CLINICAL VIGNETTE

Adult Still's Disease Complicated by Macrophage Activation Syndrome

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Case Presentation

A 31-year-old female presented to the Emergency Department for evaluation of fever and joint pain for 9 months. Her fevers were episodic with temperatures as high as 105 degrees F. Her joint pain was most prominent in the ankles, hips, and small joints of her hands. She also reported significant fatigue and an evanescent rash involving her face, chest, arms, and legs. Extensive workup had been pursued at outside hospitals to exclude an infectious cause such as tuberculosis, HIV, and infective endocarditis. She even underwent lymph node biopsy, bone marrow biopsy, and splenectomy for massive splenomegaly. Pathology for all of these returned unrevealing.

Upon arrival in the Emergency Department, the patient was febrile to 101.7 degrees F, lethargic, reporting diffuse joint pain. Her exam was notable for tender cervical and inguinal lymphadenopathy, hepatomegaly, and tenderness with passive range of motion in the hips and ankles. Laboratory workup was notable for a white blood cell count of 23.7 with 79% neutrophils. Other initial laboratory studies were notable for AST 156, ALT 32, alkaline phosphatase 385, total bilirubin 0.7. Due to her persistent symptoms with no clear diagnosis from the workup done to date, the patient was admitted for evaluation of her fever of unknown origin.

Blood and urine cultures returned without significant growth. Additional serologies were sent to exclude atypical infections (i.e. Tuberculosis Cryptococcosis, Aspergillosis, EBV, CMV, among others) and autoimmune conditions (i.e rheumatoid arthritis, lupus). All returned negative. Given her negative serologies and constellation of clinical features, a diagnosis of Adult Still's disease was made.

Interestingly, some of the patient's laboratory findings could not be solely attributed to her new diagnosis of Adult Still's Disease. Serum ferritin level of 14,649 ng/mL (normal range: 8-180 ng/mL) was out of proportion to what might be seen in anemia caused by chronic inflammation alone. Additionally, her low serum fibrinogen level required frequent cryoprecipitate transfusions. These lab abnormalities prompted further serologic workup, revealing a low natural killer cell activity and high IL-2 receptor level. These findings, in combination with her fevers and history of splenomegaly, fulfilled criteria for a secondary diagnosis of hemophagocytic lymphohistiocytosis.

Our patient was started on high dose prednisone at 1 mg/kg with rapid improvement in her symptoms. She was discharged with plans to complete a slow prednisone taper over the several months. She has recently undergone evaluation for treatment with Anakinra, a recombinant IL-1 receptor antagonist that may provide more targeted immune-modulating therapy.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal condition characterized by inappropriate macrophage activation and excessive cytokine production. While some cases of HLH occur as a result of genetic mutations, most are due to acquired infections, malignancies, or autoimmune conditions, such as Adult Still's Disease. HLH occurring in the context of an autoimmune condition is formally referred to as Macrophage Activation Syndrome (MAS). Cases of MAS are most often reported in patients with Adult Still's disease or its pediatric counterpart, systemic juvenile idiopathic arthritis (sJIA). Less commonly, MAS has been described in the context of rheumatoid arthritis and lupus.[1]

MAS is commonly triggered by an occult infectious process or flare in the underlying autoimmune disease. MAS may develop at any time, but most commonly manifests around the time of disease onset. Recent literature reports up to 15.8% of patients with Adult Still's develop MAS at some point in their disease course. However, this percentage may not capture cases of subclinical MAS, which are thought to be quite common.[2]

The diagnosis of HLH/MAS may be challenging due to the absence of any pathognomonic physical exam or laboratory findings. Prolonged fever, hepatosplenomegaly, and cytopenias are considered the cardinal manifestations of HLH. Other lab abnormalities such as transaminitis, hypertriglyceridemia, and hyperferritinemia are also frequently seen. Macrophages actively phagocytosing different hematopoietic elements may be seen on bone marrow biopsy, but the absence of these macrophages should not preclude the diagnosis. A set of diagnostic guidelines (table 1) set forth by an expert panel is often utilized to facilitate the diagnosis of HLH. Unfortunately, even when all of the required criteria are met, the manifestations of MAS are nonspecific and overlap considerably with the signs and symptoms of Adult Still's disease. Both conditions are known to cause high fevers, hepatosplenomealy, liver enzyme abnormalities, and hyperferritinemia.[3] These similarities can

make the diagnosis of MAS difficult to differentiate from uncomplicated Adult Still's disease alone.

Table 1.

The diagnosis of HLH may be established if one of either the following is fulfilled:

1. A molecular diagnosis consistent with HLH is made, or

2. Diagnostic criteria for HLH is fulfilled (5 of the 8 criteria below):

- Fever
- Splenomegaly
- Cytopenias affecting 2-3 lineages in the peripheral blood
- Hypertriglyceridemia ($\geq$ 265 mg/dl) and/or hypofibrinogenemia ($\leq$ 1.5 g/L)
- Hemophagocytosis in the bone marrow, spleen, or lymph nodes
- Low or absent NK-cell activity (according to local laboratory references)
- Ferritin $\geq$ 500 ng/L
- Soluble CD25 (i.e., sIL2r) $\geq$ 2400 U/mL

In contrast to Adult Still's disease, mortality rates in MAS are cited to be as high as 20 to 30%.[4] This is thought to be due to the higher rates of hypotension, hypoxic respiratory failure, and disseminated intravascular coagulation seen in patients with the latter. Thus, new thrombocytopenia or a relative decline in cell counts should raise concern for impending MAS. Rising ferritin levels and persistent, as opposed to cyclical fevers may also be early signs of the cytokine storm that is characteristic of MAS.[5]

Of note, some degree of hyperferritinemia is to be expected in Adult Still's, with or without MAS, due to the pro-inflammatory nature of the disease. Not uncommonly, ferritin levels in excess of 10,000 ng/L may be seen.[6,7] Ferritin levels of this magnitude are characteristically seen in only a handful of conditions, including advanced liver disease, hemochromatosis, HLH, and Adult Still's disease. Thus, a markedly elevated serum ferritin should signal clinicians to consider rare but potentially fatal conditions such as HLH, Adult Still's, or in our patient's case, a hybrid of the two.

Because both Adult Still's disease and MAS are so rare, management of these conditions is based largely from case reports and small retrospective studies. Non-steroidal anti-inflammatory drugs are often used to manage the acute pain and inflammation seen in Adult Still's. However, the vast majority of patients will require steroids to control their disease.[8] Systemic corticosteroids remain the most widely used empiric treatment for Adult Still's, with or without MAS. Initial steroid dosages depend on symptom severity but typically range from 0.5 to 1 mg/kg/day. Interestingly, Adult Still's patients treated with doses between 0.8 to 1 mg/kg/day were found to achieve faster remissions and have fewer relapses.[9,10] Cases of MAS tend to be treated with more aggressive immunosuppression, typically in the form of adjunctive cyclosporine. Less commonly, methotrexate or IVIG may be used.[11]

Long-term management of Adult Still's and MAS continues to evolve in the age of biologic therapy. Anti-TNF agents such as etanercept and infliximab have been used with variable success in steroid refractory cases of Adult Still's.[4] Meanwhile, IL-1 blocking agents such as Anakinra have shown significant promise in cases of MAS as well as steroid-refractory Adult Still's disease. Anakinra is administered as a daily subcutaneous injection and may be co-administered with methotrexate to improve response rates.[5] The targeted nature of these biologic agents makes them a favorable alternative to long-term, high-dose steroids.

Conclusion

Macrophage activation syndrome is a rare, potentially fatal complication of various autoimmune conditions. The diagnosis of MAS is challenging and often delayed due to its nonspecific symptoms that overlap with features of other inflammatory states, such as Adult Still's disease. Rising ferritin levels, declining cell counts, and persistent fevers may help to identify cases of impending MAS. Early recognition of this syndrome is critical to preventing significant morbidity and mortality.

REFERENCES

1. **Bae CB, Jung JY, Kim HA, Suh CH**. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features, predictive factors, and prognosis in 21 patients. *Medicine (Baltimore)*. 2015 Jan;94(4):e451. doi: 10.1097/MD.0000000000000451. PubMed PMID: 25634183; PubMed Central PMCID:PMC4602979.
2. **Asanuma YF, Mimura T, Tsuboi H, Noma H, Miyoshi F, Yamamoto K, Sumida T**. Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. *Mod Rheumatol*. 2015 May;25(3):393-400. doi: 10.3109/14397595.2014.974881. Epub 2014 Nov 10. PubMed PMID: 25382730.
3. **Arlet JB, Le TH, Marinho A, Amoura Z, Wechsler B, Papo T, Piette JC**. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. *Ann Rheum Dis*. 2006 Dec;65(12):1596-601. Epub 2006 Mar 15. Review. PubMed PMID: 16540551; PubMed Central PMCID: PMC1798476.
4. **Schulert GS, Grom AA**. Macrophage activation syndrome and cytokine-directed therapies. *Best Pract Res Clin Rheumatol*. 2014 Apr;28(2):277-92. doi: 10.1016/j.berh.2014.03.002. Review. PubMed PMID: 24974063; PubMed Central PMCID: PMC4074772.
5. **Lenert A, Yao Q**. Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature. *Semin Arthritis*

Rheum. 2016 Jun;45(6):711-6. doi: 10.1016/j.semarthrit.2015.11.002. Epub 2015 Nov 10. PubMed PMID: 26672682.

6. **Efthimiou P, Paik PK, Bielory L**. Diagnosis and management of adult onset Still's disease. *Ann Rheum Dis*. 2006 May;65(5):564-72. Epub 2005 Oct 11. Review. PubMed PMID: 16219707; PubMed Central PMCID: PMC1798146.
7. **Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X**. Adult haemophagocytic syndrome. *Lancet*. 2014 Apr 26;383(9927):1503-1516. doi: 10.1016/S0140-6736(13)61048-X. Epub 2013 Nov 27. Review. Erratum in: Lancet. 2014 Apr 26;383(9927):1464. PubMed PMID: 24290661.
8. **Yoo DH**. Treatment of adult-onset still's disease: up to date. *Expert Rev Clin Immunol*. 2017 Sep;13(9):849-866. doi: 10.1080/1744666X.2017.1332994. Epub 2017 Jun 5. PubMed PMID: 28540751.
9. **Kim YJ, Koo BS, Kim YG, Lee CK, Yoo B**. Clinical features and prognosis in 82 patients with adult-onset Still's disease. *Clin Exp Rheumatol*. 2014 Jan-Feb;32(1):28-33. Epub 2013 Sep 18. PubMed PMID: 24050706.
10. **Colina M, Zucchini W, Ciancio G, Orzincolo C, Trotta F, Govoni M**. The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. *Semin Arthritis Rheum*. 2011 Oct;41(2):279-85. doi: 10.1016/j.semarthrit.2010.12.006. Epub 2011 Mar 5. PubMed PMID: 21377714.
11. **Ahn SS, Yoo BW, Jung SM, Lee SW, Park YB, Song JJ**. Application of the 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome in Patients with Adult-onset Still Disease. *J Rheumatol*. 2017 Jul;44(7):996-1003. doi: 10.3899/jrheum.161286. Epub 2017 Apr 15. PubMed PMID: 28412707.

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