# Inflammatory Sarcoma Presented as a Case of Fever of Unknown Origin

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Fever of unknown origin (FUO) is defined as the repeated occurrence of elevated body temperature above 38.3°C (101°F) lasting for at least 3 weeks with no clear diagnosis despite a thorough investigation of more than one-week duration. FUO cases could be categorized into three major etiologies: infectious, neoplastic, and systemic inflammatory. Despite novel diagnostic modalities, clinicians still encounter a significant number of unresolved FUO cases, accounting for as many as 50% of cases [1]. Prolonged futile FUO investigations may be a source of frustration for many clinicians [2]. We described a unique cause for FUO that shares the complexity of the diagnostic workup and emphasizes the importance of $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT) modality in the process of investigating FUO.

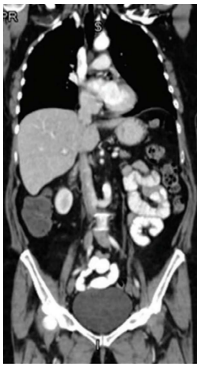
## PATIENT DESCRIPTION

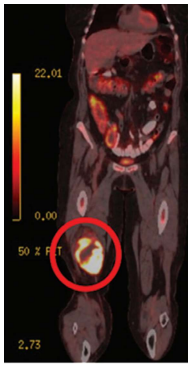
A 76-year-old woman presented to the emergency department (ED) of our tertiary care center with a 4-week history of high-grade fever, headache, and fatigue. Her medical background was notable for hypertension, nephrolithiasis, and depression. The patient did not complain of night sweats, blurred vision, weight loss, abdominal discomfort, skin rash, jaw claudication, or arthralgia. Likewise, exposure to animals and the initiation of new medications were denied. The patient was diagnosed with FUO before her admission to the ED, following a thorough laboratory investigation at the community clinic including a transthoracic echocardiogram (TTE) which was unremarkable. One week before her admission, the patient was diagnosed with polymyalgia rheumatica at an outpatient rheumatology clinic. Therapy with prednisone, 15 mg per day, was initiated, without an evident clinical benefit, and thus was halted within ten days. On arrival at the ED, the patient's vital signs were normal, except for a mild elevation of systolic blood pressure. Physical examination was unremarkable with no findings of murmurs, carotidynia, temporal tenderness, lymphadenopathy, hepatosplenomegaly, palpable masses, rash, or arthritis. Laboratory results revealed leukocytosis (14,000 109/L), thrombocytosis (650,000 109/L), microcytic anemia (hemoglobin 11.7 gr%), elevated inflammatory markers, erythrocyte sedimentation rate (126 mm/HR), and C-reactive protein (22 mg %). The blood smear displayed a leukemoid reaction, with no evidence of blasts. The chest X-ray was normal. During her hospitalization, the patient underwent further investigations. Infectious serologies for human immunodeficiency virus, *Coxiella burnetti*, *Brucella melatensis*, parvovirus, Epstein-Barr virus, cytomegalovirus, and hepatitis B and C virus were negative. In addition, stool and blood cultures were negative. Likewise, immune serologies, including antinuclear antibody (ANA), anti-double-stranded DNA, antiphospholipid antibodies (APLA), cytoplasmic, and perinuclear anti-neutrophil antibodies were all unremarkable. Complement

**Figure 1.** Computed tomography (CT), $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT), and magnetic resonance imaging (MRI) scans

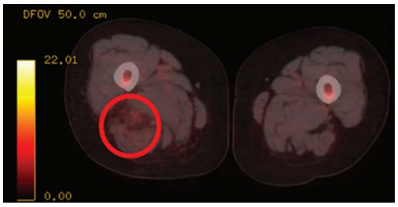
**[A]** Chest, abdominal, and pelvic (CT) scan, coronal view demonstrating a mixed sclerotic-lytic lesion in the right proximal femur

**[B]** PET/CT, coronal view

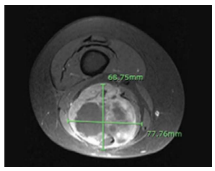





**[C]** PET/CT, axial view demonstrating a space occupying lesion in the right distal thigh, measuring 16.1 × 5.6 × 7.8 cm, with necrotic and solid components




**[D]** MRI scan, axial view demonstrating a soft tissue mass in the right thigh, measuring 7 × 8 × 14.5 cm



proteins were also within normal limits. Moreover, free light chains in blood, temporal ultrasonography, and repeat TTE were noncontributory.

A typical CT scan of the chest, abdomen, and pelvis [Figure 1A] ruled out infection, vasculitis, or neoplastic findings. However, it demonstrated a small uterine myoma and mixed sclerotic lesion in the right proximal femur. The latter was unchanged when compared to a previous CT scan. Considering the lack of a clear diagnosis, a bone marrow core biopsy was conducted, which ruled out any gross pathology. While hospitalized, the patient developed right upper quadrant pain with persistently elevated liver enzymes. As abdominal ultrasonography found no focal lesions, a liver biopsy was undertaken, demonstrating an inflammatory infiltrate in the portal spaces with neutrophils and some activated macrophages in addition to Kupffer cell granulomas. These findings were considered nonspecific and could be explained by a toxic, infectious, or inflammatory process. Considering the new ache and edema developed in the patient's right thigh Doppler ultrasonography was conducted, with no pathologic findings, which ruled out a deep vein thrombosis. Since the thorough diagnostic workup did not reveal the etiology of the patient's FUO, and due to the persistent fever, it was decided to perform a PET/CT scan. Surprisingly, the test revealed a space-occupying lesion in the patient's right distal thigh, measuring 16.1 × 5.6 × 7.8 cm in size and consisting of necrotic and solid components [Figures 1B and 1C]. A magnetic resonance imaging (MRI) scan was subsequently conducted to better characterize the lesion, demonstrating a soft tissue mass. In T2, the lesion displayed a heterogenic enhancement with central necrosis [Figure 1D], compatible with sarcoma. A biopsy was undertaken, with the pathology results demonstrating an undifferentiated, inflammatory type pleomorphic sarcoma.

The patient underwent radiotherapy, followed by surgical tumor resection. Unfortunately, 8 months later, she was diagnosed with metastasis to the right gastrocnemius muscle and lungs. Despite chemotherapy with doxorubicin, the disease progressed. Treatment with immune checkpoint inhibitors was attempted. The latter was not tolerated due to side effects. Two years following the initial diagnosis, the patient died.

## COMMENT

We have reported the case of a 76-year-old female, presenting with FUO with the final diagnosis being undifferentiated pleomorphic sarcoma, inflammatory type. The use of PET/CT was the cornerstone for the correct diagnosis. Sarcomas are a heterogeneous group of malignant tumors of mesenchymal origin, representing roughly less than 1% of all adult malignancies. Neoplastic fever secondary to bone and soft tissue sarcomas is estimated to occur in 6% of these patients [3]. Inflammatory sarcomas are infrequent tumors, presenting in a salient manner, painless, and slow growing, and thus are often missed and underdiagnosed. They have been rarely described as a cause of FUO. In our case, while a dedicated limb imaging study was not conducted early in the diagnosis due to the lack of symptoms, the use of PET/CT led to the definitive diagnosis. The role of PET/CT in the context of FUO investigation has been emphasized over the last few years. Meller and colleagues [4] described the importance of using PET/ CT in FUO workup, especially when the underlying cause is oncologic. In their study, PET/CT assisted in reaching the final diagnosis in 25–69% of the cases. In addition, a systematic review demonstrated that PET/CT has a 90% sensitivity and 89% specificity in diagnosing osseous and soft tissue sarcomas [5].

## CONCLUSIONS

Our case has several unique aspects. First, inflammatory sarcomas remain a rare cause of FUO. Second, the use of PET/CT uncovered the diagnosis after an exhausting investigation. The metastatic nature of sarcomas, even after resection, is also noteworthy. One should consider early utilization of PET/CT in elderly patients due to the higher prevalence of malignancy in this population. We propose that the earlier utilization of PET/CT in the workup of FUO could significantly improve the diagnostic and therapeutic outcomes and perhaps prevent implementation of unnecessary invasive procedures.

### Correspondence

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**The thing that makes you exceptional, if you are at all, is inevitably that which must also make you lonely.**
Lorraine Hansberry (1930–1965), playwright and painter