CLINICAL VIGNETTE

A Case of Fever of Unknown Origin in an Older Man

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Case Presentation

An 81-year-old male with history of polycythemia vera and transverse myelitis presented to the hospital with hematemesis, melena, and symptomatic anemia. His symptoms developed the day preceding hospitalization, with black stools and coffee-ground emesis. The patient had been taking aspirin for his myeloproliferative disorder. Other medical history was significant for benign prostatic hyperplasia and hypertension. His social history was notable, as he was a practicing physician, with no history of tobacco use.

During the hospitalization esophagogastroduodenoscopy, found a bleeding duodenal ulcer that was cauterized. Culture of the biopsy was positive for *Helicobacter pylori*.

He also developed low grade fevers in the range of 37.5-38.5 C. Initially, the fevers were attributed to bilateral arm thrombophlebitis and treated with warm compresses. Blood cultures, urine culture, and chest x-ray did not indicate a cause for his fevers. Before discharge to a skilled nursing facility, his medical team prescribed amoxicillin, clarithromycin, and pantoprazole for *H. pylori* infection.

At the skilled nursing facility, he participated well with physical and occupational therapy, but he continued having recurrent daily fevers as high as 38.9 Celsius without other localizing symptoms of infection. The only new symptom that developed during the nursing facility stay was pain in his right hip worsened by activity. Two weeks after SNF admission the patient was readmitted to the hospital with recurrent fevers.

Upon admission, he was found to have an acute inferior pubic ramus fracture. Orthopedic surgery recommended nonsurgical treatment with pain control and physical therapy. He also underwent an extensive evaluation for recurrent fevers, thought less likely related to thrombophlebitis, which had already resolved. Complete blood counts did not show leukocytosis. C-reactive protein was 13.9 (normal is below 3). Other tests including urine cultures, blood cultures, rheumatoid factor, cytomegalovirus antibody, Epstein-Barr antibody, tickborne panel, HIV, hepatitis panel were negative. PET computed tomography of the chest and abdomen did not suggest malignancy or localized infection.

He returned to SNF, participated with physical therapy, and was successfully discharged home, ambulating well with a front-wheeled walker. At an outpatient follow up with his hematologist-oncologist two months after the initial hospitalization, he was noted to still have persistent fevers, with no cause yet found.

Discussion

Prolonged fevers are often described as a “fever of unknown origin”. However, the criteria that Petersdorf and Beeson developed specifically define a fever of unknown origin (FUO) as fever of greater or equal to 38.3C (101F) for more than three weeks that remains undiagnosed after a hospital workup.[1] The initial diagnostic approach should be based on the history and physical exam, which should help identify the appropriate broad category of FUO. The three broad categories of FUO: neoplastic diseases, infections, and rheumatologic/ autoimmune diseases. Neoplastic diseases may be associated with anorexia and weight loss, infections may have rigors as a more prominent component, and rheumatologic or autoimmune diseases are more likely to have joint involvement. The history should also identify risks for a potential infectious source, including recent travel, blood transfusions, and animal contacts.

Initial testing should include routine blood counts and routine blood chemistries, as well as urinalysis with culture, blood cultures, and a chest x-ray. More specific further testing should be guided by the possible category of FUO, as well as clues to what organ systems may be involved.

Further investigation may include nonspecific markers of inflammation, such as erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and C-reactive protein (CRP).[2] Acute phase reactants like ESR or CRP may be helpful despite poor specificity. One study, of patients with ESR elevations above 100 mm/hr, 58 percent were found to have malignancy, and 25 percent had infectious diseases such as endocarditis, or systemic rheumatic diseases.

Initial testing for rheumatologic disease, including rheumatoid factor, creatine kinase, antinuclear antibodies, and serum protein electrophoresis would also be appropriate. The evaluation should also include testing for tuberculosis and HIV. Finally, if the initial testing does not provide adequate direction, computed tomography (CT) of the chest, abdomen, and pelvis may be included. F-fluorodeoxyglucose positron emission tomography (FDG-PET), is another emerging imaging modality, though evidence of its diagnostic efficacy is still limited.[3]

CT imaging has largely replaced invasive tests like exploratory laparotomies in the diagnostic workup of FUO. Findings of masses or lymph nodes may then lead to subsequent biopsies.

The fraction of FUOs that remain undiagnosed after a thorough round of testing has changed over time. In the 1930s, it was almost 75 percent, and it dropped to less than 10 percent in the 1950s. Since then, the fraction of undiagnosed FUOs has steadily increased to about 50 percent in the early 2000s. The causes of FUO have also changed since the 1950s. In the 1950s, 36 percent of FUOs were found to be infectious, 19 percent malignant, and 18 percent inflammatory, with only 9 percent with no diagnosis. By the early 2000s, only 16 percent were found to have infectious causes, 7 percent malignant, 22 percent inflammatory, and 51 percent were found to have no diagnosis.[4]

Patients who remain undiagnosed after an extensive evaluation tend to have a good prognosis. In one series of 199 patients with FUO, 61 (30 percent) were discharged from the hospital without a diagnosis. Thirty-one of those patients became symptom-free during hospitalization or shortly after discharge, 18 had persisting fevers for several months or years after discharge (but 10 of those were considered to be ultimately cured), and four were treated with glucocorticoids or non-steroidal anti-inflammatory drugs. Only six died, and in only two of those cases was the cause of death considered to be related to the disease that caused the FUO.[5]

In older patients, inflammatory diseases such as rheumatologic disorders (including polymyalgia rheumatica and vasculitides) account for about 30 percent of FUO cases, infections account for 25 percent, and neoplasms about 12 percent.[6] In children, by contrast, about a third of cases are due to self-limited viral syndromes.[7]

Our patient was an older male who met the diagnostic criteria for FUO, in that he had fevers that remained undiagnosed for more than three weeks, which included an extensive hospital workup. Despite his fevers, he remained functional and asymptomatic outside of his fevers. This is consistent with case reviews showing that older patients with undiagnosed FUOs tend to have a good prognosis.

Conclusion

The diagnosis fever of unknown origin requires temperatures above 38.3C longer than three weeks that remains undiagnosed after a hospital workup. For older patients, infections, inflammatory disorders, and malignancies are the most common causes, but a large group of patients remain undiagnosed. These undiagnosed patients tend to have a good prognosis.

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