CLINICAL VIGNETTE

Fever of a Sarcoid Origin: An Unusual Presentation

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Introduction

Fever of unknown origin (FUO) was initially described in 1961 with a clinical definition of febrile illness in an adult of at least 3 weeks' duration with no established diagnosis after a week of hospital investigation.[1] The differential for FUO remains broad and presents a diagnostic challenge as the evaluation is rarely cost-effective or efficient. Many patients undergo a bevy of tests, often of low diagnostic yield. We present a case of a patient with multiple admissions for recurrent fevers, found ultimately to have acute pulmonary sarcoidosis, a frequently overlooked cause of FUO.

Case Report

A 63-year-old male with a history of hypertension was admitted for recurrent fevers, drenching sweats, and a dry cough. He had been admitted twice before in the prior two months for the same symptoms. On his initial admission a chest X-ray showed a left hemithorax opacification and he was treated with ceftriaxone and azithromycin for presumed community acquired pneumonia. He presented two weeks later without resolution of his symptoms and although chest imaging was unremarkable, he was given two weeks of levofloxacin for presumed non-resolving community acquired pneumonia. His symptoms improved initially, but recurred shortly after.

On his third admission, a CT scan of his chest revealed mediastinal and hilar lymphadenopathy thought reactive or neoplastic in nature. His white blood cell count was 20,000/mm^3, with a neutrophil predominance and lymphopenia; largely unchanged from prior admissions. Sedimentation rate was elevated at 97 mm/hour (reference range 0 – 20 mm/hour) and C-reactive protein at 14.1 mg/dL (reference range < 0.744 mg/dL). Sputum culture returned with mixed respiratory flora, and he was treated with ampicillin-sulbactam for a presumed pulmonary infection. Malignancy evaluation included CT of the abdomen and pelvis, which revealed an expansile lytic lesion of his left iliac wing. Subsequently, a positron emission tomography/computed tomography (PET/CT) scan showed fluorodeoxyglucose (FDG) uptake in the same lytic lesion (Figure 1), as well as multilevel FDG uptake in the mediastinal and hilar lymph nodes (Figure 2). A hematologic malignancy—specifically, a plasma cell dyscrasia—was suspected and revealed monoclonal gammopathy of unknown significance. A CT-guided biopsy of the left iliac bone lesion revealed a benign chondromyxoid fibroma.

A simultaneous extensive infectious evaluation was largely unremarkable (Table 1). The patient had multiple known exposures including recent hiking, without known tick or flea bites, extensive mold in his home, recent construction work on the carport beneath his residence, and prior exposure to industrial solvents, including benzenes.

Ultimately, the patient was discharged home to continue testing as an outpatient with counseling to maintain supportive care and hydration for recurrent fevers. A bone marrow biopsy showed normal bone marrow aspirate. Flow cytometry did not show any monotypic cell populations. Finally, endobronchial ultrasound and transbronchial needle aspiration was done of the stage 7, 4R, and 11R lymph nodes that were FDG-avid on prior PET/CT. Biopsy returned with non-caseating granulomas consistent with a diagnosis of sarcoidosis.

The patient was diagnosed with stage I sarcoidosis and had complete resolution of his prior symptoms. In the absence of any pulmonary symptoms, corticosteroids were deferred. He continues to do well and is being monitored by pulmonology.

Discussion

The majority of "classic" FUO cases can be attributable to three broad categories: infection, malignancy, and systemic rheumatic disease.[2] According to Petersdorf and Beeson's classic article defining FUO, 36% were attributed to infection, 19% to malignancy, 19% to collagen vascular diseases, and 19% to miscellaneous causes—including drug fever and no identifiable etiology (in 7% of cases).[3] Other considerations include deep vein thrombosis and temporal arteritis. These broad categories have remained relatively stable over the years, with fewer cases of FUO now attributable to an infectious etiology, given improved testing and advances in diagnostic imaging. However, an increasing number of cases have no identifiable etiology.

Given the wide variety of underlying diagnoses of FUO, its diagnostic workup presents a challenge to clinicians. While there is no established comprehensive diagnostic evaluation for FUO, the first step common to all pathways is to confirm that a true fever exists. Confounding factors such as medications commonly known to cause fever should be discontinued to rule out drug-induced fever. A thorough history including travel, animal exposure, immunosuppression, and localizing symptoms can reveal subtle findings. Minimal diagnostic workup

includes a comprehensive history and physical exam, complete blood cell count with differential, blood smear, routine blood chemistry, urinalysis and microscopy, blood and urine cultures, antinuclear antibodies, rheumatoid factor, and screening of infectious etiologies such as human immunodeficiency virus (HIV) and cytomegalovirus (CMV).[4] If there are specific exposure risk factors, select infectious etiologies can be considered, including Q-fever, tuberculosis, and hepatitis. Travel to the Midwest region of the U.S. should prompt screening for histoplasmosis, and, in endemic areas on the West coast, for coccidioidomycosis. Lastly, infective endocarditis (IE) accounts for 1-5% of FUO cases[5] and should be considered in the diagnostic evaluation. Clinicians must be mindful that IE causing FUO is likely to be culture negative (especially as patients with FUO are frequently given empiric antibiotics) or caused by fastidious organisms such as *Bartonella*.

Abdominal imaging has the highest diagnostic yield and is most likely to identify common causes of FUO such as intra-abdominal abscesses and lymphoproliferative disorders.[4] In addition, CT scan of the chest is also invaluable in identifying pulmonary nodules—whether caused by fungal, mycobacterial, or nocardial infections, or malignancy. Based on a study of 73 patients with FUO from the Netherlands, CT chest was helpful in making the diagnosis in 20% and resulted in a false positive result in 17%.[6] The presence of hilar or mediastinal adenopathy can also prompt appropriate biopsy and diagnosis of lymphoma, histoplasmosis, or sarcoidosis. There is additional utility in nuclear imaging studies, particularly Technetium ^{99m}Tc scans, which provide a high specificity (93-94%) and ability to be diagnostically helpful with a positive likelihood ratio of 5.7-12.5.[5] Newer imaging techniques such as F-18-fluorodeoxy-glucose positron emission tomography/computed tomography (18-FDG-PET/CT)[4] can be helpful to identify sources of increased uptake representative of malignancy or infection. Nuclear imaging studies can identify potential biopsy sites for definitive diagnosis, as was found in this case.

While a rare cause of FUO, sarcoidosis is frequently found incidentally and is often a diagnosis of exclusion upon finding noncaseating granulomas.[7] The initial presentation can be highly varied. Classically, patients present initially with pulmonary symptoms. While sarcoidosis is 3 to 4 times more commonly diagnosed in African Americans and tends to present with more severe symptoms, Caucasians tend to present with asymptomatic chronic disease. Prevalence is estimated at 10 to 20 per 100,000 population. The most common presenting symptoms are cough, dyspnea, and chest pain, but patients also often report fatigue, malaise, fever, and weight loss.[8] Systemic symptoms such as fever and malaise are more commonly reported in patients over the age of 70.

Our patient presented with vague systemic symptoms and multiple diagnostic clues that ultimately proved to be incidental findings. In the end, the mediastinal and hilar lymphadenopathy on CT chest and 18-FDG-PET/CT were crucial in localizing a target for biopsy that ultimately confirmed the diagnosis. As the diagnosis of FUO is challenging due to the wide breadth of possible etiologies, clinicians must use diagnostic clues from a thorough history with support from advanced imaging techniques when appropriate to streamline the evaluation. Finally, as elderly patients may present with nonspecific systemic symptoms, clinicians should remember not to overlook sarcoidosis as a possible etiology of FUO, especially in the presence of asymptomatic bilateral hilar lymphadenopathy.[9,10]

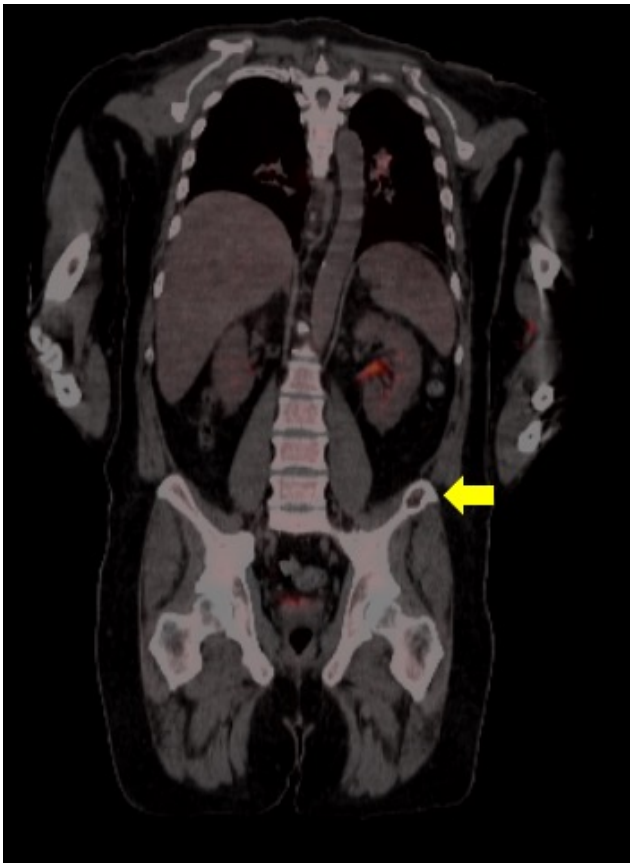

Figure 1. PET/CT coronal view showing moderate FDG uptake in an expansile lytic lesion in the left iliac wing. Note there is also diffuse intense FDG uptake in the entire skeletal system.

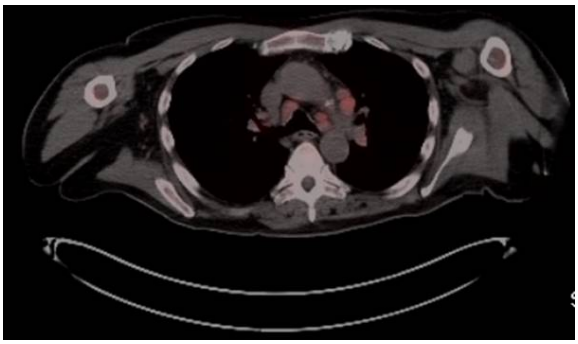

Figure 2. PET/CT transverse view showing multiple enlarged mediastinal and pulmonary hilar lymph nodes with intense FDG uptake.

Table 1 – Diagnostic Tests

	Diagnostic Test	Reference Range	Result
Serum Studies	Bacterial blood culture	Negative	Negative
	Fungal blood culture	Negative	Negative
	HIV Ab panel, p24 Ag	Nonreactive	Nonreactive
	QuantiFERON-TB Gold	Negative	Negative
	Hepatitis Panel *Hepatitis B surface Ag* *Hepatitis B surface Ab* *Hepatitis B core Ab* *Hepatitis B e Ag* *Hepatitis C total Ab*	Nonreactive	Nonreactive
	Epstein-Barr virus (EBV) DNA Quantitative PCR, serum	< 2.30 log copies/mL	3.34 log copies/mL
	Coccidioides Ab Panel (IgM, IgG)	Negative	Negative
	Fungal serology panel (includes the following): *Aspergillus fumigatus* *Aureobasidum pullulans* *Pigeon serum* *Micropolyspora faeni* *Thermoactinomyces vulgaris* *Thermoactinomyces candidus* *Thermoactinomyces viridis* *C. immitus* *Histoplasma* *Blactomyces*	Negative	Negative
	Rickettsia rickettsia IgM, IgG	Not detected	Not detected
	Rickettsia typhi IgM, IgG	Not detected	Not detected
	Bartonella henselae IgM, IgG	Negative	Negative
	Q fever IgM Phase 1 & 2, Q fever IgG Phase 1 & 2	Negative	Negative
	Brucella IgM, IgG	< 0.80 (for both IgM, IgG)	0.17 (IgM), 0.23 (IgG)
Respiratory Studies	Respiratory culture	Negative	Mixed respiratory flora
	SARS-CoV-2 nasopharyngeal PCR	Negative	Negative
	Influenza A, B nasopharyngeal PCR	Negative	Negative
Urinary Studies	*L. pneumophila* urine antigen	Not detected	Not detected
	S. pneumoniae urine antigen	Negative	Negative
	Histoplasma urine antigen	Negative	Negative

Abbreviations (alphabetical): Ab = antibody, Ag = antigen, HIV = human immunodeficiency virus, IgG = immunoglobulin G, IgM = immunoglobulin M, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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