Fever of Unknown Origin in a 15-year-old after A Desert Field Trip

Jonathan Su, MD, Christine Thang, MD

Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA

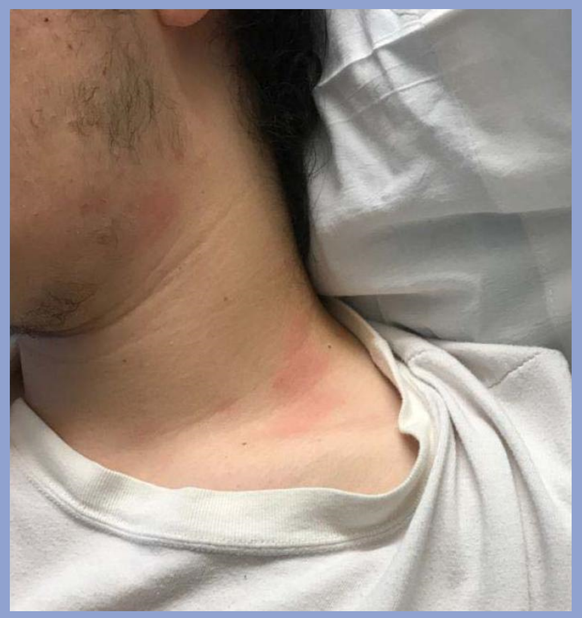
CASE REPORT

- A 15-year-old previously healthy adopted male presents **after three weeks of daily high spiking fevers** without a clear source. His chief complaints are fevers, fatigue, and achy right thigh pain.
- Symptoms started a week after a high school field trip to Anza-Borrego Desert State Park, a California state park located near San Diego, CA.
- A week after returning home, he started having fevers (up to 103 degrees Fahrenheit), sore throat, and malaise. Symptoms were initially attributed to a viral infection.
- Another week passed, and he continued to have unrelenting high fevers with an unintentional 10-pound weight loss, night sweats, and new onset right thigh achiness and weakness during the febrile episodes.

Initial Laboratory Results

Labs	Result
WBC	35,000/uL [3.5 x 10^9/L]
Diff	86% neutrophil predominance
BMP	Unremarkable
LFT	Mild transaminitis
ANA	Negative

- Due to the **persistence of fevers** and **markedly elevated inflammatory** markers, he was admitted to the hospital for workup of **fever of unknown origin.**
- On admission, an initial diagnostic workup was performed for suspected **infectious, hematologic, and rheumatologic etiologies** for fever and inflammation. The development of **a rash (see below) and resulting findings from a bone marrow biopsy ultimately synched the underlying diagnosis**. Subsequently with the **initiation of a particular medication,** the patient demonstrated an **immediate improvement** (within 24 hours) in his fever curve, symptoms, and biochemical profile.

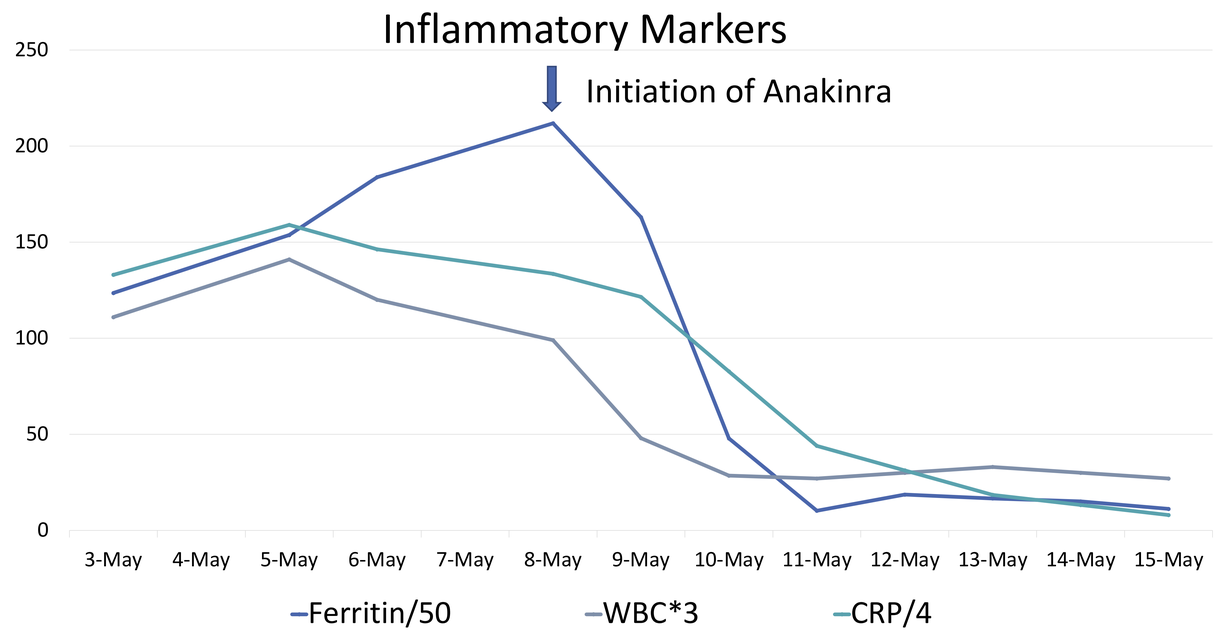


HOSPITAL COURSE

Infectious
- Empiric cefepime, azithromycin, and fluconazole without improvement
- Viral (Respiratory viral panel, EBV, CMV, HIV) – all negative. EBV serologies indicative of past infection, but not current infection.
- Bacterial (Blood cultures, Bartonella, Chlamydia, Mycoplasma, Syphilis, TB) – all negative
- Fungal (Blood cultures, Aspergillus, Coccidioides, Histoplasma) – all negative

Hematologic/ Oncologic
- Peripheral blood smear/flow cytometry – leukocytosis void of abnormal B-cells, T-cells, or blasts
- Tumor lysis labs – no rapid cell turnover
- CXR – no masses
- CT abd/pelvis – no masses
- Bone marrow biopsy – **Hemophagocytic histiocytes and low NK cell activity**

Rheumatologic
- ANA – negative
- RF – negative
- Proteinase 3 Ab – negative
- Myeloperoxidase Ab – negative
- Familial Mediterranean fever - negative
- **JIA – diagnosis of exclusion**
- **Initiation of anakinra** (see below) with immediate improvement, aiding diagnosis of JIA



FINAL DIAGNOSIS

Our patient was diagnosed with **Adult Onset Still's Disease** (AOSD) complicated by **Macrophage Activation Syndrome** (MAS).

DISCUSSION

- Adult Onset Still's Disease (AOSD) has bimodal peaks at ages 15-25 and 36-46
- Typical triad of **fevers, arthritis and maculo-popular salmon-colored evanescent skin rash**
- **Diagnosis of exclusion** after ruling out infection, malignancy, and other febrile etiologies
- **Macrophage activation syndrome** (MAS) is a life-threatening complication of AOSD. It is a form of hemophagocytic lymphopsitiocytosis (HLH), which is caused by **excessive immune activation.**
- **Treatment** for AOSD remains **empirical** and include anti-inflammatory drugs, corticosteroids, disease-modifying antirheumatic drugs, immunologics (such as Anakinra, an IL-1 antagonist) and TNF inhibitors.

Yamaguchi Criteria (for AOSD):
- Exclusion of infection, malignancy, or other rheumatic disorder
- Presence of 5 criteria, two of which must be major
- Major diagnostic criteria
  - Fever >39C for at least one week
  - Arthalgias or arthritis for at least two weeks
  - Salmon-colored skin rash
  - Leukocytosis >10,000/micro
- Minor diagnostic criteria
  - Sore throat
  - Lymphandenopathy
  - Hepatomegaly or splenomegaly
  - Abnormal liver function studies
  - Negative ANA and RF

TAKE HOME POINTS

- Fever of unknown origin encompasses a broad differential diagnosis which includes infectious, malignant, and rheumatologic etiologies. A focused approach depending on symptomatology, fever pattern, environmental exposures, and personal and family histories will help guide timely diagnosis and treatment.
- Adult Onset Still's Disease (AOSD) is a clinical diagnosis, made after excluding other infectious, malignant, and rheumatologic causes. The triad of symptoms include high spiking fevers, arthritis, and evanescent salmon-colored rash.
- Macrophage Activation Syndrome (MAS) is a form of Hemophagocytic Lymphohistiocytosis (HLH), which is a life-threatening complication of AOSD, and should be suspected in a patient with persistent fevers and extremely elevated ferritin (>5,000 ng/mL) in the setting of a suspected rheumatologic process.
- Treatment of AOSD is still based on empiric evidence, although generally involves systemic corticosteroids, DMARDs, and immunologic therapies inhibiting IL-1 (e.g. Anakinra) and IL-6. Response to therapy is often prompt (within 24 hours of initiation) with resolution of fevers and improving laboratory values.

REFERENCES

1. Attard L, Tadolini M, De Rose DU, Cattalini M. Overview of fever of unknown origin in adult and paediatric patients. *Clin Exp Rheumatol*. 2018;110(1):10-24.

2. Still GF. On a form of chronic joint disease in children. *Archives of Disease in Childhood.* 1941;16:156-165.

3. Bywaters EG. Still's disease in the adult. *Ann Rheum Dis.* 1971;30(2):121-133.

4. Magadur-Joly G, Billaud E, Barrier JH, et al. Epidemiology of adult Still's disease: Estimate of the incidence by a retrospective study in west France. *Ann Rheum Dis.* 1995;54(7):587–590.

5. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. *J Autoimmun*. 2018;93: 24-36.

6. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease, *J Rheumatol*. 1992;19(3):424–430.

7. Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: Diagnosis, genetics, pathophysiology and treatment. *Genes Immun.* 2012;13(4):289-298.

8. Castaneda, S, Blanco R, Gonzalez M. Adult-onset Still's disease: Advances in the treatment. *Best Pract Res Clin Rheumatol*. 2016;30(2):222-238.

QR CODE FOR FULL CASE REPORT ARTICLE