CLINICAL VIGNETTE

A Challenging Patient with Prolonged Nightly High Fever

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Case

A generally healthy 70-year-old Caucasian female, presented with fevers for two months. She reported abrupt onset of fevers with rigors and myalgias associated with drenching night sweats and profound fatigue. The fevers occurred every evening, beginning around 5 PM, peaked around 8:30 PM, then subsided with 1gram acetaminophen. She had mild headache at the onset of fevers, but at time of presentation denied headache, jaw claudication, scalp tenderness, chest pain, abdominal pain, weight loss, joints symptoms or skin rash. She remained very active and enjoyed daily hiking. There was no history of fishing or camping, but she had hiked in the rural Pacific Northwest a few weeks before her symptoms started. She had extensive prior evaluation by her primary care physician and infectious disease and hematology consultants without identifying a cause. She was prescribed empiric doxycycline which made symptoms worse, and changed to levofloxacin which transiently helped for 2 days before her symptoms returned. She also received a 3rd empiric antibiotic. Cefdinir with relapsed fevers. Fevers relapsed despite on antibiotics. Her highest fever was 104.9°F, usually peaked ranging 102°-103° F. Her vital signs were normal and she was afebrile during her office visit. Physical exam was unremarkable except for osteoarthritis changes in her hands.

Her labs showed a markedly elevated ESR of 114 mm/h, CRP of 8.8 mg/dL, hemoglobin of 9.9 g/dL, leukocytosis with a white count of 12.45, neutrophilia, thrombocytosis of 568 x10E3/uL, and mildly elevated liver chemistries, Alk Phos 223 U/L, ALT 57 U/L and hypoalbuminemia of 2.8 g/dl. LDH was normal and ferritin was elevated 867 ng/ml. SPEP and serum immunofixation showed elevated globulins and low albumin but no evidence of abnormal monoclonal bands. Testing for numerous infections: CMV, EBV, HIV, HBV, HCV, Cryptococcus, Coccidiodes, Syphilis, Brucella, Coxiella, QuantiFERON, Bartonella, Rickettsia, Leishmania, Toxoplasma, Francisella, and malaria were all negative. Additional tests included negative urine and blood cultures, lyme serology, influenza and rapid strep throat. She had slight elevation of soluble IL 2 receptor, elevated fibrinogen and D-dimer; which was thought to be a non-specific acute response. Her Triglycerides, NK function and flow cytometry were also normal and her hematologist concluded that myeloproliferative disorders were unlikely a cause of her fevers. Imaging included CT chest, abdomen and pelvis and did not reveal any underlying malignancies. She had trace left pleural effusion, trace perisplenic ascites, and mild hepatosteatosis without evidence of abscess. CT angiogram and ultrasound doppler of lower extremities were negative for thromboembolism. Echocardiogram was normal without suggestion of infective endocarditis.

Because prior extensive evaluation for infectious and hematologic etiologies were negative, she was referred to Rheumatology for persistent fever with markedly elevated inflammation markers. Adult onset Still disease was considered but she did not have typical skin rash or joint findings or symptoms. Lupus and vasculitis remained on the differential diagnoses. She denied symptoms of polymyalgia rheumatica (PMR) or giant cell artheritis (GCA). Also, she did not have cardinal features of lupus or other connective tissue diseases, although atypical presentations were considerations. Comprehensive Rheumatology testing was unremarkable, including - ANA and ANA subtypes, dsDNA, C3, C4, Rheumatoid factor, CCP, vasculitis serologies (ANCA, cryocrit), serum ACE and IgG4. A PET scan, showed intense FDG uptake in the cecum, and terminal ileum extending to the ascending colon. This was non-specific, but raised suspicion for possible colitis. GI performed colonoscopy with biopsies and sigmoid biopsy showed focal active colitis. The morphologic findings were suggestive of ischemic colitis without evidence of vasculitis. MRA of the neck, chest, abdomen, pelvis did not show evidence of large vessel arteritis. There was focal moderate to high-grade stenosis of the celiac trunk estimated at 60% to 70% and some atherosclerotic changes. Cardiology and vascular consultants did not think atherosclerosis explained the localized ischemic colitis. She then underwent temporal artery biopsy which showed active atypical arteritis. She was started on oral prednisone 60 mg per day with dramatic response. Her fevers resolved within 24 hours and her inflammation markers normalized within 2 weeks. Her constitutional symptoms gradually resolved within a month. Her prednisone was tapered slowly and she is doing well at one year follow up on low dose steroid monotherapy. She did not require any steroid sparing agents.

Discussion

Fever of unknown origin (FUO) remains one of the most challenging conditions for many clinicians. Differential Diagnosis include more than two hundred diseases.[1,2] Most patients with FUO have an atypical presentations of a common diseases as this case illustrates.[3] Twenty to forty percent are due to infections, 20-30% malignancy, 10-30% non-infectious inflammatory diseases including rheumatological disorders and

10-20% miscellaneous etiologies.[1] Etiology remains unknown in up to 50% of cases.[4] Bacterial infections including abdominal or pelvic abscess, dental abscess, endocarditis, sinusitis, tuberculosis, urinary tract infection: viral infections such as Epstein-Barr virus, Cytomegalovirus, malignancies e.g. colorectal cancer, leukemia, lymphoma are common causes of FUO.[3] Miscellaneous causes of FUO include drug-induced, thromboembolic disease, thyroiditis and factitious fever.[3] Common rheumatological diseases that can present with FUO include connective tissue diseases such as adult onset Still disease, systemic lupus erythematosus, rheumatoid arthritis; granulomatous diseases such as sarcoidosis and vasculitides such as Giant cell arteritis.[3]

Giant cell arteritis (GCA) is the most common vasculitis among adults over 50 years in the United States and Europe.[5,6] GCA is a chronic granulomatous systemic arteritis affecting the aorta and its main branches with potentially devastating complications including stroke, aortic aneurysm and permanent vision loss.[6,7] It is classified as large vessel vasculitis but it typically also affect medium size arteries. GCA predominantly affects cranial arteries and the GI tract is rarely involved.[8] Diagnosing GCA can be challenging due to lack of cardinal symptoms in 5% to 38% of cases.[7] This case demonstrated lack of cardinal symptoms of GCA as well as no symptoms of vascular insufficiency due to colonic ischemic. The dominating manifestations are those of systemic inflammatory syndrome presented with "fever without typical ischemic symptoms". The diagnosis was delayed due to the atypical, uncommon presentation.

Temporal artery biopsy remains the gold standard to diagnose GCA.[9] In evaluating FUO, nuclear imaging studies are useful to locate a potential site of infection, inflammation or malignancy.[10] If diagnosis remains unknown, an invasive procedure such as liver, lymph node, or temporal artery biopsy may help establish a diagnosis. One study reported biopsies produced up to a 35% diagnostic yield, especially if performed later in the evaluation when infection is less likely.[11] Bone marrow biopsy is useful, particularly if suspicion is high for infectious disease such as tuberculosis or neoplasm.[12]

Conclusion

This case represents atypical presentation of common disease, GCA as prolonged nightly high fevers. A high index of suspicion is essential for early diagnosis and prompt treatment in order to avoid devastating complications of GCA.

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