FEVER AND LYMPHADENOPATHY IN A 28-YEAR-OLD FEMALE: ATYPICAL SYSTEMIC LUPUS MASQUERADING AS ADULT STILL DISEASE

Manzy Byrd M.S, D.O[1]. & Samuel Corbman D.O[2].

INTRODUCTION

Adult Still disease is a rare inflammatory disorder that is cyclic in nature. The essential features consist of a triad of spiking fevers, maculopapular exanthema, and arthralgia, accompanied frequently by lymphadenopathy. Adult Still disease is rare and predominantly found in females and the pathophysiology is yet to be clearly defined. Like many autoimmune disorders, there is a considerable amount of overlap between syndromes and many non-specific symptoms. We will describe a case in which a working diagnosis of Adult Still Disease was ultimately proven to be SLE despite initial ANA negativity and overlap with many major criteria and minor criteria for Adult Still Disease.

CLINICAL PRESENTATION

The patient was a 28-year-old female with history of of two weeks of nausea and non-bloody, non-bilious vomiting. It had occurred in the past around the onset of her menses. Social history was non-contributory to the case. Review of systems was positive for her chief complaints as well as diffuse myalgias. On presentation, the patient was hypotensive to 88/59, tachycardic to 124 b/m, and afebrile. Physical exam was remarkable only for diffuse lower abdominal tenderness. Initial labs were significant for microcytic anemia with a hemoglobin of 8.5 and a CK of 1,243. CT imaging showed bilateral axillary and supraclavicular lymphadenopathy and mesenteric retroperitoneal and bilateral inguinal lymph nodes.

During her admission, the patient had relapsing and remitting low grade fevers with maximum temperatures around 100.6F. While admitted, her ferritin was elevated to 3453. Non-specific markers of inflammation such as CRP and ESR were elevated. She was positive for SS-A and negative for SS-B, Anti-dsDNA. Though not immediately available, the patient had a positive ANA with 1:320 titer in a speckled pattern and showed signs of possible cytoplasmic-targeting autoantibodies. This finding is in contrast to previous ANA testing.

Lymph node biopsy revealed reactivity with foci of necrosis that stained negative for PAS and AFB.

On follow up evaluations with Rheumatology post-discharge, SLE diagnosis was confirmed with decreased C3 levels. She also had overall high levels of IgG at 2x normal value with positivity for CMV and EBV IgG but not IgM. Aldolase levels were elevated in line with prior myositis. Anti-Jo1, Anti-Centromere B, Anti-Cardiolipin and anti-dsDNA antibody levels remained negative.

DISCUSSION

Systemic Lupus Erythematosus (SLE) and Adult Still Disease (ASD) are both clinically similar autoimmune mediated diseases. While both present with fever of unknown origin (FUO), the constitutional symptoms most common at initial presentation in SLE differ from those in Adult Still Disease.

In SLE, the symptoms that make up "constitutional manifestations" include fever, malaise, arthralgias, myalgias, headache, and loss of appetite. The initial work up and diagnosis of SLE generally begins with testing for antinuclear antibodies (ANA). Positive ANA is highly sensitive for the disease, though not specific as it is seen in 97% of cases, and can be associated with many other autoimmune conditions. Further markers can provide a picture of what intracellular component is involved within the cell signaling cascade. Anti-ds DNA antibody is commonly seen and has specificity of over 95% for SLE. Anti-Ro, Anti-La, and Anti-Smith antibodies are also commonly seen. Anti-Smith antibody is seen more frequently in African Americans. A joint effort from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) provide specific criteria for diagnosing Lupus. With this criteria the patient must be ANA positive and score at least 10 based on clinical and immunologic findings.

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

DISCUSSION

In ASD, primary clinical features include fever, rash, arthritis or arthralgia. Some or all of these symptoms are seen in 75-95% of patients. In ASD, fever is usually quotidian in nature. Generally speaking <10% of patients present ANA positive, and frequently have ferritin 5x the normal limit (>3000). Diagnosis is made by Yamaguchi Criteria. It requires 2 of 4 major criteria and at least 5 total criteria to confirm ASD.

Five of the following criteria should be met for a diagnosis of ASD. Two criteria must be major

Major criteria

1. Fever of at least 39°C (102.2°F) lasting at least 1 week
2. Arthralgias or arthritis lasting 2 weeks or longer
3. A non-pruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
4. Leukocytosis (10,000/μL or greater), with at least 80% granulocytes

Minor criteria

1. Sore throat
2. Lymphadenopathy
3. Hepatomegaly or splenomegaly
4. Abnormal liver function studies, particularly elevations in AST, ALT and LDH concentrations
5. Negative tests for ANA and RF

Image Courtesy of Researchgate.net, Criteria for the Diagnosis of AOSD

CONCLUSION

Our patient received IV fluids for her rhabdomyolysis secondary to myopathy. She also received acetaminophen and ondansetron for symptomatic relief. The patient was started on systemic glucocorticoid therapy with improvement in symptoms.
Ultimately, our patient was successfully treated with disease modifying medication including methotrexate and hydroxychloroquine. Steroid therapy with prednisone was successfully tapered over the course of a few weeks without relapse of symptoms. The patient continues to follow-up with outpatient Rheumatology at an outside institution, but is agreeable to continued monitoring of treatment course. During follow up, inflammatory markers have decreased with therapy..

REFERENCES

1. Balk, R. A. (2014). Systemic inflammatory response syndrome (SIRS) Where did it come from and is it still relevant today?. Virulence, 5(1), 20-26.
2. Butenandt, O., Kelch, A., & Rajmann, E. (1974). Growth hormone studies in patients with rheumatoid arthritis with or without glucocorticoid therapy. Zeitschrift für Kinderheilkunde, 118(1), 53-62.
3. Aringer M, Costenbader K, Daikh D, et al2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Annals of the Rheumatic Diseases 2019;78:1151-1159.
4. Guillermo J. Pons-Estel, Laura Andreoli, Francesco Scanzi, Ricard Cervera, Angela Tincani,The antiphospholipid syndrome in patients with systemic lupus erythematosus,
Journal of Autoimmunity,Volume 76,2017,
Pages 10-20,