CASE REPORTS

UnMASking the diagnosis: Acute severe necrotizing pancreatitis in the setting of systemic lupus erythematosus complicated by macrophage activation syndrome

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ABSTRACT

Systemic lupus erythematosus (SLE) is a common rheumatologic condition with known GI involvement. Acute pancreatitis (AP) is a rare GI complication of SLE and is typically associated with increased disease activity. Macrophage activation syndrome (MAS) is an unusual, hyper-inflammatory response to a rheumatologic stimulus characterized by hyperferritinemia, pancytopenia, thermal dysregulation and multi-organ dysfunction. MAS, more commonly seen in children, has been reported to complicate both adult onset SLE and AP. We present a case of necrotizing AP secondary to an SLE flare complicated by MAS in an adult patient successfully treated with anakinra.

Key Words: Pancreatitis, Anakinra, Macrophage activating syndrome

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic immune-mediated disease, likely affecting greater than 0.1% of Americans.[1] SLE has numerous gastrointestinal manifestations such as ulcerations throughout the GI tract, mesenteric vasculitis and hepatobiliary disease.[2] Acute pancreatitis (AP) secondary to lupus is a rare gastrointestinal complication. It is thought that 0.7% to 4% of cases of AP in SLE are secondary to SLE.[3] SLE-associated AP is much more common in children than adults. Additionally, SLE flares may lead to macrophage activation syndrome (MAS): A hyperinflammatory response to uncontrolled rheumatologic disease.[4] In these patients, rapid decompensation is common and often necessitates aggressive supportive care. Prognosis is often grim even with successful treatment of the underlying rheumatologic disorder. Anakinra is an IL-1 antagonist, which has been successfully used in cases of MAS.[5] Adult cases of SLE-associated AP complicated by MAS are very rare. We present a unique case of and adult with SLE-associated AP who ultimately developed MAS requiring anakinra.

2. CASE REPORT

A 29-year-old female with untreated SLE (diagnosed 5 years prior to current presentation, manifested by ANA 1:1,280, RNP positive, Anti-smith positive, and complicated by Grade 5 SLE nephritis) was transferred to our hospital for severe

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necrotizing AP. She complained of epigastric pain, nausea and oral intolerance. Labs and imaging revealed a lipase > 3,000 U/L with a CT scan demonstrating necrosis and inflammation of the pancreatic head (see Figure 1). Resuscitation and antibiotics were initiated immediately upon arrival along with stress-dosed steroids. Despite prompt therapy, the patient developed tachycardia, hypothermia, lactate elevation to 17.2 mmol/L, and signs of impending respiratory failure. A chest radiograph was obtained, consistent with pulmonary edema. An APACHE-II score was calculated (see Table 1) to be 17. Given the patient's rapid decompensation, she was transferred to the medical ICU, intubated and placed on mechanical ventilation. Lab results following transfer demonstrated evidence of disseminated intravascular coagulation with pancytopenia, elevated ANA and dsDNA, as well as ferritin of 1,332 ng/ml. Resuscitation with intravenous fluids and cryoprecipitate was started. After alternative causes for AP were ruled out, the patient was treated with methylprednisolone for SLE-associated AP. After several days of therapy, she improved significantly and was extubated. However, shortly after de-escalation of therapies the patient decompensated. Her serum ferritin was rechecked and found to be > 2,000 ng/ml. This finding in the setting of the patient's pancytopenia and hypofibrinogenemia raised concern for MAS. While the patient continued to deteriorate, we elected to to start anakinra following expert consultation and case review. Over the next several days, the patient showed significant improvement and was discharged.

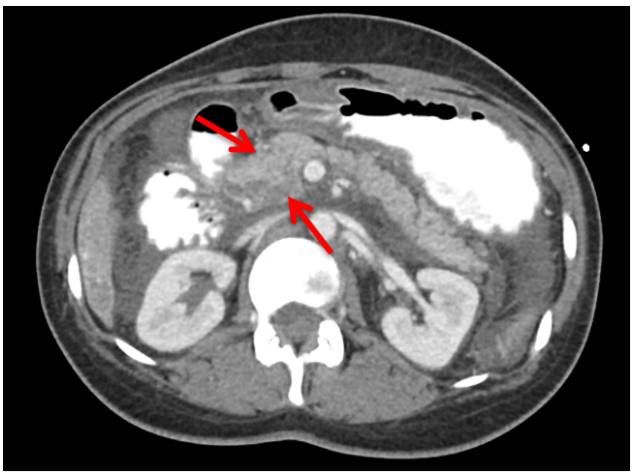

Figure 1. CT scan of the abdomen with contrast. Red arrows showing heterogeneous appearing pancreatic head and uncinate process suggestive of pancreatitis, with necrotic foci in pancreatic head.

3. Discussion

Pancreatitis is a common condition causing a wide spectrum of disease.[6] SLE is a rare cause for pancreatitis; however, an important one to consider in patients with SLE. AP occurs in 1%-8% of SLE patients and is proposed to be the result of vascular damage.[7] The diagnosis of SLE-related pancreatitis requires the exclusion of more common causes for pancreatitis, as well as evidence of increased disease activity. The treatment for SLE-associated AP includes the standard care for pancreatitis, however, immunomodulatory drugs are necessary in order to control the underlying SLE. In the acute or severe setting, this traditionally includes corticosteroids, sometimes combined with calcineurin inhibitors such as tacrolimus and cyclosporine.[8,9] In this patient, initial treatment with methylprednisolone was not adequate to achieve complete therapeutic response necessitating an alternative therapeutic strategy.

Table 1. Patient's APACHE-II score

Physiologic Variable	Value	Score
Temperature	**34.7℃**	**1**
MAP	95 mmHg	0
HR	106	0
RR	**38**	**3**
Oxygenation	95 mmHg	0
pH	**7.25**	**2**
Sodium	132 mmol/L	0
Potassium	5.0 mmol/L	0
Creatinine	1.24 mg/dl	0
Hct	**24.5%**	**2**
WBC	**2.2×10^3**	**2**
GCS (15-X)	15	0
HCO_3	**19 mmol/L**	**2**
Immunocompromised?	**Yes**	**5**
	Total Score:	17

During her ICU course, the patient's ferritin downtrended appropriately. When the patient began exhibiting signs of worsening after extubation, a repeat ferritin level was higher than any previously recorded. This finding raised concern for MAS as a complication of SLE-associated AP. MAS complicates approximately 5.5% of childhood SLE compared to 0.7% of adult SLE.[10] In both adult and pediatric populations, MAS and SLE have been documented to occur in the setting of pancreatitis. When seen with AP-associated SLE, MAS has a very high mortality. This makes maintaining a high index of suspicion for MAS in critically ill SLE-associated AP important.

MAS is fundamentally the same condition as hemophagocytic lymphohistiocytosis (HLH) when seen in a patient with a rheumatologic etiology. Therefore, the HLH-2004 criteria are used to diagnose MAS (see Table 2).[11] However,

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these criteria were developed primarily for pediatric patients and not specifically for MAS. Thus, it is not necessary for the criteria to be met in adults if the clinical presentation is highly suggestive of MAS.[12] In this particular case, only three of the classic diagnostic criteria were met, however, the presentation was convincing enough to initiate therapy. Given the patient's brisk response, we are confident in this diagnosis.

Table 2. Diagnostic criteria for HLH/MAS

Fever ≥ 38.5°C
Splenomegaly
Peripheral blood cytopenia, with at least two of the following:
Hemoglobin < 9 g/dl (hemoglobin < 10 g/dl for infants < 4 weeks)
Thrombocyte count < 100,000/ml
Absolute neutrophil count (ANC) < 1,000/ml
Fasting triglycerides > 265 mg/dl and/or Fibrinogen < 150 mg/dl
Hemophagocytosis in bone marrow, spleen, lymph node, or liver
Low or absent NK cell activity
Ferritin > 500 ng/ml
Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms (or > 2,400 U/ml, often cited in the literature)

When considering treatment options, our initial inclination was towards cyclophosphamide given that it is effective for lupus and has been shown to be useful in cases of MAS.[13] However, cyclophosphamide is well known for significant hematologic and urologic side-effects. Thus, in the absence of progressive lupus nephritis, there was no compelling indication for this drug. Etoposide, a drug recommended in several treatment protocols for HLH, also carries with it several organ toxicities and is known to cause bone marrow suppression.[14] Anakinra is an IL-1 antagonist which has been studied extensively and found to be very effective in Adult Onset Still's Disease (AOSD), a process driven in part by IL-1b.[15] In AOSD complicated by MAS, anakinra resulted in complete resolution of MAS symptoms.[16] MAS itself is associated with a tremendous "cytokine storm" including IL-1. This provides a mechanistic explanation for the efficacy of anakinra in such patients. Furthermore, the side effect profile of this drug is more favorable than the options available for the treatment of MAS. We therefore opted for treatment with anakinra, resulting in brisk and sustained clinical improvement.

This case uniquely illustrates a rare etiology of AP complicated by MAS. It highlights the importance of recognizing SLE as a cause pancreatitis in lupus patients without an alternative explanation. It further demonstrates a complication that clinicians must be cognizant of when taking care of critically ill patients with SLE-associated AP since recognition and prompt therapy are vital. Finally, to the best of our knowledge, this is the only reported case of refractory MAS due to SLE induced AP necessitating treatment with anakinra.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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