myositis antibodies negative (antisynthetase antibodies such as anti-threonyl-transfer RNA synthetase antibody (PL-7), anti-analyl-transfer RNA synthetase antibody (PL-12), anti-glycyl-transfer RNA synthetase antibody (EJ), anti-isoleucyl-transfer RNA synthetase antibody (OJ), anti-Ku (KU), auto antibodies to spliceosome components such as anti-U2 sn (small nuclear) RNP Antibody (U2 SN RNP), and anti-signal recognition particle (SRP)). Given the presence of systemic inflammatory

response syndrome criteria, high fevers, tachycardia and hypotension to 89/45 mm Hg that patient developed shortly after admission, along with lactate elevation to 4.9 mmol/L (reference 0.5–2.2 mmol/L), infectious aetiologies were suspected and so patient was started on broad-spectrum antibiotics including intravenous vancomycin and cefepime. Routine infectious workup including blood cultures, chest radiograph and urine cultures was negative, and patient did not improve. Further infectious studies including fungal blood cultures and CMV blood PCR were sent. Infectious workup was notable for a CMV PCR of 15 600 copies/mL (increased from prior 2340 copies/mL 1 month prior). Treatment for CMV was started with valganciclovir 900 mg twice daily. Rheumatology recommended ordering anti-dsDNA antibody, rheumatoid factor (RF) due to concern for lupus overlap syndrome given appearance of malar rash and the positivity of anti-RNP antibody and anti-Ro (SSA) antibody, and also started intravenous immunoglobulin (IVIG) (two doses), prednisone and mycophenylate 500 mg twice daily. Rheumatoid factor resulted as normal (11 IU/mL, reference 0–14.0 IU/mL) and anti-dsDNA antibody was negative. After receiving IVIG, her rash improved and several days later her leucopenia resolved. Given DM, a diagnostic workup of malignancy was pursued with CT chest/abdomen/pelvis which was negative for any findings suggestive of malignancy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis after initial presentation included sepsis from CMV infection or another source, lupus overlap syndrome, DM flare, marantic endocarditis and MAS.

TREATMENT

Unfortunately, the patient significantly decompensated and required intubation due to hypoxia, and chest radiograph showed diffuse pulmonary infiltrates. Her leucopenia recurred and her white cell count was 2.85 (reference $4.22\text{--}10.33 \times 10^9/\text{L}$). Bronchoscopy was performed and bronchoalveolar lavage sent for infectious workup including aerobic cultures, anaerobic cultures, *Legionella* culture, *Pneumocystis jiroveci* DFA, *Nocardia* culture, fungal culture and smear, viral culture and acid-fast bacilli cultures all of which were negative. Lumbar puncture also performed and studies were unremarkable. CMV titer subsequently rechecked and was 2200 copies/mL. Leucopenia worsened, although this was felt to be due to drug side effect of valganciclovir and not worsening of disease process at the time.

Haematology was consulted due to continued high fevers, elevated ferritin and concern for MAS. Soluble CD25 was elevated at 9910 pg/mL (reference <1033 pg/mL) and IL-237 900 pg/mL (<1033 pg/mL). Bone marrow biopsy was performed 18 days after admission and showed pancytopenia with hypercellular marrow, megakaryocytic and granulocytic hypoplasia and haemophagocytosis (figure 1). Ferritin had increased to 18 409 ng/mL. Anakinra was started and steroids were switched to dexamethasone. Unfortunately, patient did not improve; she was started on etoposide also without improvement. Ferritin further increased to 82 000 ng/mL.

OUTCOME AND FOLLOW-UP

Patient subsequently deteriorated haemodynamically requiring vasopressors and was found to have polymicrobial gram-negative bacteremia with *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and extended-spectrum beta-lactamase producing *Escherichia coli* thought to be secondary to a hospital acquired

Figure 1 Bone marrow biopsy aspirate smear showing histiocyte proliferation and phagocytosis of cellular components in the cytoplasm of histiocytes.

urinary tract infection. At the time, patient also had an arterial line, a central venous catheter at right internal jugular vein and foley catheter. Given deterioration and poor prognosis, family decided to withdraw care and the patient passed away.

DISCUSSION

MAS in patients with DM is recognised as a rare phenomenon and has been described only in case reports.^{12 21–23} Early diagnosis of MAS is beneficial for patients, before inflammatory tissue damage has become irreversible. In our case, rheumatology considered MAS in the differential diagnosis on initial consultation; however, biopsy of bone marrow, soluble CD25 and IL-2 were not pursued initially as the patient's presentation was thought to be due to DM flare or CMV viraemia and not MAS, and she initially improved with IVIG. Her leucopenia worsened during admission; however, this was thought to be related to other factors, namely, drug side effect of valganciclovir or infection with CMV.

In terms of how to expedite the diagnostic process for patients with MAS, several suggestions have been made including earlier bone marrow biopsies or changing the ferritin threshold. Bazan-Socha *et al* propose that patients with autoimmune disease who have high fevers that do not respond to other therapy should be considered for bone marrow biopsy if cytopenias are present.²¹ Atteritano *et al* suggest that clinicians taking care of such a patient should have a higher clinical suspicion for MAS and check pertinent labs and consider bone marrow biopsy earlier in the course of the illness.¹ However, early bone marrow biopsy may not be the most beneficial path, given that it is an invasive test and studies show that it is only 60% specific and 83% sensitive for haemophagocytosis.^{24 25}

Increasing the ferritin threshold used for the HLH criteria has also been studied in order to aid in diagnosis.^{26–29} The ferritin level for HLH criteria is $>500 \mu\text{g/L}$; however, ferritin may be much higher than this in patients with MAS/HLH.¹³ In one study in the paediatric population, ferritin $>10\,000 \mu\text{g/L}$ had a 90% sensitivity and 96% specificity for HLH.²⁷ Unfortunately, this does not translate to the adult population. Schram *et al* investigated 113 adult patients with ferritin $>50\,000 \mu\text{g/L}$ and found that high ferritin is not specific for HLH in adults.²⁸ Further, Schraffner *et al* found that among patients with ferritin $>2000 \mu\text{g/L}$, the most common diagnosis was hepatocellular injury and HLH/MAS

only occurred in 3% of these patients.²⁹ Saeed *et al* performed a study of 344 patients admitted to the intensive care unit, nine of whom had HLH. Average ferritin for patients without HLH was $1180 \mu\text{g/L}$ and for those with HLH was $25\,652 \mu\text{g/L}$ ($p < 0.001$).²⁶ These authors suggest that based on their results, the threshold of ferritin should be increased to $3952 \mu\text{g/L}$. Consensus about a higher ferritin cut-off for HLH has not been established. None of these studies were conducted in patients with MAS, but rather with HLH. Studies in patients with MAS are needed in order to define a ferritin cut-off (perhaps higher than $500 \mu\text{g/L}$) to aid in the rapid diagnosis of these cases.

Finally, the use of glycosylated ferritin has been investigated as a tool to aid in the diagnosis of HLH.³⁰ In a study of 23 patients, low percentage ($\leq 20\%$) of glycosylated ferritin was strongly consistent with a diagnosis of HLH.³¹ Based on the results of these small studies, low glycosylated ferritin may be a useful tool to identify patients with HLH who would benefit from treatment.

The creation of specific guidelines for sepsis management in patients with autoimmune conditions would benefit patients with MAS. Diagnostic criteria specific for MAS in adults would also be beneficial as recognising these syndromes is challenging. The applicability of the diagnostic criteria for MAS due to sJIA should also be studied for other rheumatological diseases. Though clinical trial data is needed to support these practices, the unfortunate rarity of this condition is a major barrier to obtaining this information.

Learning points

- Macrophage activation syndrome (MAS) is a rare disease that is commonly recognised in children with systemic juvenile idiopathic arthritis, but can also occur in adults with other rheumatological diseases such as dermatomyositis.
- Clinicians should have a high level of suspicion to diagnose MAS in patients with dermatomyositis with high fevers, cytopenias in two cell lines and high serum ferritin.
- Early diagnosis and treatment may benefit these patients; however, objective data in this area is lacking due to rarity of this disease and lack of clinical trials.

Contributors AVL was the resident who took care of the patient. She wrote the manuscript of the case report and coordinated all edits between the other authors. AB was the wards attending who took care of the patient. She has read and edited the manuscript significantly and approves this draft. SK was the rheumatology attending who saw the patient as a consultant. He read and edited this draft and approves this version. He also answered numerous questions I had about his decision making when I was writing up the case. WC read the bone marrow biopsy and provided the description of the image. She read the draft and provided significant edits. She approves this manuscript.

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