Fever of Unknown Origin in an Elderly Man

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Dr WILLIAM A. NORCROSS (*Professor of Clinical Family Medicine, UCSD School of Medicine*): I will begin by presenting the case of one of my own patients. Dr J.C. is an 80-year-old white married man who is a professor emeritus of economics from a major East Coast university. He came to the UCSD Medical Group facility early in February 1989. He complained of a 5-month history of daily fevers ranging from 100°F to 102°F; an intermittent, dry, nonproductive cough; fatigue; weight loss of 20 pounds; and intermittent, bifrontal, dull, mild headaches.

His symptoms started in October 1988 following what he described as a typical viral respiratory tract syndrome, characterized by a nonproductive cough and coryza with a low-grade fever. He saw his local physician, who gave him antibiotics for bronchitis. He was seen 1 month later because his symptoms did not resolve, at which time a further evaluation revealed mild anemia. A chest x-ray examination was performed, which was reported to be within normal limits. Because of the anemia, he was scheduled to see a gastroenterologist, who recommended a colonoscopy. He denied melena or hematochezia, but he had a history of intermittent, dull, left lower quadrant pain, which was mild in nature and not associated with diarrhea or constipation. He declined the endoscopic evaluation.

In August 1988 he underwent a transurethral resection of the prostate for symptoms of urinary retention, felt to be secondary to benign prostatic hypertrophy. He was also noted to have a prostatic nodule, biopsy of which revealed a well-differentiated adenocarcinoma of the prostate. At that time he elected to decline any further treatment. He had no symptoms of bone pain, and his urinary symptoms responded well to the procedure. Past medical history revealed that the patient was a smoker but gave up the habit in 1938. He drank three or four drinks per week, but had no history of alcohol or drug abuse. In 1972 he was treated for diverticulitis. In 1968 he amputated his right index finger in a lawnmower accident. His father died at age 74 years of "arteriosclerosis," and his mother died of "old age" at age 95 years.

Physical examination revealed an afebrile, well-developed, well-nourished, pleasant, and cooperative elderly man in no acute distress, who looked much younger than his stated age. His thought processes and content were intact. Recent and remote memory was intact. The neck was supple, and one small, right anterior, cervical node was mobile and slightly tender. Ear, nose, and throat examination was unremarkable. Ophthalmic examination was within normal limits. The temporal arteries, bilaterally, were 2+, were unremarkable to palpation, and were nontender. There were no carotid or intracranial bruits. The chest was clear to percussion and auscultation. The jugular venous pulses were normal, and findings on examination of the heart and abdomen were also unremarkable. Rectal examination revealed a small prostate with a 5 × 5-mm nodule on the left lateral lobe. There were no rectal masses, the stool was brown, and a test for occult blood was negative. Examination of the skin and extremities was unremarkable, except for the amputation of his right index finger. Neurological examination was completely within normal limits.

An outpatient investigation was begun. The complete blood count revealed a hemoglobin of 100.3 g/L (10.3 g/dL) and a hematocrit of 0.31. Leukocyte count was 8.3 × 10^9/L, with 0.86 segmented neutrophils, 0.07 band cells, 0.09 lymphocytes, 0.03 monocytes, and 10.0 eosinophils. The mean corpuscular volume was 86.7 fL (86.7 μm^3). The sedimentation rate was 130 mm/h. Skin tests revealed anergy with no response to protein purified derivative (PPD) tuberculin intermediate strength, *Candida*, or coccidioidomycosis. The urinalysis showed a trace of protein, but was otherwise unremarkable. Findings on the chest x-ray examination were within normal limits for age. The serum protein electrophoresis revealed a mild increase in α_2-globulins, compatible with acute inflammation. Two stool specimens were negative for occult blood,

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ova, and parasites. Two sputum examinations were negative for acid-fast bacilli in the smear, and revealed some *Candida albicans* in culture. The sensitive thyrotropin returned at 2.98 mU/L (2.98 μU/mL), which is within normal limits. The serum iron was 4.30 μmol/L (24 μg/dL), which is low, and the total iron-binding capacity was 40.12 μmol/L (224 g/dL). The chemistry panel was unremarkable, except for a cholesterol of 3.46 mmol/L (134 mg/dL). An abdominal ultrasound revealed a normal liver and gallbladder. An echogenic focus in the perinephric area was felt to be of questionable significance. A barium enema was within normal limits.

Approximately 2 weeks after his initial presentation, the patient was admitted to the UCSD Medical Center for further diagnostic evaluation. A rheumatology consultation was obtained, but the consultant did not believe there was sufficient evidence to consider his disease to be a rheumatologic disease. The suggestion was made by the rheumatologist to consult a gastroenterologist as well as a pulmonary specialist. A computed tomographic (CT) study of the abdomen was performed and the findings were unremarkable. Specifically, the questionable renal abnormality noticed on ultrasound was not apparent on the abdominal CT scan. A hematologist was consulted, and a bone marrow aspiration was performed, which was within normal limits.

Throughout the hospital stay, the patient was documented to have fevers spiking as high as 102°F. A repeat of the erythrocyte sedimentation rate returned at 140 mm/h. Four blood cultures were negative, and stool tests for occult blood were persistently negative. Multiple sputum smears were negative for acid-fast bacilli and fungus. A perfusion scan of the lungs was within normal limits. A pulmonary specialist was consulted, and a bronchoscopy revealed some minor inflammation, but no other abnormalities were noted. Smears and washings from the bronchoscopy also returned negative. A bone scan was within normal limits. An upper gastrointestinal series with small bowel follow-through was negative. Sinus films were negative. Pulmonary function studies were within normal limits for his age. A flexible sigmoidoscopy was within normal limits. The patient was discharged from the hospital 8 days after admission, still without a diagnosis.

I would like to introduce our discussant, Dr Navin Amin, an outstanding clinician and teacher of family medicine. We are very pleased to have him with us.

DR NAVIN AMIN (*Chairman, Department of Family Practice, Kern Medical Center*): As you can probably see, this patient is an individual who has certain fundamental problems that need to be addressed. One of the most frustrating problems that you will face, whether you are a primary care physician or in another specialty, is the pressure you feel, both from yourself and from your patient and his or her family, to arrive at a diagnosis and to cure the problem. A common expectation is that if you cannot find a diagnosis, then treat something. Let me caution you that you must avoid the temptation to try empiric therapy, whether it be antibiotics, steroids, or whatever. You must "hang tough" and methodically work your way to a diagnosis.

Let me start by reviewing some pertinent features at hand. First, Dr J.C. is an elderly person, but as Dr Norcross said, a fit and healthy elderly person who looks younger than his stated age. Second, his symptoms were many months in duration. Third, his symptomology was characterized by fevers, spiking from 100°F to 102°F, intermittent dry cough, fatigue, and weight loss of 20 pounds. The intermittent, bifrontal, dull headaches are also noteworthy.

On physical examination there are a few findings that bear discussion. The patient was well built and well nourished. There was no evidence of emaciation. As you will see, this finding is important. The discovery of one small anterior cervical node is of uncertain importance at this stage. The findings of normal temporal arteries, bilaterally, does not rule out a vasculitis.

The laboratory findings of note include a mild normocytic, normochromic anemia, a normal white blood count and differential, and an impressive erythrocyte sedimentation rate of 130 mm/h. The latter finding is of particular importance. The discovery of anergy to PPD tuberculin intermediate strength, *Candida*, and coccidioidomycosis is of uncertain significance. Anergy may be related to his underlying disease process, his advanced years, or both. A search for a malignancy was begun on this patient. A serum protein electrophoresis showed an elevation in γ_2-globulin, suggesting an acute inflammatory response, but was reassuring that the patient did not have multiple myeloma. Likewise, the absence of occult blood in the stool on multiple occasions and the negative barium enema were also reassuring. Multiple sputum cultures were obtained in search of acid-fast bacilli and fungus, all of which were negative. Tuberculosis should always be ruled out in an elderly patient with a cough and fever.

Although the bone marrow aspiration in this patient was normal, it was certainly a reasonable study to obtain. Not only does a bone marrow aspirate give information about leukemia, lymphoma, multiple myeloma, and other primary bone marrow abnormalities, but it also will frequently be diagnostic in cases of disseminated mycobacterial and fungal infections. The normal bone scan is reassuring that this problem is unlikely to be due to his adenocarcinoma of the prostate and, again, gives some reassurance that he does not have multiple myeloma. Four negative blood cultures give a high degree of reassurance that he is free of bacteremia.

Some of you may be wondering why the ventilation-perfusion scan was performed; patients with recurrent

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pulmonary emboli may present in just the same fashion as Dr J.C. Many people do not have the typical textbook presentation of pulmonary embolism and may have only mild pulmonary symptoms with fever and completely normal findings on a chest x-ray examination. Fortunately, the ventilation-perfusion scan was negative in this case, as were the bronchoscopy and bronchoscopic washings and smears. The CT scan of the abdomen also was a good idea. Clearly, a disease process was not readily apparent in this patient. Therefore, one must think of somewhat unusual diagnoses such as perinephric, subphrenic, or subhepatic abscesses.

So what are the conclusions? After an extensive inpatient evaluation, we have an elderly gentleman who is not emaciated and who has a fever of prolonged duration. He had mild anemia, and a very high erythrocyte sedimentation rate. This patient qualifies as having a fever of unknown origin. To qualify as a "fever of unknown origin," the patient must have an illness for longer than 3 weeks, and the fever at some time must reach 101°F.[1] An additional criterion in this case is that the patient's diagnosis remained uncertain after 1 week of rather intensive investigation in the hospital. We can definitely conclude that Dr J.C. had a fever of unknown origin.

DIFFERENTIAL DIAGNOSIS OF FEVER OF UNKNOWN ORIGIN

The differential diagnosis of fever of unknown origin is extraordinarily large. In modern times, however, the distribution of causes of fever of unknown origin are approximately 30% infection, 30% neoplasm, 15% collagen vascular diseases, and 25% miscellaneous. It is interesting that in this era of high-technology medicine about 1 in 10 patients, even under the most intensive diagnostic evaluations, will remain with their conditions undiagnosed despite the best efforts.

Now, let's try to look at the differential diagnosis in more detail to help develop a systematic method of evaluating patients with fever of unknown origin.

The first to consider is a systemic or localized infection. The most common diseases to keep in mind, even in this modern era, are tuberculosis and atypical mycobacterial infections. Bacterial endocarditis is another major cause of longstanding fever. Remember that a patient may not have a murmur but still have endocarditis. Endocarditis in the elderly may be a particularly subtle disease, so you must maintain a high index of suspicion. Additionally, endocarditis may not be caused by routine organisms; patients may be infected with fastidious organisms, which have to be cultured for a prolonged period of time. One must also be vigilant for the possibility of human immunodeficiency viral disease, though it is more likely in younger populations. This patient did not have a recent transfusion or any other risk factors for human immunodeficiency viral disease. In immunosuppressed patients or patients who have received an organ transplant, cytomegalovirus can also present as a fever of unknown origin.

There are a number of other infectious diseases that must be kept in mind. Brucellosis is one example. In the last year, we have diagnosed three cases of brucellosis at the Kern Medical Center. Similarly, listeriosis, and particularly *Listeria* endocarditis, can be a very baffling disease. Syphilis, particularly in the secondary and tertiary phases, may present with longstanding pyrexia. Rickettsial diseases must also be considered. At the Kern Medical Center, we have diagnosed quite a number of cases of Q-fever because this disease is commonly found among farmers who have cattle. If an individual has been exposed, either through unpasteurized milk or by assisting at the delivery of calves, Q-fever can be a possibility. Recurrent episodes of fever, pulmonary symptoms, and bacterial endocarditis can all be caused by Q-fever.

Although there is no history of foreign travel in this patient, travelers' diseases must be kept in mind. Malaria has become endemic in northern San Diego County and can no longer be considered solely a disease of travelers. Additionally, malaria can strike many years after the individual has been infected. There has been one case reported of an individual, after having left the malarial endemic area 23 years ago, developing infection with *Plasmodium malariae*. Toxoplasmosis, particularly in immunosuppressed individuals, can produce prolonged fever. Amebiasis will present with a fever of unknown origin in the setting of an amebic hepatic abscess. Often, the patient may have right upper quadrant tenderness, and an abdominal CT scan should suggest the right diagnosis. Other diagnoses that must be considered in travelers include leishmaniasis, schistosomiasis, and trypanosomiasis.

Endemic fungal diseases should be considered: coccidioidomycosis on the West Coast, histoplasmosis on the East Coast, and blastomycosis in the Southern states. Let me remind you that it is not necessary to be living in one of the endemic areas to be affected by the endemic organism. Many people do a great deal of traveling, either as part of their occupation or for recreation, and subsequently are exposed to a wide variety of diseases. Additionally, meteorologic events can spread endemic diseases far beyond their customary areas. A good example of this was the dust storm of 1976, which carried coccidioidomycosis as far away as Sacramento.

Osteomyelitis, particularly osteomyelitis of the spine, can be difficult to diagnose. We recently had a patient with salmonella osteomyelitis whose presentation was very perplexing, and it took us 9 months to arrive at a diagno-

sis. Mycobacterial osteomyelitis can also be very indolent.

Consider now the collagen vascular diseases. Systemic lupus erythematosus is generally a disease of younger people, predominantly women. Fever of unknown origin would be a somewhat unusual presentation of systemic lupus erythematosus. Rheumatoid arthritis, particularly when it is extra-articular, may present as a fever of unknown origin. Temporal arteritis is a disease being diagnosed more frequently, predominantly because it is being considered more frequently in the differential diagnoses. The presentation of temporal arteritis can be very subtle, and includes fever of unknown origin.[2] A patient need not present with visual symptoms, headaches, or the typical jaw claudication. Polymyalgia rheumatica very commonly presents with stiffness and pain in the proximal musculature, particularly about the shoulders and hips. The diagnosis of temporal arteritis requires a high index of suspicion.

Wegener's granulomatosis can also be an illusive diagnosis. Usually, it presents as either an upper respiratory tract infection or in the kidney manifesting with gross or microscopic hematuria, but ultimately may present with a generalized vasculitis. In this case, the urinalysis, chest x-ray film, and sinus films were normal and reassuring. Polyarteritis nodosa may present with fever of unknown origin. This disease is found more predominantly in men, and may present with hypertension, eosinophilia, asthma, or monoeuritis multiplex. It may also present with hematuria or progressive renal failure.

Another unusual cause of fever of unknown origin is Goodpasture's syndrome, which may present with hemoptysis and hematuria. Behçet's syndrome, a vasculitis of unknown cause, presents typically with oral and genital ulcerations. One may also have pulmonary, central nervous system, or arterial involvement. A biopsy of the involved area may suggest the diagnosis. The disease is typically responsive to steroid therapy. An unusual variant of rheumatoid arthritis that typically presents without joint involvement or splenomegaly is adult Still's disease. Frequently, this disease only presents with a fever and a linear salmon-pink rash. Still's disease requires a high index of suspicion and can be a very difficult diagnosis of exclusion.

What about neoplasms as the cause of fever of unknown origin? The most common neoplasms to cause fever of unknown origin are lymphoma, leukemia, and multiple myeloma. Among the solid tumors, the most common cause of fever of unknown origin is hypernephroma, followed by hepatoma and myxoma. Many other tumors, however, can present as fever of unknown origin. Tumors of the pancreas, prostate, and testicle can present this way. Metastatic disease from the breast, ovary, and lung, and melanoma can also present as fever of unknown origin.

In the category of miscellaneous causes of fever of unknown origin, one must always be vigilant to the possibility of sarcoidosis. Although this disease is more common in blacks, it is also known to occur in whites. Adenopathy, myopathy, rash, and uveitis should alert one to the possibility of sarcoidosis. Hypercalcemia and an elevated angiotensin-converting enzyme level may also increase the suspicion that the patient has sarcoidosis.

Drug fever must also be considered in the differential diagnosis of fever of unknown origin. Obviously, the finding of drug ingestion in the history is quite suggestive, but may not be present in all patients. Drug fevers often result in fever spikes, yet the patient does not look toxic. Typically there is a dissociation between the pulse and the temperature in drug fever. For example, the patient may have a temperature of 102°F, yet the pulse rate may hover around 80 beats per minute. There are only a few diseases that will do that, and drug fever is one. Other causes of fever that may cause fever-pulse dissociation include *Legionella*, psittacosis, and Q-fever. Fictitious fever is not at all uncommon. I can relate stories of people chewing on the thermometer bulb or doing other unusual things to artificially increase the thermometer reading. A simple way to alleviate this problem is to have the patient provide a urine specimen under observation and measure the temperature of that urine. Also, a rectal temperature taken under the direct observation of the nurse or physician is very difficult to alter.

Other uncommon and miscellaneous causes of fever of unknown origin include familial Mediterranean fever, which occurs in people native to the Mediterranean area, and presents with recurrent episodes of fever, peritonitis, or pleuritis; Whipple's disease, which presents with malabsorption and low-grade fever; Weber-Christian disease, which is a nonsuppurative panniculitis; and eosinophilic fasciitis, which presents with bronchial asthma, eosinophilia, and inflammation of the fascia, presenting as areas of induration, particularly in the upper extremities.

CLINICAL FOLLOW-UP

In summary, the evaluation of Dr J.C. revealed no evidence of malignancy. No evidence of emaciation leads me away from the diagnosis of a chronic infection. I believe that he was afflicted by a disease process in the group of collagen vascular diseases. Of these, the most likely is temporal arteritis. My belief is that Dr Norcross decided to bring in a vascular surgeon to perform a temporal artery biopsy.

DR NORCROSS: Thank you very much, Dr Amin. I

would now like to introduce Dr Sidney Saltzstein, from the Department of Pathology.

DR SIDNEY L. SALTZSTEIN (*Professor of Clinical Oncology and Pathology, UCSD School of Medicine*): The procedure was correctly surmised. We received a biopsy of the patient's temporal artery. Microscopic sections revealed remnants of the elastic tissue of the wall, a feature of temporal arteritis (sometimes termed *granulomatous arteritis*). Regular breaks in the artery were noted, and in some places an ongoing granulomatous inflammation was observed. Everything fits quite nicely with the diagnosis of temporal arteritis or granulomatous arteritis.

DR NORCROSS: Congratulations, Dr Amin, for arriving at the correct diagnosis; you certainly did it more quickly than I did. After the diagnosis was made, the patient was started on prednisone, and felt much better within 24 hours. This remarkable response to prednisone therapy is one of the typical features of temporal arteritis. Given the dreadful differential diagnostic possibilities of fever of unknown origin in an elderly gentleman, temporal arteritis was really a happy outcome for this man.

References

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