Fever of Unknown Origin Clinical Vignette: When a basic workup is Still not enough

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Introduction

Objectives:

1) Review most common causes of Fever of Unknown Origin (FUO)
2) Highlight ASD as a potential cause of FUO in Western adult patients
3) Describe immune activation syndrome, its relationship to ASD, and the need for prompt treatment given its high priority

Presentation

HPI:

- 26-year-old man with PMH of JRA treated as a child in Mexico presented to outside care with symptoms of fever, sore throat, macular rash, abdominal pain and diarrhea
- Diagnosed with and treated for Strep and Campylobacter infection
- Persistent fevers led to rheumatologic workup including negative ANA, ANCA, CCP, and RF.
- Rash and arthralgias resolved briefly on methylprednisone in context of presumed drug eruption to ASA
- Four weeks later, he presented to our care with continued daily fevers (101-105F), severe joint pains, shortness of breath and 50 lb weight loss.

Physical Exam: Only remarkable for subtle synovitis to left 5th PIP and point tenderness to lateral right ribs.

Initial Workup & Clinical Course

LFT's: 6.1 | 2.4 | 0.4 | 0.2 | 43 | 53 | 87

CBC: 8.9 | 29.2 | 504 | 28.5

BMP: 136 | 107 | 7 | 92 | 3.2 | 21 | 0.62

Additional Labs:

- ESR: 66 (0-10 mg/dL)
- CRP: 145.6 (0-10.0 mg/dL)
- CK: <10 (30-223 U/L)
- ANA: negative
- RF: negative
- UA: negative
- Ferritin: 4124 (24-336 ng/mL)
- Blood Culture: negative
- Urine Culture: negative
- Quantiferon Gold: negative
- IL-2 receptor: 4631 (175-858 pg/mL)
- Infectious Disease PCR Panel: negative

Clinical course prior to dx:

Before malignancy and TB workup could be completed, the patient developed vasodilatory shock refractory to aggressive fluid resuscitation and vasopressors, which promptly resolved with IV methylprednisone.

Further Workup and Final Diagnosis

Imaging and Pathology:

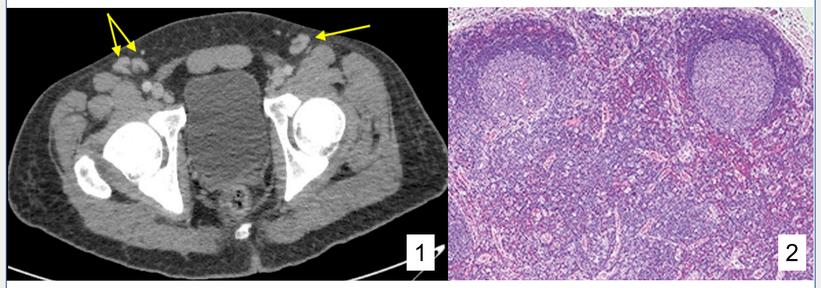

Image 1. Patient's CT scan demonstrating inguinal adenopathy (indicated in yellow);
Image 2. Example lymph node biopsy demonstrated normal phenotypic and morphologic characteristics[1].

Final Diagnosis:

In the context of improvement on methylprednisone and negative workup for malignant, infectious, and other rheumatologic causes, our patient was diagnosed with Adult Still's Disease.

Yamaguchi Criteria for Adult Still's Disease[3]

≥ 5 total criteria with ≥ 2 major criteria, in absence of exclusion criteria

1. Major Criteria:
- ☑ Fever ≥39 °C lasting ≥ 1 week
- ☑ Arthralgia or arthritis lasting ≥ 2 weeks
- ☑ Typical rash
- ☑ Leukocytosis demonstrating ≥ 10,000 cells/mm^3 with ≥ 80% neutrophils

2. Minor Criteria:
- ☑ Sore throat
- ☑ Recent development of significant lymphadenopathy
- ☑ Hepatomegaly or splenomegaly
- ☑ Abnormal liver function tests
- ☑ Negative tests for antinuclear antibody and rheumatoid factor

3. Exclusion Criteria:
- ☒ Infection
- ☒ Malignancy
- ☒ Other rheumatic disease (esp. vasculitis)

Figure 1: Our patient met Yamaguchi criteria for ASD. While technically meeting MAS criteria as well, according to the North American Consortium for Histiocytosis (NACHO), cytopenias are ubiquitous in HLH/MAS, and lack of cytopenias should make the clinician doubt the presence of this syndrome. Our patient demonstrated anemia without thrombocytopenia or neutropenia.

Discussion

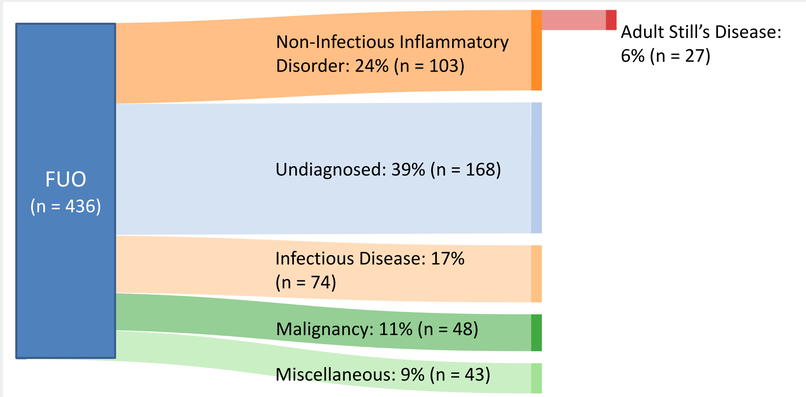

Figure 2: Vanderschueren et al (2014) documented NIID as the most common cause of FUO in a Western, developed country (Belgium), with ASD as the primary diagnosis in 6% of patients in a retrospective study conducted on 436 patients with FUO[2].

- Most common cause of FUO in developed countries: NIID with 6% of FUO cases resulting in a primary diagnosis of ASD[2,5].
- MAS and reactive HLH are major forms of immune activation in JRA and ASD
- Mainstay of treatment for ASD is steroids and can be life saving in setting of severe immune activation syndromes, which affect up to 17% of patients[3].

Conclusion

In western FUO patients, clinicians should have a low threshold for empiric treatment of NIID and immune activation syndrome when patients demonstrate a pertinent history in the context of hemodynamic instability.

References

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