

## CLINICAL VIGNETTE

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# Pulmonary Embolism and Recurring Fever: An Uncommon Presentation of a Common Problem

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Pulmonary embolism is a common and potentially fatal disease. Early diagnosis can significantly reduce mortality and morbidity. The most frequent presenting symptoms of pulmonary embolism (PE) are dyspnea on exertion, pleuritic chest pain and cough.<sup>1,2</sup> However, in older individuals, atypical symptoms may occur making a diagnosis more difficult.<sup>3</sup> We present a case where intermittent fever was the presenting sign in a case of PE in an elderly female which took more than a year to identify.

### **Case Report**

An 81-year old female presented to primary care for intermittent episodes of fever to 39.1°C, chills, headaches, total body pain, and malaise beginning one year previously without a clear precipitating event. Symptoms resolved within 2–3 days irrespective of treatment with antibiotics. The fevers had largely been attributed to recurrent urinary tract infections, for which the patient was eventually prescribed vaginal estrogen by a urologist. Febrile episodes became more frequent over time despite treatment and were occurring on a monthly basis. The day prior to her initial primary care visit she was evaluated by a rheumatologist who thought neither chronic shoulder pain with effusion (which was aspirated) nor polymyalgia rheumatica were a likely cause of her symptoms. The patient's past medical history was significant for osteoarthritis, fibromyalgia, and rheumatoid arthritis that was managed without disease modifying anti-rheumatic drugs. On presentation, the patient appeared well-developed and well-nourished. Physical exam findings included normal vital signs, a mild systolic murmur consistent with aortic sclerosis or stenosis, and a slightly enlarged, non-tender thyroid gland. A workup for fever of unknown origin was initiated and the patient, who was asymptomatic, was encouraged to return to clinic immediately for any future febrile episode.

Results of initial workup included a normal urinalysis and liver function tests, a white blood cell count of  $11.59 \times 10^3/\mu\text{L}$ , aortic sclerosis on echocardiogram, and a thyroid gland at the upper limits of normal size on ultrasound. Two weeks later the patient returned to primary care for fever, chills, headache, and body aches that began several hours earlier. Physical exam was remarkable for a pulse = 114 bpm, temperature = 38.7°C, respiration = 20 per minute, SpO<sub>2</sub> = 95%, but no other new findings. The differential diagnosis considered at the time

included infectious causes such as recurrent urinary tract infection, relapsing fever, an occult abscess, malignancies such as lymphoma, and food or drug allergies. Genetic syndromes associated with intermittent fever were thought to be unlikely due to the late onset of symptoms. Given the patient's acute presentation with fever and mild hypoxia, the patient was sent directly to an emergency department where a diagnosis of pyelonephritis was made and treatment with ciprofloxacin initiated.

Approximately 2 weeks after discharge from the emergency department the patient followed up with primary care for recurrent symptoms. She reported dysuria, fever, chills, and joint pains lasting 3-4 hours the day before which resolved spontaneously. As previously, the patient was entirely asymptomatic between febrile events. Results of a urine dipstick were negative, and no environmental, drug-related, or other precipitating causes could be identified. The workup for fever of unknown origin was extended to include CT scans of the chest, abdomen, and pelvis, as well as referrals to Hematology-Oncology and Infectious Disease subspecialists. Further testing for tuberculosis, hepatitis, HIV, coccidiomycosis, Q fever, and syphilis, as well as serum antibody levels and tumor markers was unrevealing. Beta-2 microglobulin and CRP were mildly elevated, and an ESR was within normal limits. Chest CT showed segmental filling defects within bilateral lower, left upper and right middle lobes consistent with pulmonary embolism (PE). Abdominal CT was remarkable for findings suggestive of focal portal vein branch thrombosis.

Therapy with apixaban was initiated immediately. The intermittent fevers, associated symptoms, and neutrophilia promptly resolved. Additional history subsequently obtained was notable for a family history of thromboembolism (her mother died from blood clots) and an ankle fracture that occurred over a year preceding her symptoms. In addition, she admitted to taking an overseas airplane flight, and recalled swelling in her ankle and leg preceding her first febrile episode. Further diagnostic work-up showed a d-dimer level >2000 ng/mL. Due to her family history, a work-up to identify thrombophilia, including tests for Factor V Leiden, prothrombin gene mutation, anti-phospholipid antibodies, and levels of protein c and protein s were performed. All were negative or within normal limits. Bilateral duplex ultrasound of the lower extremities demonstrated all veins to be patent and compressed.

sible without any evidence of thrombosis. Transthoracic echocardiogram showed no significant valvular disease, intracardiac clot or atrial enlargement, a normal ejection fraction, and mild concentric left ventricular hypertrophy. Because of her intermittent leukocytosis, a heme sequencing panel was sent to rule out an underlying myeloproliferative disorder and was also negative.

### Discussion

While the vast majority of pulmonary emboli are believed to originate in the deep veins of the body, fewer than 30 percent of individuals who experience PE have symptoms of DVT. Instead, the most common symptoms are shortness of breath on exertion, pleuritic chest pain and cough. Researchers have found that in primary care a diagnostic delay of more than a week in the diagnosis of pulmonary embolism is common, and more likely to occur when classical PE symptoms are absent.<sup>4,5</sup>

Most recently in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, a large study conducted by the National Heart Lung and Blood Institute of the National Institute of Health, fever without another cause was present in 14% of patients.<sup>6</sup> Fever has long been recognized as an accompanying sign of PE, with case reports published as early as 1937.<sup>7</sup> In 1957, Israel and Goldstein a description of common clinical characteristics of 90 patients with PE, among whom 78.9% had fever.<sup>8</sup> They noted temperatures below 39.4°C in 90% of patients, as well as frequent response to anticoagulation. More recently, Saad and colleagues reported a case of saddle pulmonary embolism presenting with a temperature of 38°C which increased to 40°C over 4 days until a diagnosis of PE was made.<sup>9</sup> The patient defervesced after treatment with tissue plasminogen activator and anticoagulation was initiated.

Fever accompanying pulmonary embolism may also be associated with higher clot burden and morbidity. In a retrospective review of 241 patients with PE, those with fever within 1 week of a PE diagnosis compared to those without fever were more likely to have massive and sub-massive clots.<sup>10</sup> In this study, the cohort with fever also had longer lengths of hospital stay and had higher rates of admission to intensive care and mechanical ventilation. In a multivariate model, inpatient mortality did not differ between the cohorts. However, in an international observational registry of people with acute deep venous thrombosis who subsequently developed PE, fever at presentation was associated with both higher overall mortality (5.8% and 2.9%  $p < 0.001$ ) and mortality attributed to PE (0.7% and 0.1%,  $p = 0.005$ ).<sup>11</sup>

The pathophysiology of fever in PE is not well understood. It is suggested that a variety of mechanisms may be responsible such as infarction and tissue necrosis, hemorrhage, vascular inflammation, or atelectasis.<sup>12</sup> These changes may result in elevated leucocyte count, which is typically modest.<sup>13</sup> However, fever associated with PE most commonly results from a secondary cause such as malignancy or infection, these states

are typically associated with higher white blood cell counts than PE alone.<sup>13,14</sup>

This case is unique as in our review of the literature we did not find any reports of PE as a cause of intermittent fever. This case is also somewhat unusual because the patient's temperature was high ( $\geq 39^\circ\text{C}$ ) and no other cause of fever, such as malignancy or infection, was identified. We speculate that her large clot burden at presentation was likely responsible for this. At the time of this report, the patient is doing well and tolerating apixiban twice daily with no return of fever, shortness of breath or subsequent symptoms.

### Conclusion

Diagnostic delay of pulmonary embolism is common in primary care, especially if classical PE symptoms are absent. Awareness of PE as a possible cause of a wide range of symptoms such as fever in the appropriate setting might help to avoid delayed diagnoses in the elderly. Reducing the time from presentation to establishing a diagnosis of PE can allow for prompt initiation of anticoagulation, and lower associated morbidity and the risk of mortality.

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