CLINICAL VIGNETTE

Adult-onset Still's Disease with Macrophage Activation Syndrome

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Clinical History

A 38-year-old female with no significant past medical history presented to Rheumatology with a diffuse rash and acute polyarthritis. She initially developed a light pink, slightly itchy rash over her arms and legs. Three days later she developed pain initially in her left shoulder and left knee, then right shoulder and right knee, followed by wrists, hands, ankles and feet. Acetaminophen, ibuprofen and naproxen were ineffective. She noted one episode of shaking chills without fevers. She had mild rhinorrhea two weeks prior, without other infectious symptoms.

Exam was notable for a light pink, blanching, non-tender maculopapular rash over her upper arms, chest and legs. Joint exam was notable for tenderness to palpitation in bilateral shoulders with significantly limited range of motion, significant synovitis in multiple proximal interphalangeal joints of her hands, and painful range of motion in her elbows, wrists, knees and ankles.

Laboratory testing revealed leukocytosis (white blood cell count 15.9 x 10E3/uL), mild anemia (hemoglobin 11.5 g/dL), thrombocytosis (platelets 427 x 10E3/uL), elevated ALT (105 U/L), elevated sedimentation rate (61 mm/hr), elevated C-reactive protein (8.3 mg/dL) and elevated ferritin (1724 ng/mL). Rheumatoid factor, Anti-cyclic citrullinated protein antibody, Anti-nuclear antibody and subserologies, HLA-B27 and Anti-neutrophil cytoplasmic antibodies were negative, as was her infectious testing including blood cultures and serologies for Parvovirus, Coccidioides, Streptococcus, Syphilis, Hepatitis B and C, HIV, and Tuberculosis.

The patient was diagnosed with Adult-Onset Still's Disease (AOSD) based on the Yamaguchi classification criteria.[1] She was initially prescribed prednisone 30 mg daily with only mild improvement. Prednisone was increased to 60 mg daily with resolution of fevers and rash, and significant improvement in arthritis. Anakinra 100 mg subcutaneous daily was started for longer term therapy.

A few weeks later, she was hospitalized for fevers, recurrent diffuse rash and arthritis in the setting of tapering prednisone to 30 mg daily. She had new pancytopenia with white blood cell count 2.0 x 10E3/uL, hemoglobin 11.0 g/dL, platelets 73 x 10E3/uL and normal sedimentation rate. Ferritin was increased to 24,000 ng/mL, were elevated (AST 1217 U/L, ALT 985 U/L), as well as soluble IL-2 receptor (2906 units/mL.

Altogether this was consistent with macrophage activation syndrome (MAS). She was treated with pulse methylprednisolone 1000 mg IV daily for 3 days and intravenous immunoglobulin (IVIg) 2 grams over 2 days. Anakinra was increased to 100 mg subcutaneous twice daily without benefit, so she was switched to IV tocilizumab.

The patient's fevers, arthritis and inflammatory markers all improved. However, one day after her tocilizumab infusion, she developed a new diffuse, itchy, pink macular rash over her face, trunk and all extremities. Skin biopsy was consistent with a drug eruption, which Dermatology suspected was due to prior anakinra use given the timing.

She transitioned to tocilizumab 162 mg subcutaneous weekly and tolerated a gradual prednisone taper over several months, maintaining disease remission. She is currently doing well on a gradual tocilizumab taper.

Discussion

Adult-onset Still's disease is a systemic autoinflammatory disorder of unknown etiology that most commonly affects young adults. The exact etiology is unknown, but is thought to involve environmental triggers in conjunction with genetic susceptibility. AOSD typically presents with quotidian high fevers, evanescent salmon-colored maculopapular rash and polyarthritis, and can be accompanied by sore throat, weight loss, lymphadenopathy, hepatosplenomegaly and serositis. It is a highly inflammatory disorder, as evidenced by leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate, C-reactive protein and notably ferritin. Elevated liver enzymes may also be seen.[2]

As there are no blood or imaging tests specific to AOSD, it is important to exclude other diagnoses such as other types of inflammatory arthritis, rheumatoid arthritis, Lupus, spondyloarthritis, vasculitis, infection, malignancy, other autoinflammatory diseases and drug reactions. The Yamaguchi classification criteria are the most commonly used and the most sensitive.[1]

Given the rarity of the disease, there is a lack of randomized, controlled trials studying AOSD treatments. Mild disease can be treated with non-steroidal anti-inflammatory drugs (NSAIDs). However, most patients require stronger therapy with corticosteroids, which are considered first-line treatment.

In patients with moderate to severe disease, immunosuppressive medications including IL-1 inhibitors (e.g. anakinra and canakinumab) or methotrexate are added.[1,3] Currently canakinumab is the only FDA-approved medication for AOSD (6).[4] TNF inhibitors (e.g. adalimumab and infliximab) or IL-6 inhibitors (e.g. tocilizumab) may be considered in refractory disease (2, 4, 5).[2,5,6]

Macrophage activation syndrome is a rare but life-threatening complication of AOSD. It is estimated to occur in up to 15% of patients with AOSD, and can be triggered by infection, AOSD flare, or medication.[7] MAS is characterized by a cytokine storm and typically presents with persistent high fevers, cytopenias (with hemophagocytic lymphohistiocytosis frequently seen on bone marrow biopsy), hepatosplenomegaly with elevated liver enzymes, and lymphadenopathy. Ferritin is oftentimes dramatically elevated, and erythrocyte sedimentation rate can normalize due to hypofibrinogenemia – the latter can be an important clue to diagnosing MAS.[8]

MAS secondary to AOSD is treated by addressing the underlying AOSD, typically with high-dose corticosteroids plus a non-steroidal immunosuppressive medication such as anakinra. In this case, the patient failed anakinra but responded to high-dose corticosteroids with tocilizumab.

Regarding prognosis, AOSD can follow a monocyclic, polycyclic or chronic pattern. Given the severity of this patient's disease, we have continued treatment with tocilizumab for 16 months to date. We have successfully tapered her tocilizumab by gradually spacing out the dosing interval, and plan to taper off in the future while monitoring for recurrent disease.

Conclusion

This patient demonstrates a severe case of Adult-onset Still's disease, a relatively rare systemic autoinflammatory disease of unknown etiology that can cause significant morbidity and even mortality in young adults, especially when complicated by macrophage activation syndrome. AOSD should be considered in a patient presenting with a triad of fevers, rash and arthritis. MAS should be considered in a patient with AOSD who develops persistent high fevers and cytopenias, as well as falling erythrocyte sedimentation rate in the setting of persistently elevated C-reactive protein and markedly elevated ferritin.

The IL-1 inhibitor anakinra often results in rapid improvement in AOSD symptoms within days. However, for this patient, anakinra was inadequate and also caused a drug-induced skin rash. This case demonstrates the efficacy of tocilizumab, an IL-6 inhibitor, as an alternative therapeutic agent in refractory AOSD with MAS.

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