CASE RECORDS

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A 74-year-old man with persistent fevers

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Abstract

An elderly man with a history of extensive world travel presents with a chronic illness and fevers. The febrile illness has been present for eight years, and no diagnosis has been made despite extensive evaluation and testing. The differential diagnosis of this unusual case of fever of unknown origin is discussed.

Presentation of case

A 74-year-old African-American man was admitted after an episode of syncope. He had had several coronary angioplasties performed previously, but had no angina associated with this episode. His electrocardiogram revealed no significant interval change from prior tracings, and an echocardiogram showed normal left ventricular function without segmental wall motion abnormalities. The event was witnessed and no obvious seizure activity was noted. In the emergency room the patient was found to have significant orthostatic hypotension, which responded to intravenous volume loading. The patient gave a history of decreased oral intake and fever. He was admitted for further evaluation.

The patient described an eight-year history of recurrent fevers, with temperature peaks as high as 105°F. The fevers occurred daily between 2:00 and 3:00 p.m., occasionally with chills, shortness of breath, a dry cough, diffuse headache, fatigue, and malaise. Relief was obtained with the use of nonsteroidal antiinflammatory agents or acetaminophen. He denied substantial weight loss over this period, and could recall no exposure to tuberculosis. The patient had an extensive travel history that included multiple trips to Africa, the Middle East, and Southern Europe. He denied any significant illnesses during or immediately after these trips and none of his family members, who had accompanied him on these trips, were ill.

The patient had benign prostatic hypertrophy, for which he had undergone a transurethral resection. He had a history of a herniated nucleus pulposus in the lumbar spine. His only medications were isosorbide dinitrate and enteric coated aspirin. He had a distant history of tobacco use and did not drink alcohol. He was retired from military service. He was married and was monogamous.

His temperature was 99.4°F, pulse was 80 and regular, respirations were 20, and blood pressure was 115/50 mm Hg. He appeared comfortable and was thin, but not wasted.

There was no rash or adenopathy, and there were no joint abnormalities. The liver was normal in size and the spleen could not be palpated. A grade I systolic ejection-quality murmur was present along the left lower sternal border. Inspiratory rales were present at the base of the left lung. The remainder of the examination was normal.

Routine serum chemistries, transaminases, and bilirubin, alkaline phosphatase, total protein and albumin, and coagulation parameters were all normal. A urinalysis was normal except for 1+ proteinuria. A 24-hour collection of urine yielded 0.53 of total protein. Hematologic values from admission are shown in **Table 1**.

Routine cultures of blood, sputum, and urine obtained during fever were negative. A 5-tuberculin unit PPD was negative at 48 and 72 hours. A chest x-ray showed blunting of both costophrenic angles (**Figure 1**), and a computed tomogram of the chest confirmed bilateral pleural effusions and showed a mild, nonspecific parenchymal density at the left base without evidence of adenopathy or a mass (**Figure 2**). A gallium scan localized activity to the left lower lobe and pleural effusion. A left thoracentesis was performed and yielded cloudy yellow fluid with a glucose of 82 mg/dl, a total protein of 4.4 g/dl, and an LDH of 610 U/liter. There were 9,225 white blood cells/μL (16% polynuclear, 50% lymphs, 24% monocytes, 10% mesothelial) and 6,500 red blood cells/μL. Gram's stain and acid-fast stain of the fluid revealed no organisms. Routine culture, as well as culture for acid-fast organisms and fungi, were negative. Cytological examination of the fluid showed no evidence of malignancy. A thoracoscopic biopsy of the left upper lobe, the superior segment of the left lower lobe, and the pleura showed only mild chronic inflammation of the pleura with focal mesothelial hyperplasia.

Thick and thin smears of blood for malaria, and serology for cryptococcal antigens, tularemia, chlamydia, legionella, mycoplasma, and human immunodeficiency virus (HIV) were all negative. IgG antibodies to toxoplasmosis were present. Antibodies to histoplasma, coccidiomyces, blastomyces, and aspergillus were all negative in serum. Rheumatoid factor and antinuclear antibodies were not detected in serum. Smith antibodies and antibodies to ribonucleoprotein, SS-A and SS-B (antinuclear antibiotics associated with speckled pattern) were not detected in serum.

Fevers continued and the patient was empirically treated with ticarcillin/clavulanic acid and clarithromycin. Fever subsided and the patient felt better. He was discharged on oral ciprofloxacin and clarithromycin. The patient continued to improve at home, remained afebrile, and had increased strength and appetite. He complained of intermittent low back pain and anterior left thigh pain, and a magnetic resonance image of the lumbosacral spine showed a nonspecific wedge-shaped area of low signal intensity on T1-weighted images at L3, with diffusely increased signal intensity of the body of L3 on T2-weighted images. Degenerative disc disease was noted at the L4-L5 level. A three-phase bone scan was performed that revealed mild to moderate tracer accumulation within the vertebral body of L3, which was felt to be atypical for degenerative disease, and the possibility of a metastatic focus raised. Focal soft tissue accumulation in the anterior left thigh was thought to represent heterotopic calcification.

Antibiotics were discontinued after one month. Approximately one week later, daily fevers of greater than 102°F resumed as before, accompanied by a dry cough, rigors, fatigue, headache, anorexia, and a seven-pound weight loss. He was again admitted to the hospital. A detailed history revealed that during the patient's travels dietary precautions were minimal and he described drinking unfiltered water and eating local dairy products, particularly cheeses. He kept no pets and had no significant exposure to farm animals. The physical examination was unchanged with the exception that the prostate was tender, although not en-

TABLE 1. Hematologic values

	Admission #1	Admission #2
White blood cells	12.9 K/μL	12.1 K/μL
Granulocytes	74.9%	64.4%
Lymphocytes	20.1%	28.4 %
Monocytes	5.0 %	7.2%
Hemoglobin	8.7 g/dl	7.3 g/dl
Hematocrit	25.3%	21.3%
MCV	88.1 fL	86.1 fL
MCH	30.3 pg	29.6 pg
Platelets	259 K/μL	154 K/μL
Erythrocyte sedimentation rate	–	80 mm/hr.

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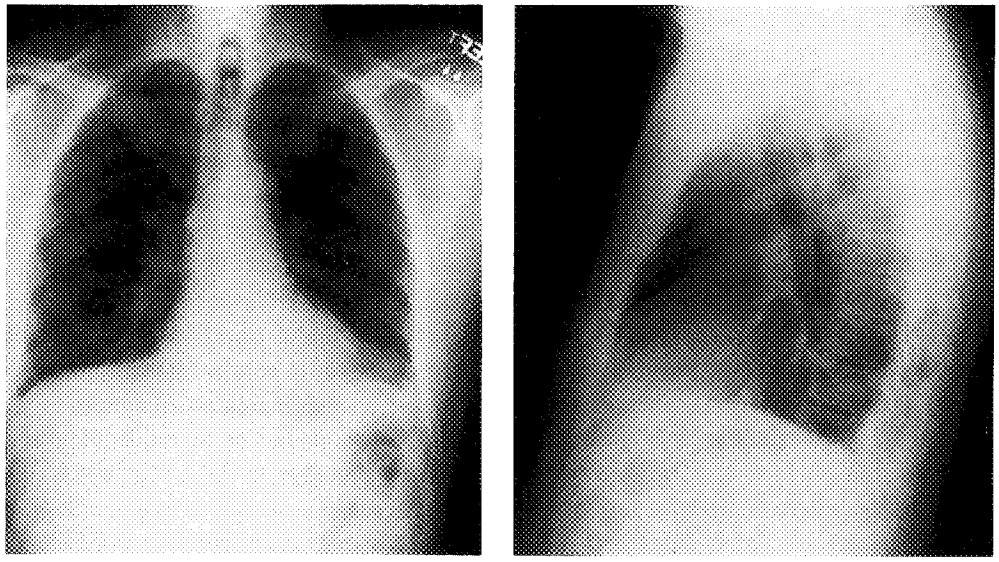

Figure 1. PA and lateral chest X-Ray, demonstrating bilateral small pleural effusions.

larged, and a possible nodule was palpated in the right lobe.

A computed tomogram of the abdomen and pelvis revealed no evidence of tumor, abscess, or adenopathy. Multiple calcified gallstones were noted, without radiographic evidence of cholecystitis. A transrectal ultrasound of the prostate revealed no evidence of abscess, but showed calcifications within the right lobe. Biopsies of the right and left lobe of the prostate revealed no significant pathology, and the prostate specific antigen was 0.5 ng/ml. A posteroanterior and lateral chest x-ray again showed blunting of the left costophrenic angle and air-space disease at the left base. A fiberoptic bronchoscopy was performed that showed "yellowish plaque-like areas" involving the mucosa of the right middle lobe. Bronchoalveolar lavage was performed in this area, and the fluid was negative for malignancy on cytological evaluation, and showed no organisms on silver methenamine staining. Routine cultures, and acid fast bacillus and fungal cultures of the lavage fluid were negative. A transbronchial biopsy was performed in the posterolateral segment of the left lower lobe and showed mild interstitial fibrosis and intraalveolar fibrin deposition. No viral changes were seen on H&E stain, methenamine silver staining for *Pneumocystis* was negative and periodic-acid Schiff-base staining for fungi was also negative.

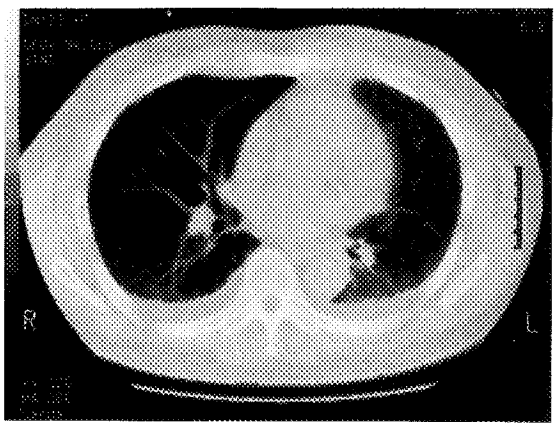

Figure 2. CT scan of the chest demonstrating bilateral pleural effusions and a non-specific parenchymal density at the left base.

Discussion

The patient whose case is presented to us today has been vexed by an illness-causing fever for several years. Despite several attempts at diagnosis and therapy, the cause of his illness is unknown. The approach to this problem was first codified in a classical article by Petersdorf and Beeson[1] in *Medicine* written in 1961. These authors created the modern definition of the fever of unknown origin: an illness of more than three weeks duration, with documented fever greater than 101°F, and with no diagnosis after one week of inpatient evaluation. These criteria have been modified by more recent writers, but the original definition serves our purpose well to this day.

As we were taught in medical school, all diagnosis begins with a complete history and physical examination. This is never more true than when approaching a difficult case such as this one. There are three general strategies of diagnostic reasoning techniques used by clinicians: probabilistic reasoning, causal reasoning, and deterministic reasoning.[2] Causal

reasoning, the linkage of cause to effect, and deterministic reasoning, the use of compiled strategies in the form of well-defined rules, will not serve us well in cases such as the one presented to us, in which the facts of the case are well outside our usual experience. In this case, I will use probabilistic reasoning, the methodical examination of the likelihood of causality.

TABLE 2. Causes of FUO: 1960-1990

Infectious	30% to 40%
Autoimmune or Hypersensitivity	10% to 20%
Neoplasm	20% to 30%
Miscellaneous	15% to 20%
Undiagnosed	5% to 15%

Categorizing and examining the causes of fevers of unknown origin (FUO) may enable us to grapple with this daunting task. Many authors have periodically reviewed the causes of prolonged fevers that fulfill the criteria of FUO, and the predominance of causes of FUO has shifted over the years. As noninvasive and invasive diagnostic techniques have improved, infectious and neoplastic causes of FUO have diminished in frequency, and those due to other causes have increased in frequency (**Table 2**).[1,3]

The single most striking feature of this patient's history is the extreme duration of his febrile symptoms. An FUO of this extreme duration is very uncommon, as untreated infection or neoplasm usually becomes manifest over a prolonged period without appropriate diagnosis or therapy. The fact that this patient has suffered fevers for eight years paradoxically simplifies our task. The first task of the clinician in such a case is to document that fever is actually observed, and if possible, to rule out factitious fevers. In this case, fevers were documented in the hospital. In addition, the findings of pleural effusion, leukocytosis, and anemia all suggest the existence of a truly pathological condition, and militate against factitious fever. Given these facts, a relatively small set of unusual diseases must be considered as causes of FUO of extreme duration[4] (**Table 3**). Let us examine some other facts of the case to focus our search further.

The patient is 74 years old; symptoms began at the age of 66. This allows us to eliminate several possibilities. Fevers due to familial Mediterranean fever usually begin in childhood and may be intermittent. Since there is no history of fever prior to age 66 this can be discounted. Similarly, this would be a very advanced age of onset for adult Still's disease, and associated symptoms such as rash, lymphadenopathy, or splenomegaly were not reported. Other collagen-vascular or autoimmune diseases (**Table 4**) could cause prolonged fever, but again the late onset of disease and the lack of serologic or other symptomatic evidence makes this diagnosis less likely. Polymyalgia rheumatica bears consideration, as it occurs in old age, but none of its classical characteristics — shoulder or hip pain, evidence of inflammatory arthritis, or rapid response to antiinflammatory agents — are reported. Fever induced by medication ("drug fever") is always a possibility, and a trial of discontinuation of medications should always be considered. In this case the patient's medications seemed unlikely to be the cause of the FUO.

Granulomatous hepatitis merits some consideration, as this disease most often develops later in life. Granulomatous hepatitis results from mycobacterial or parasitic infection, or the use of medications such as dilantin, penicillin, or isoniazid, and commonly causes liver function test abnormalities, although cases have rarely been reported in the absence of these findings. Liver biopsy is diagnostic, but my clinical suspicion of granulomatous hepatitis in this case is not high enough to warrant this invasive test.

As the incidence of neoplasm rises in old age, let us consider possible neoplastic causes of FUO. The most common neoplastic causes of FUO are lymphoma, adenocarcinoma, hypernephroma, hepatoma, and atrial myxoma. The duration of this patient's symptoms makes lymphoma or adenocarcinoma unlikely.

TABLE 3. Prolonged FUO (> 1 year)

No documented fever	27%
Undiagnosed	19%
Miscellaneous	13%
Factitious	9%
Granulomatous hepatitis	8%
Neoplasm	7%
Adult Still's disease	6%
Infections	5%
Collagen-vascular disease	4%
Familial Mediterranean fever	2%

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Computerized tomography of the chest showed only a pleural effusion, and subsequent thoracentesis and bronchoscopy were unrevealing. Imaging of the abdomen and pelvis were performed and, similarly, did not yield a specific diagnosis. A bone marrow biopsy should be done if it was not performed during the recent previous evaluations. All of these studies should be carefully reviewed to ensure that they were of optimal quality, and if not, they should be repeated. A liver or renal tumor should be detected by such studies. A small atrial myxoma might be difficult to detect, and transthoracic echocardiography should be considered if this has not already been performed.

TABLE 4. Autoimmune causes of FUO

- Erythema multiforme
- Still's disease
- Polymyalgia rheumatica
- Drug fever
- Hypersensitivity angiitis
- Systemic lupus erythematosus
- Periarteritis nodosa
- Other vasculitis
- Rheumatic fever
- Serum sickness
- Mixed connective tissue disease

So we return to consider possible infectious causes of FUO. Several points of this case lead us to be suspicious of infectious FUO at the outset. The extremity of the fevers reported (105°F) and the apparent response to ciprofloxacin therapy lead us to consider an infectious disease. Although a soft sign, the mildly elevated white blood cell count suggests an infectious etiology.

The patient's history includes a striking amount of travel in the developing world and exposure to unfiltered water and unpasteurized dairy products. One can therefore assume that this patient could have acquired virtually any of the infectious pathogens associated with FUO (**Table 5**). Given the comprehensive evaluation that the patient has undergone, most of these pathogens should have been detected if they were present. However, one pathogen that is both well known to be difficult to detect and reported to be capable of causing disease for years following its acquisition is brucellosis.

This patient is likely to have brucellosis, a disease caused by a Gram-negative coccobacillus. *Brucella* are divided into several subspecies: *abortus* (cattle), *melitensis* (goats and sheep), *suis* (swine), and *canis* (dogs). The organism has a worldwide distribution, but is especially prevalent in the Mediterranean (where our patient has spent some time), India, and South and Central America.

B. abortus and *B. suis* are transmitted after contact with livestock; *B. melitensis* is primarily food-borne and transmitted through consumption of unpasteurized dairy products. The slow growth of these organisms in laboratory can hinder diagnosis. Brucellae can require up to four weeks to grow, and the microbiology laboratory will usually have to be asked to hold the sample for prolonged culture.

Brucellosis can involve any organ, but usually localizes to the reticuloendothelial system, typically the hepatobiliary system. It can also involve the bones and joints as a cause of chronic osteomyelitis, the pulmonary system, genitourinary tract, central nervous system, and the cardiovascular system, especially as a cause of chronic endocarditis.

Known classically as undulant fever, Malta fever, or Mediterranean remittent fever, brucellosis was first described in 1859. *B. melitensis* was first isolated from the spleens of British soldiers dying of Malta Fever by Sir David Bruce in 1886. *B. abortus* was first isolated from cattle in 1897, and from a human in Baltimore in 1922. *Brucella* can cause a subclinical, acute, relapsing, or chronic infection. The chronic form of *Brucella* infection can present as an insidious disease, an acute illness followed by relapses (as I believe it is in this case), or a localized infection. Constitutional symptoms are common, with headache, lassitude, depression, insomnia, and other neuropsychiatric symptoms frequently seen. Local-

TABLE 5. Infectious causes of FUO

- Bacterial abscess
- Salmonella
- Leishmaniasis
- Rat bite fever
- *Bartonella*
- Lyme disease
- Histoplasmosis
- Cytomegalovirus, Epstein-Barr virus, HIV
- Subacute endocarditis
- Toxoplasmosis
- Relapsing fever (*Borrelia*)
- Actinomyces
- *Brucella*
- Osteomyelitis
- Malaria
- Tuberculosis
- Q fever
- *Listeria*

ized disease may cause a wide variety of symptoms related to the anatomic area involved (for example, osteoarticular symptoms or heart valve dysfunction).

Definitive diagnosis is made by culture or serum agglutination test for specific antibodies. Titers are diagnostic if $\geq$ 1:160, or if a fourfold rise is seen on serial samples. Blood cultures are positive in as few as 10% in cases where the infection is old or partially treated, or as many as 85% of acute cases. The frequency of pathogen isolation decreases with duration of infection. Therefore, chronic brucellosis is usually a serologic diagnosis.

In summary, it is most likely that this patient acquired *B. melitensis* by a food-borne route. Exposure to unpasteurized goat, sheep, or even camel dairy products is the most common source of brucella in those who travel.[5] It is likely that this diagnosis was made by serology. Given the long duration of this infection, I would favor treatment with two drugs rather than one. Although ciprofloxacin has activity against brucellae, fluoroquinolones are not the treatment of choice for this infection, and relapses have been reported following quinolone monotherapy.[6] Treatment with six weeks of doxycycline and two weeks of gentamycin, or six weeks of doxycycline and rifampin is indicated.

Diagnosis and Clinical Course

There was no serologic evidence of Q fever or Lyme disease. *Brucella* antibodies were positive in a titer of 1:160, which was considered presumptive evidence of current *Brucella* infection. The patient enjoyed cheeses greatly, and on his travels had eaten "fresh" (unpasteurized) cheese and goat cheese, and this was considered to be the probable source of *Brucella* infection. The patient was treated for two months with doxycycline, 100 mg bid, and rifampin, 600 mg/day. The patient's fevers resolved within two weeks of initiation of therapy and exercise capacity improved considerably. After one month of therapy the patient had gained weight and had no fevers greater than 99°F, but described shortness of breath that occurred at approximately 3:00 p.m. daily. After two months of therapy these symptoms resolved, the patient continued to gain weight and had no further fevers. A repeat *Brucella* titer was < 1:20.

References

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