

**Case:** ID/CC: 56 yo male patient with history of Hepatitis C secondary to remote IVDU and recent history of carotid endarterectomy who presents with three months of recurrent fevers up to 40.1 °C lasting 2-3 days every two weeks accompanied by drenching sweats and unintentional weight loss. The patient's review of systems was otherwise notable for severe fatigue and joint aches in his hands and feet without notable swelling. He denied all other symptoms. The patient had been seen several times in his primary care clinic in eastern Washington. CBC with differential, routine chemistries, urinalysis/urine culture and chest x-ray at the time of clinic visits were all within normal limits.

On presentation the patient's examination was remarkable only for a temperature of 39.7° and rigors.

What is your differential diagnosis? What additional laboratory and diagnostic tests would you consider? How would you treat the patient and what would you tell him about his prognosis?

## Fever of Unknown Origin (FUO)

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### Does this patient meet criteria for having a fever of unknown origin?

FUO is a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing. The initial definition by Petersdorf and Beeson (1961) included three criteria:

- 1) Fever higher than 38.3°C on several occasions
- 2) Duration of fever for at least three weeks
- 3) Uncertain diagnosis after one week of study in the hospital

#3 was modified to "after one week of appropriate investigation"

Prior to defining an FUO the following must have been unrevealing:

- 1) H&P
- 2) CBC with differential and platelet count
- 3) Routine blood chemistries including liver enzymes and bilirubin
- 4) Urinalysis including culture
- 5) Chest x-ray

Prevalence in hospitalized patients: ~2.9%

### What is your differential diagnosis?

#### *Etiologies*

Most common etiologies:

- 1) Infections (~28%; 25% in elderly >65)
- 2) Malignancies (~17%; 12% in elderly >65%)
- 3) Inflammatory diseases/collagen-vascular diseases (~21%; 31% in elderly >65)
- 4) No diagnosis 19%

- 1) Infections
  - a. TB is the most common cause of FUO in non-elderly adults (particularly extra-pulmonary or miliary)
  - b. Occult abscesses - often in abdomen or pelvis
  - c. Osteomyelitis
  - d. Bacterial endocarditis

- 2) Malignancies
  - a. Lymphoma (particularly non-Hodgkin's)
  - b. Leukemia
  - c. Renal cell (fever is the presenting sx ~20%)
  - d. Hepatoma or other tumors metastatic to the liver
  - e. Atrial myxomas (fever is presenting sx ~33%)
- 3) Collagen-vascular diseases/rheumatologic disorders
  - a. Temporal arteritis (~15-17% cases in the elderly)
- 4) Drugs
  - a. Cause fever by stimulating an allergic or idiosyncratic reaction
  - b. +/- rash and eosinophilia
  - c. most common antibiotics, anti-histamines, anti-epileptics, NSAIDs, anti-hypertensives, anti-arrythmics, contaminants of injected drugs; digoxin and aminoglycosides rarely cause fever
  - d. drugs usually cause fever soon after starting (but may be delayed)
  - e. to diagnose discontinue the drug (usually defervesce within 72 hours)

Less common causes of FUO include factitious fever (injection of foreign matter, thermometer manipulation), DVT/PE (~2-6%), hematoma, alcoholic hepatitis, dental abscesses, other (rare) infections: (Q fever, leptospirosis, psittacosis, tularemia, secondary syphilis, disseminated gonorrhea, Whipple's disease, yersinia), hyperthyroidism and subacute thyroiditis, pheochromocytoma, adrenal insufficiency.

The etiology of FUO varies with age, geography, subpopulation [HIV, neutropenia, etc.] *Remember that FUO is more likely caused by an uncommon presentation of a common problem than by a rare disorder.*

### What work-up would you do?

#### Minimum Work-Up

- 1) H&P including travel history, immunosuppression, drug and toxin history, localizing symptoms
- 2) Laboratory and diagnostic testing should include:
  - a. ESR
  - b. LDH
  - c. PPD
  - d. HIV (for patients with risk factors)
  - e. Blood cx x 3
  - f. Rheumatoid factor
  - g. ANA with reflexive panel
  - h. Abdominal CT (in one study - diagnostic yield of 19%; ~70% sens/spec) to assess for occult abscesses or hematoma

A recent review also recommends:

- 1) technetium labeled wbc scans (sensitivity 40-82%/spec 69-94%)
- 2) Duke criteria to assess for endocarditis (specificity 99%)
- 3) Liver biopsy (diagnostic yield 14-17%)
- 4) Temporal artery biopsy (in elderly)
- 5) Lower extremity dopplers

Results of the noted work-up should prompt more specific work-up such as biopsy, lumbar puncture, etc.

### How would you treat this patient?

Therapeutic trials of antibiotics or steroids rarely establish a diagnosis

### **What would you tell this patient?**

Overall FUO has a good prognosis. >50% of patients recover spontaneously. In one recent study of almost 200 hospitalized patients with FUO 30% (61) were discharged without a diagnosis, 6% (12) had a definitive diagnosis within two months of discharge, 15% (31) became symptom-free during hospitalization or shortly after discharge and 9% (18) had persistent or recurring fevers after discharge for months to years.

### ***Case 1 Follow-Up***

The patient was admitted to the hospital and had an extensive work-up. CBC with differential and platelet count, blood cultures, routine blood chemistries, liver enzymes, urinalysis and urine culture as well as chest x-ray were all again within normal limits. Further questioning, however, revealed that the patient had had symptoms for several months consistent with Raynaud's phenomenon and that he had intermittently had a malar rash on his face. Further laboratory testing revealed an erythrocyte sedimentation rate of 110 and an ANA of 1:>640 in a speckled pattern. Anti-double stranded DNA was 12; anti-Smith antibody (99% specific for systemic lupus erythematosus) was strongly positive. He has since developed anemia, leukopenia (on more than two occasions) and persistent proteinuria and meets the criteria for having systemic lupus erythematosus. He is followed in Rheumatology Clinic and is currently taking prednisone, hydroxychloroquine, cell-cept nifedipine with no recent fevers or current joint symptoms.

### **References**

- Arnou PM, Flaherty JP. Fever of unknown origin. *Lancet* 1997;350:575.
- Knockaert DC, Vanderschueren S, Blackmans D. Fever of unknown origin in adults 40 years on. *J Intern Med* 2003 Nov; 253(3): 263-75.
- Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. *J Am Geriatr Soc* 1993; 41:1187.
- Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Int Med* 2003;163(5):545-51.
- Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. *Medicine* 1961;40:1.
- Vanderschueren S, Knockaert D, Adiaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. *Arch Int Med* 2003;163:1033-41.

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