

A patient with unexplained fevers and persistent fatigue

Cases that involve prolonged fever for which no cause can be identified are challenging. This one illustrates the deductive reasoning required of an excellent clinician.

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CASE

A 52-year-old white male presented to our urgent care facility with a 12-day history of fevers ranging from 101°F to 103°F (38.3-39.4°C). Acetaminophen helped bring down his temperature for a few hours, but then the fever returned. The patient thought he had some type of “flu bug” that would go away on its own. He reported feeling very fatigued with no energy. He denied muscle aches, but he did have chills and soaking sweats with the fevers. He described a dry cough and one bout of diarrhea. He had a slight headache when he had the fevers, and he thought he had lost a few pounds. He had no significant medical history. He had first come to our facility only 1 month before this current visit, and before that, he was relatively “undoc-tored” by his own admission.

While he was in urgent care, his fever spiked to 102.2°F (39°C), and he was diaphoretic and ill-appearing on examination. The rest of his physical examination was unremarkable. The results of pertinent laboratory tests are shown in Table 1 (page 40). All other laboratory test results, including those for the CBC, urinalysis, and comprehensive metabolic profile (CMP), were normal. Results of a hepatitis profile were negative, and blood cultures showed no growth after 48 hours. The chest film was clear.

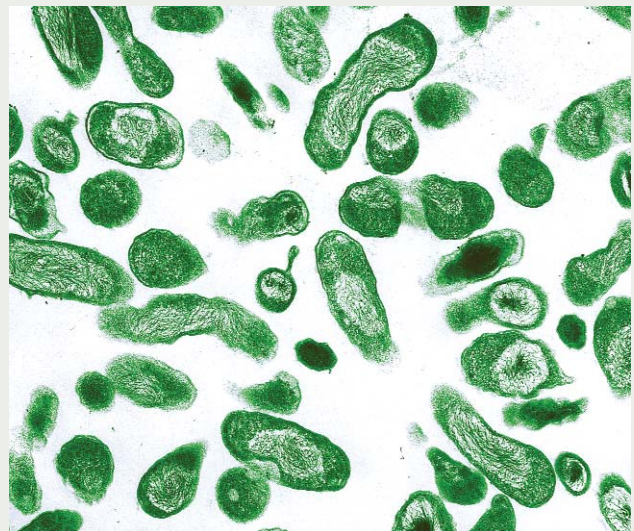
In urgent care, the patient was given acetaminophen for his fever. The staff suspected lymphoma or an abscess and recommended hospitalization and CT of chest, abdomen, and pelvis. The patient declined admission, however, citing a family obligation, and signed out against medical advice. He was instructed to continue taking OTC antipyretics and to follow up with his primary care provider if his symptoms did not improve.

CT was performed 4 days later on an outpatient basis. The CT revealed hepatosplenomegaly and a soft-tissue nodule in the right upper lobe. No lymphadenopathy was noted. CT of the head was also done, and results were normal, with no evidence of encephalitis or mass effect. The patient was referred to the gastroenterology clinic for follow-up of his abnormal liver function tests and hepatosplenomegaly.

The patient visited his primary care provider 11 days after his first visit to urgent care with the continued complaint of persistent fevers and fatigue. He had been having these fevers now for 23 days and continued to use acetaminophen daily.

The patient had traveled to southern Canada but not outside the country otherwise, although he did report extensive travel in the Midwest for his job, which involved driving the Amish on errands in town as well as across the Midwest to visit relatives. He denied any travel to the Southeast or Southwest. He denied any exposure to livestock, though he did have a pet pit bull that was up to date on shots. He had no known tick or insect bites and no exposure to new food or water. He denied any activity in, or near, standing or murky water.

He denied any intravenous drug use or illegal drug use of any kind. He had never been incarcerated, and he denied hemoptysis or known exposure to tuberculosis. He had not been exposed to sick relatives, had no history of unprotected sexual intercourse, and had no history of sexually transmitted disease. He did have one tattoo,



Coxiella burnetii, the organism that causes Q fever

which was 30-years old. He smoked 1 pack of cigarettes per day and had a history of heavy alcohol use, though he had been sober for about 25 years. He denied dysuria or nocturia. After 23 days of this febrile illness, he had lost approximately 20 lb.

The physical examination in the primary care provider's office included a digital rectal examination and was again unremarkable. The patient was afebrile. He did not appear acutely ill but did look fatigued. Extensive laboratory testing was ordered, including tests for HIV and a VDRL for syphilis, both of which were negative. Another set of blood cultures was ordered, which again showed no growth in 48 hours. Urinalysis and urine culture results were normal, as were those for prostate-specific antigen, thyroid-stimulating hormone, anti-nuclear antibody, and rheumatoid factor. A purified protein derivative was placed and was negative 72 hours later. The CBC and CMP results were all normal. At this point, the possibility of malignancy and/or collagen vascular disease appeared slight. The last major category in the diagnostic pathway for fever of unknown origin (FUO) is infection, and the infectious disease (ID) service was consulted.

ID recommended a urine test for *Histoplasma* antigen, given our agricultural Midwest clinical setting. This test came back negative. The ID clinic arranged to see the patient as an outpatient 7 days later, and by then his liver function tests were normalizing and his fevers were improving. The ID fellow ordered tests for *Coxiella burnetii* for Q fever and *Brucella* for brucellosis, although his suspicions were low. Other tests included serologies for *Histoplasma*, *Blastomyces*, *Bartonella*, and *Coccidioides*.

The results of all of these tests were negative, except that the Q fever phase I and phase II serology results were elevated above the diagnostic range. Thus, 30 days after the patient began having fevers, the diagnosis of Q fever was made. Although the patient had had no known direct contact with livestock, he may have become infected by his close contact to the Amish agricultural community. No exact source of exposure was ever identified.

DISCUSSION

The term *fever of unknown origin* is often used in clinical medicine, but to be more accurate, clinicians should use

terms such as *fever without initial obvious etiology* or *fever without localizing signs* instead. Usually, affected patients are worked up in the inpatient setting so the source of the fever can be determined as quickly as possible. To truly be classified as FUO, the fever must be higher than 100.9°F (38.3°C) on several occasions, persist for more than 3 weeks, and have an uncertain diagnosis after 1 week of inpatient care.¹

Cases involving prolonged fever present the clinician with a challenge. The appropriate laboratory and diagnostic studies must be completed in a timely, organized fashion to narrow the possible causes. An accurate history is crucial to steer the clinician toward or away from known causes of febrile illness. The three general categories in the diagnostic pathway causing fever are infection, malignancy, and collagen-vascular disease.

Q fever is a worldwide zoonotic infection caused by the obligately intracellular gram-negative coccobacillus *C burnetii*. The organism can survive extracellularly for weeks in spore form, and inhalation of a single organism can cause infection in humans. Cattle, goats, and sheep are natural reservoirs; ticks may also transmit the infection, although this appears to be rare. Q fever is not transmitted person to person. Infected animals will shed the organism in milk, urine, feces, and birth products, and common causes of infection are inhalation of organisms, handling of infected birth products, and skinning or transporting infected animals.

Q fever can infect humans at any age, although most infections occur in those aged 30 to 79 years. There is no geographic pattern of disease. Men have more occupational exposures than women and so are more frequently infected, and the infection seems to cause fewer symptoms in women and children than in men. Those at greatest risk are persons in contact with farm animals or downwind from contaminated dust, manure, or straw from farms. Laboratory workers are also at risk when handling of infected specimens. Urban outbreaks can be traced to infected cats, dogs, rabbits, or rats.²

We assumed that our patient became infected while picking up or dropping off the Amish at their farms. If he was downwind from a cattle pasture or animal enclosure, he could easily have inhaled *C burnetii*.

The incubation period for Q fever is 2 to 4 weeks. Humans are the only animals who become sick from exposure

TEACHING POINTS

- The term *fever of unknown origin* is often used, but to be more accurate, clinicians should use terms such as *fever without initial obvious etiology* or *fever without localizing signs* instead.
- Cases involving prolonged fever without an obvious cause are challenging, requiring a timely and organized approach to the diagnostic workup. The three general categories in the diagnostic pathway causing such fevers are infection, malignancy, and collagen-vascular disease.
- Q fever, which afflicted the patient in this case, is very infectious to humans, for whom inhalation of a single organism can cause illness. Cattle, goats, and sheep are natural reservoirs, and ticks have also been implicated. Q fever is not transmitted person to person.
- Current therapy for acute Q fever is doxycycline, 100 mg twice a day for 14 days. Hydroxychloroquine, 200 mg three times a day, is considered the best regimen for Q fever endocarditis, which is the most serious and sometimes fatal form of chronic Q fever.

COMPETENCIES

●●●● Medical knowledge

●●● Interpersonal & communication skills

●●●● Patient care

●● Professionalism

●● Practice-based learning and improvement

●● Systems-based practice

CASE REPORT | Fever of unknown origin

to *C burnetii*. The most common manifestation is a self-limiting, febrile, flulike illness, such as the one that afflicted our patient. Hepatitis, pneumonia, and endocarditis also occur,³ and Q fever can cause spontaneous abortion or premature labor as well as fever in pregnant women.⁴

Our patient had acute respiratory Q fever manifested by his fevers and cough. That stage was followed by Q fever hepatitis, with elevated transaminases and hepatosplenomegaly as seen on CT. His Q fever serology showed his phase I titer (antibodies to the phase I antigen) to be greater than 1:2048 and his phase II titer (antibodies to the phase II antigen) to be greater than 1:4096. At our laboratory, any titer less than 1:16 is considered negative for infection, and any titer greater than 1:256 is considered diagnostic.

In the acute stage of Q fever, phase II titers are greater than phase I titers. Phase II organisms are virulent and react with active sera. Phase I organisms are seen in the convalescent stage and are avirulent.³

Q fever endocarditis is the primary manifestation of chronic Q fever, which serologically is determined by an elevation in phase I titer. The diagnosis of Q fever endocarditis is difficult to make clinically because cardiac findings can be ambiguous, blood cultures usually show no growth, and vegetations are rarely seen on echocardiography. Because of the lack of clinical symptoms in most cases, an elevated phase I titer has

a high predictive value, and it alone is enough to diagnose Q fever endocarditis.

Q fever endocarditis is the most serious and sometimes fatal form of chronic Q fever. *C burnetii* are found multiplied in macrophages, and a prolonged rickettsemia is noted. The resulting immune complexes and antibodies directed at clearing the organism cause most of the symptoms in chronic Q fever. The heart is the organ most commonly infected, followed by the arteries, bones, and liver. Evidence of liver involvement is also seen frequently with Q fever endocarditis and gives another clinical clue toward the diagnosis.⁵

Q fever endocarditis should be considered in any patient with known valvulopathy and culture-negative endocarditis. Up to 90% of the cases of Q fever endocarditis occur in patients with pre-existing abnormal valves.⁶ In our patient, we did not know at presentation whether he had any pre-existing valvular lesions, but because of his elevated phase I titer, he was empirically started on treatment for endocarditis. Transesophageal echocardiography was performed after diagnosis and did not show vegetations or abnormal valves; however, the management of the patient's chronic Q fever did not change.

Current therapy for acute Q fever is doxycycline, 100 mg twice a day for 14 days. Most cases of acute Q fever resolve spontaneously within a few weeks. Our patient was started

TABLE 1. The patient's laboratory results

Test	Urgent care visit (Fever day 12)	Primary care visit (Fever day 23)	Infectious disease consult (Fever day 30)	After 4 mo on drug therapy	Laboratory reference range
Erythrocyte sedimentation rate	44	82	Not drawn	Not drawn	0-15 mm/h
C-reactive protein	121.99	75.48	65.76	0.55	0.10-5.00 mg/L
Aspartate aminotransferase	62	34	43	24	7-40 U/L
Alanine aminotransferase	98	47	49	25	7-40 U/L
Alkaline phosphatase	269	258	228	83	30-115 U/L

TABLE 2. Current treatment recommendations

Syndrome	Drug of choice for adults	Alternative therapy	Drug of choice for children
Acute Q fever	Doxycycline, 100 mg orally twice daily for 14 d	<ul style="list-style-type: none"> Erythromycin has shown questionable efficacy Chloramphenicol has also been used but only as IV therapy 	<ul style="list-style-type: none"> No standard treatment recommendation for children; however erythromycin has shown questionable efficacy Chloramphenicol has also been used but only as IV therapy Use doxycycline if life threatening
Q fever endocarditis	Doxycycline, 100 mg twice daily; plus hydrochloroquine, 600 mg orally once daily, for 1.5-3 y		
Q fever-associated meningitis	Use fluoroquinolones, which penetrate the CSF		

on doxycycline along with hydroxychloroquine (Plaquenil), 200 mg three times a day, which is considered the best regimen for Q fever endocarditis.⁷ Current treatment guidelines for Q fever are listed in Table 2.

Our patient will remain on his regimen of doxycycline and hydroxychloroquine for at least 18 months, and the infectious disease clinic will continue to monitor his serology. After about 3 weeks of treatment, his phase II titer had fallen but was still greater than 1:2048, and his phase I titer remained elevated to the initial level. He had a baseline ophthalmologic examination to assess potential retinal toxicity from the hydroxychloroquine, and he will continue to be examined every 6 months while on treatment. At the time of this writing, the patient was tolerating therapy well. It will continue until his IgA to phase I is negative and his IgG titer to phase I is less than 1:400.

CONCLUSION

In an ideal world, our patient would have been admitted when he first presented to urgent care, and the diagnosis of Q fever would have been reached earlier in its clinical course. Most likely, Q fever would have been picked up either by an inpatient ID consult or on liver biopsy as part of the workup for hepatitis. Hepatitis caused by Q fever typically has a granulomatous pathology, with a characteristic doughnutlike shape to the granulomas.⁷ Because we do not know what the patient's Q fever titers were on initial presen-

tation, we do not know whether the diagnosis of endocarditis—and the resulting prolonged course of antibiotics—could have been avoided.

We will never know how our patient contracted Q fever. This case taught the providers involved with the patient's care that in an agrarian Midwest setting, zoonotic infections cannot be ruled out in patients just because they have no physical contact with farm animals. The way this case of FUO unfolded reminds us all of the deductive reasoning necessary to be excellent clinicians and how sometimes a case can just take us by surprise. **JAAPA**

Katie Iverson practices at the Emergency Trauma Center, University of Iowa Hospitals and Clinics, Iowa City. She has indicated no relationships to disclose relating to the content of this article.

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