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Case Report

Fever of Unknown Origin: A Hot Diagnosis in the Outpatient Setting

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Abstract

A 63-year-old man presents to the primary care office with a productive cough, myalgias, fatigue, and a temperature ranging from 100.1 to 101 F for a one-week duration. He has atrial fibrillation, hypertension, benign prostatic hypertrophy, and a history of pancreatic cancer status post partial pancreatectomy and splenectomy three months prior, resulting in uncontrolled, post-surgical diabetes. He is taking amiodarone, carvedilol, hydrochlorothiazide, and metformin. He denies any other recent procedures, hospital admissions, or sick contacts.

Keywords: hot diagnosis; cough; myalgias; fatigue

Case Presentation

A 63-year-old man presents to the primary care office with a productive cough, myalgias, fatigue, and a temperature ranging from 100.1 to 101 F for a one-week duration. He has atrial fibrillation, hypertension, benign prostatic hypertrophy, and a history of pancreatic cancer status post partial pancreatectomy and splenectomy three months prior, resulting in uncontrolled, post-surgical diabetes. He is taking amiodarone, carvedilol, hydrochlorothiazide, and metformin. He denies any other recent procedures, hospital admissions, or sick contacts.

Physical examination, including vital signs, is unremarkable. Rapid COVID-19 NAAT testing was negative. However, due to the patient's fever and productive cough, the patient was diagnosed with clinical pneumonia and prescribed levofloxacin and guaifenesin for seven days.

The patient's symptoms improved initially, but within two days of completing his antibiotic course, the patient presented to the Emergency Department (ED) for low-grade fevers and a dry cough. Physical examination was unremarkable again except for a fever of 101 F. Laboratory evaluations were significant for a mild leukocytosis with left shift and elevated c-reactive protein (CRP). See Table 1. Chest radiograph, urine testing, and COVID-19 PCR testing were negative. The patient was diagnosed with tracheitis and discharged with acetaminophen, guaifenesin with codeine, and prednisone.

Tests	Results	Reference Range & Units
WBC	**12.900**	3.4 - 10.8 x10E3/uL
RBC	4.93	3.77 - 5.28 x10E6/uL
Hemoglobin	14	11.1 - 15.9 g/dL
Hematocrit	43.90	34.0 - 46.6 %
Platelets	231.000	150 - 450 x10E3/uL
Neutrophils	**87**	45.0 - 85.0 %
Immature granulocytes	**0.8**	0.0 - 0.5 %
BUN	16	6 - 24 mg/dL
Creatinine	0,84	0.57 - 1.00 mg/dL
Sodium	133	134 - 144 mmol/L
Potassium	4.7	3.5 - 5.2 mmol/L
Bilirubin, Total	0.6	0.0 - 1.2 mg/dL
Alkaline Phosphatase	58	39 - 117 IU/L
AST	19	0 - 40 IU/L
ALT	20	0 - 32 IU/L
GGT	22	0 – 65 IU/L
Pro-BNP	242.6	0 - 210 pg/mL
CRP	**53.1**	0 - 10 mg/L
ESR	**42**	0 – 32 mm/hr

Table 1. *Laboratory results (abnormal results in bold)*

Two weeks after ED evaluation, the patient presented to his primary care physician with unresolved low-grade fevers and generalized malaise. Although vital signs were unremarkable, a new III/VI systolic heart murmur was noted at the bilateral upper sternal borders. In addition, the following physical exam findings were not present: rashes, dental caries, ophthalmic changes, extrapulmonary sounds, or lower extremity swelling. The patient then mentions that he has known heart valve problems but that "his heart is fine." At this point, the patient was urged to present to the hospital for further evaluation of his fevers and new heart murmur. Unfortunately, the patient disagreed with the recommendation due to his fear of prolonged hospitalization, similar to his recent pancreatectomy.

The diagnosis

Since the patient refused hospitalization and was clinically stable, an Infectious Diseases physician was consulted in the outpatient setting. Under specialty recommendation, the patient completed the following outpatient evaluation: serial blood cultures, tuberculosis screening, complete blood and metabolic panels, CRP, echocardiogram, and computed tomography (CT) of the chest and abdomen and pelvis.

Findings were significant for mild leukocytosis with left shift and slightly down-trending CRP. Tuberculosis screening was negative despite a CT chest that showed calcifications in the upper lobe of bilateral lungs (Figure 1). CT abdomen and pelvis were negative for any acute changes or complications from previous abdominal surgeries. While waiting for the outpatient echocardiogram, three blood cultures were positive for gram-positive cocci in clusters.

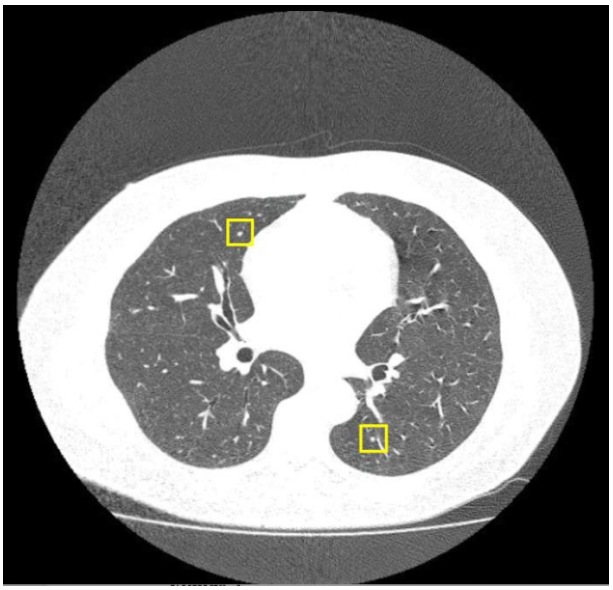

Figure 1. *CT thorax with contrast showing calcifications in the upper lobe of both lungs.*

The patient was persuaded to hospitalization with positive cultures and systemic signs of bacteremia. Blood cultures speciated to Streptococcus sanguinis and thus led to a transthoracic and transesophageal echocardiogram that revealed mitral valve prolapse with severe regurgitation and evidence of 4 mm vegetation (Figures 2 and 3). The patient was diagnosed with Streptococcus sanguinis endocarditis and subsequently treated with intravenous Ceftriaxone for four weeks. The patient is doing well and awaiting mitral valve replacement.

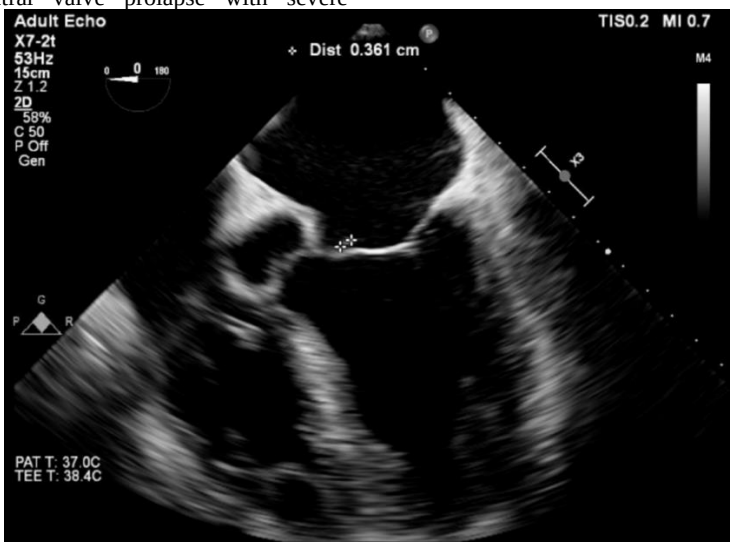

Figure 2. *Transesophageal echocardiogram showing 4 mm vegetation in the mitral valve.*

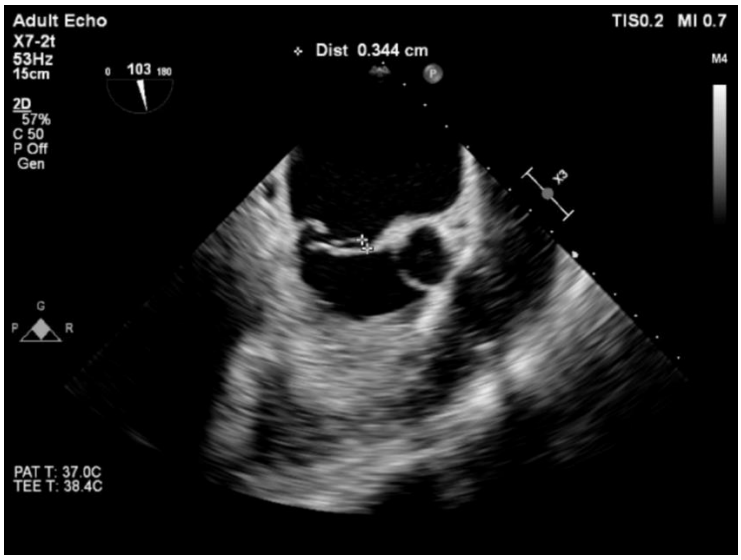

Figure 3. *Transesophageal echocardiogram showing 4 mm vegetation in the mitral valve.*

The Discussion

The initial diagnosis and treatment for clinical pneumonia were determined based on his clinical presentation – fever and productive cough. However, a more extensive evaluation was warranted after treatment failure and meeting the criteria for fever of unknown origin (FUO). Fever of unknown origin has classically been defined by [1] multiple temperature measurements > 100.9 F, [2] fever duration > three weeks, and [3] uncertain diagnosis after one week of evaluation[1]. However, the definition of FUO has varied over time, and any proposed definition is subjective. Haider and Singh proposed a broader definition in 2022 that includes the core features of fever without an identifiable cause despite reasonable investigations and a duration that is sufficient to rule out self-limiting febrile conditions[2]. The differential diagnosis for FUO is broad, including infection, rheumatic disease, and malignancy. The most common infections are tuberculosis and abdominopelvic abscess [3]

In this case, the patient was being evaluated in the outpatient setting, and ED and blood cultures may have expedited the patient's treatment. His blood cultures were eventually ordered by the Infectious Disease specialist. Blood cultures are still indicated in the ED to evaluate suspected sepsis, meningitis, complicated pyelonephritis, and endocarditis[4]. But, in the outpatient setting, blood cultures have a low yield, with clinical significance in less than 3% of tests [5]. However, in this specific case, since the patient was immunocompromised, met the definition of FUO, and was refusing evaluation in the ED, blood cultures should be considered sooner due to their higher pre-test probability.

Moreover, the patient was not forthcoming about his history of valvular disease, not understanding its importance as he was previously asymptomatic. This patient, with his asplenia, is immunocompromised and at high risk for severe infections [6,7] The clinician should have a high suspicion of atypical infections, and a more thorough dive into the patient's medical history is necessary. Specifically, this patient's asplenia and valvular disease place the patient at high risk for endocarditis.

The Takeaway

FUO is challenging to evaluate in the outpatient setting but more so in high-risk, immunocompromised patients. This case illustrates the critical need for a high index of suspicion for severe and atypical infections and consideration for hospitalization for expedited evaluation and treatment while always obtaining a thorough medical history.

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