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CLINICAL CARE CONUNDRUMS

Of Mice and Men

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 73-year-old man was admitted with 6 days of fevers, with rigors and diaphoresis, and associated frontal headache.

Fever in an elderly man is a nonspecific finding, occurring most commonly with infections but also with certain malignancies, rheumatologic disorders, and drug exposures. The complaint of rigors with diaphoresis makes an infection most likely. The acuity of his illness makes infections with more chronic presentations such as tuberculosis or actinomycosis less likely. The presence of frontal headache might suggest a sinus or brain source, but headache also occurs in generalized infections such as pneumonia, bacteremia from any cause, malaria, rickettsial infections, viral illnesses, and others. Additional history should include detailed inquiry into travel, vocational, and avocational exposures.

Since onset, the fevers had been accompanied by malaise, myalgias, decreased oral intake, nausea, and nonbloody, nonbilious vomiting and nonbloody loose stools. On the day of admission, the patient developed the inability to rise from a seated position without the use of his arms.

The patient's difficulty standing implies the development of lower extremity weakness and infections associated with neurological syndromes. His leg weakness may be related to early Guillain-Barre syndrome, which is associated most commonly with *Campylobacter jejuni*, but also other bacteria and viruses such as *Haemophilus influenza, Mycoplasma pneumonia, Influenza virus, Cytomegalovirus* and hepatitis E. Other viral infections associated with pure motor deficits include echovirus, coxsackie virus, enterovirus, and West Nile virus (WNV). The paralytic syndrome associated with enteroviruses is more common in children, whereas the neuroinvasive variant of WNV more often affects the elderly and can be associated with encephalitis as well as a flaccid paralysis. Although acute paralytic shellfish poisoning could account for both his weakness and his acute gastrointestinal syndrome, this diagnosis is unlikely because the symptoms often have a prominent sensory component, and there is usually the history of recent ingestion of the suspect bivalves. Like all adults presenting for medical care, he should be screened for human immunodeficiency virus (HIV) infection; if testing is positive, the differential diagnosis for his current illness broadens significantly. Finally, he may have a spinal cord disorder or infection such as an epidural abscess, or transverse myelitis, which would present with lower extremity weakness and fever. It would be helpful to know the time of year of his illness, exposure to mosquito bites, his neurological exam findings, and results of blood and stool cultures. If the patient had signs of meningitis or encephalitis, cerebral spinal fluid analysis would be helpful. If his neurological exam was suggestive of cord involvement, it would be helpful to know the results of magnetic resonance imaging of the spinal cord.

His past medical history was remarkable for nonobstructive coronary artery disease, paroxysmal atrial fibrillation, hypothyroidism, and prostate cancer (T2N0M0, Gleason 3+4) treated with radical prostatectomy and pelvic lymph node dissection 6 years previously. One month prior to this presentation, the patient developed a small right knee effusion, and x-ray evaluation at that time showed mild degenerative joint disease. His medications included aspirin 325 mg daily, metoprolol succinate 100 mg daily, levothyroxine 25 μg daily, and simvastatin 20 mg nightly. The patient was a lawyer, and lived in the Pacific Northwest. He had never smoked or used illicit drugs, and drank 2 glasses of red wine nightly. His travel history was remarkable for a visit to Uganda 1 year prior to admission; Zurich, Switzerland 6 months prior to admission; and Cape Cod, Massachusetts during the summer season 5 months prior to admission. His exposures included keeping chickens on his property, tending a garden, and ingestion of raw oysters 1 month prior to the onset of symptoms.

The patient's past medical history includes relatively common problems for a 73-year-old man and does not substantially influence the differential diagnosis of his current illness. His travel history to Uganda a year previously may be relevant, because malaria (*Plasmodium vivax*) could present with fever

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and weakness. Less commonly, African trypanosomiasis (*Trypanosoma brucei gambiense*) can, in the late phase, present with fever and malaise, but also typically includes symptoms of encephalitis, including depressed mental status, confusion, ataxia, and possibly personality changes. His travel to Zurich should not impose any particular infection risk, unless he was hiking in the mountains around Zurich, where he could have contracted tick-borne encephalitis; however, his travel more than 6 months prior to presentation makes this unlikely. Lyme disease due to *Borrelia burgdorferi* is also a potential exposure in the Swiss mountains, and can present with fever in the acute phase, as well as arthritis with chronic disease, but should not cause fever, rigor, diaphoresis, and headache many months later. Summering in Cape Cod puts him at risk for babesiosis, but an incubation period of 5 months is too long. Keeping chickens places him at risk for *Salmonella* exposure and typhoid fever. Ingesting raw oysters carries a risk for shellfish poisoning and *Vibrio* infections, but the incubation period (1 month) again seems too long to cause his current symptoms.

On exam, his temperature was 39.4°C, heart rate 87 beats/min, blood pressure 129/70 mm Hg, respiratory rate 18/min, with an oxygen saturation of 94% on room air. He was ill appearing. He had injected sclera bilaterally, with moist mucous membranes, no oropharyngeal lesions, and no cervical lymphadenopathy. His cardiac exam revealed no murmurs, rub, or diastolic gallops. His lungs were clear without rales or wheezes. His abdominal exam was benign, without masses or tenderness. He had no musculoskeletal tenderness, lower extremity edema, erythema, or effusion in his lower extremity joints. His neurological exam was notable for difficulty rising from a seated position. He also had a shortened stride length in his gait and a slow, deliberate 180° turn. There was no resting tremor. Romberg's sign was negative, and the remainder of neurological exam was normal.

Notable physical findings are an ill-appearing man with injected sclera and a high fever but normal blood pressure and heart rate. He also demonstrates proximal lower extremity weakness manifested by difficulty rising from a chair and a slow gait with short strides and deliberate (possibly on-block) turning. His neurological exam is most consistent with Parkinsonian symptoms that have been described in patients with severe influenza A, which would explain all of his other symptoms as well. Pulse-temperature dissociation is classically described with typhoid fever but usually occurs later in the disease course, and could be masked by the patient's metoprolol. Typhoid fever can also be associated with neurological symptoms including meningitis and movement disorders.

White blood cell count was 6060/μL, with 36% bands, hematocrit 35.5%, and platelet count of 134,000/μL. Sodium was 133 mmol/L, potassium 3.3 mmol/L, chloride 97 mmol/L, bicarbonate 30 mmol/L, blood urea nitrogen 19 mg/dL, and creatinine 1.2 mg/dL. Alanine aminotransferase was 79 IU/L (normal, 15–41), aspartate aminotransferase 82 IU/L (normal, 12–60), total bilirubin 1.8 mg/dL (normal, 0.3–1.2), direct bilirubin 0.6 mg/dL (normal, 0.0–0.3), total protein 6.6 mg/dL (normal, 6.4–8.2), albumin 2.6 mg/dL (normal, 3.5–4.7), and alkaline phosphatase 356 IU/L (normal, 56–119). Creatinine kinase was 137 IU/L (normal, 49–397). Erythrocyte sedimentation rate 44 mm/hr (normal, 0–20). Urinalysis with microscopic examination was notable for moderate blood, negative leukocyte esterase, negative nitrites, protein 100 mg/dL (normal 0–30 mg/dL), 5 white blood cells (normal, 0–5), 9 red blood cells (normal, 0–5), and 3 granular casts. Gamma glutamyl transferase (GGT) was 459 IU/L (normal, 12–98). Ferritin was 552 ng/mL (normal, 50–200), and haptoglobin 185 mg/dL (normal, 30–200). Prostate specific antigen was <0.02 ng/mL (<6.5). Chest x-ray revealed right perihilar and bibasilar atelectasis without effusions or other consolidation. Computed tomography of the head, abdomen, and pelvis was normal. Ultrasonography of the liver was revealing for mild gallbladder edema without evidence of cholecystitis and normal Doppler indices of the hepatic vessels. Magnetic resonance imaging of the complete spine (cervical, thoracic, and lumbar) was performed and was unremarkable.

The patient has a remarkable bandemia, suggesting a bacterial infection, as well as a slight reduction in hematocrit and platelet count. Additionally, his labs revealed a mild transaminitis, but with significantly elevated alkaline phosphatase and GGT, and microscopic hematuria. His ferritin is significantly elevated, which may simply represent an acute phase reactant. Infections associated with hepatitis, cytopenias, and hematuria include sepsis with disseminated intravascular coagulation, previously mentioned malaria, leptospirosis, dengue, ehrlichiosis, and rickettsial diseases, but he has no special risks for these infections, and other aspects of his illness (Parkinsonian features, bandemia) do not fit. His lung findings with hematuria might suggest a pulmonary/renal syndrome, but, once again, other features of his illness are not typical of these syndromes. Salmonella (typhoid fever) or influenza, now complicated by an early bacterial pneumonia, are viable possibilities.

Through hospital day 2, the patient continued to have fevers over 39°C about twice per day. Antibiotic therapy was not started because, other than fevers, the patient did not meet additional criteria for systemic inflammatory response syndrome (SIRS). Initial blood and urine cultures were without growth. Lumbar puncture was planned given ongoing headache symptoms.

The patient's ongoing clinical course is notable for a nontoxic (non-SIRS) appearance but continued high-grade fever with blood and urine cultures that are sterile. This argues against a common bacteremia with sepsis, and for either relapsing malaria (*P vivax)*, influenza with a Parkinsonian-like illness, typhoid fever, leptospirosis, dengue, or a rickettsial infection. Mycoplasma pneumonia is also possible given the atypical chest x-ray appearance, slightly low hematocrit with elevated bilirubin, and neurological symptoms that may represent ataxia.

Blood cultures, repeated 5 times, each drawn while the patient was febrile, were all negative. Parasite thick and thin smears, repeated 4 times, were also negative. Stool ova and parasite exam was negative, and stool cultures were negative. Antibody and antigen analysis for hepatitis A, B, and C were negative for infection. HIV antibody screen was negative, and rapid plasma reagin for syphilis was nonreactive. Parvovirus B-19 immunoglobulin (Ig)G was reactive, but IgM was nonreactive. Cytomegalovirus, Epstein-Barr virus, and respiratory virus panel polymerase chain reaction

testing was negative. Lyme antibody enzyme-linked immunosorbent assay was 0.32 Lyme index units (normal, 0.0–1.2), leptospira antibody was <1:50 (normal, <1:50), mycoplasma pneumonia IgG was 0.04 U/L (normal, <0.09), and Q fever IgG was <1:16 (normal, <1:16). West Nile and St. Louis encephalitis IgG and IgM from serum specimens were nonreactive. Hantavirus IgM and lymphocytic choriomeningitis IgM from the serum were also negative.

On the evening of hospital day 2, the patient's daughter noticed an odd smell emanating from the patient's car. Further inspection of the car by the patient's family revealed a mouse nest located in the trunk of the car, and suspected mouse urine was noted on the floorboards of the vehicle. The hospital care team was informed.

The subsequent negative laboratory tests listed are helpful in likely excluding many of the diagnoses suggested such as malaria, *Babesia*, common bacteremias, viral hepatitis, HIV, and WNV. Furthermore, the new history of mouse exposure brings to the forefront rodent-associated infections, specifically exposure to mouse urine, a vehicle for leptospirosis. The patient's hepatitis, anemia, thrombocytopenia, scleral injection, along with the rest of his symptoms in the context of exposure to mouse urine makes leptospirosis the likely diagnosis. A negative *Leptospira* antibody early in his illness does not rule out the disease, and a convalescent titer should be obtained to confirm the diagnosis.

Leptospirosis was suspected, and the patient was started on doxycycline. The patient improved after initiation of antibiotics, and was discharged on hospital day 5 with a 14-day course of antibiotic treatment. At his follow-up appointment 2 weeks after the onset of his illness, the patient denied further fevers, headache, nausea, and his weakness was improving. Repeat, convalescent *Leptospiria* antibody testing during this visit resulted positive at 1:400, confirming the diagnosis.

COMMENTARY

This case describes an elderly man who presented with a fever of unknown origin (FUO), and was eventually diagnosed with leptospirosis. FUO presents slightly differently in elderly patients, as elderly patients are less likely to mount a high fever, and when they do, the etiology is more likely to indicate a serious bacterial or viral infection. Additionally, an etiology for FUO in the elderly is found in over 70% of presenting cases, compared to 51% in patients under the age of 65 years.[1] A detailed, comprehensive social, travel, and exposure history and physical examination remains the cornerstone of elucidating the diagnosis for FUO. The exposure to mouse urine in this case was an unusual and a helpful piece of the history to further focus the differential diagnosis.

Leptospirosis is an emerging bacterial zoonosis, and causes both endemic and epidemic severe multisystem disease. The *Leptospira* spirochete is maintained in nature through a chronic renal infection in mammalian reservoir hosts, such as mice,[2,4] and is transmitted through direct or aerosolized contact with infected urine or tissue. After a mean incubation period of 10 days, a variety of clinical manifestations may be seen. In this case, the patient's clinical presentation revealed many classic symptoms of leptospirosis, including fevers, rigors, headache, lower extremity myalgias, nausea, vomiting, and diarrhea; however, these symptoms are nonspecific. The presence of a conjunctival suffusion in leptospirosis infection had a specificity of 98% in a high-incidence cohort of febrile patients in Sri Lanka,[3] and was an important diagnostic clue in this case. Leptospirosis is a self-limited illness in most patients, with an initial septicemic, febrile phase followed by an immune phase. A more severe presentation may be seen in the immune phase of the illness, which includes renal and hepatic dysfunction (known as Weil's disease), as well as cardiac, pulmonary, and central nervous system abnormalities. With a 14% case fatality rate, the risk of death has been shown to be higher in patients over 40 years old, with altered mental status and multiorgan failure.[4]

The early diagnosis of leptospirosis relies heavily on physical exam findings and epidemiologic history. In this case, the patient's laboratory abnormalities, including immature granulocytes, thrombocytopenia, hyponatremia, hypokalemia, mild hepatitis, and pyuria with granular casts are all reported with leptospirosis infection[2]; however, independently, these laboratory findings are nonspecific. Patients may not have a detectable antibody levels in the acute phase of the disease. In this case, given the strong clinical suspicion based on the findings of conjunctival suffusion and exposure to mouse urine history, the lack of a more plausible alternate diagnosis, and known delay in antibody positivity, the patient was treated empirically with doxycycline for presumed leptospirosis.[5] Forthcoming novel diagnostic strategies such as next-generation DNA sequencing techniques may provide real-time diagnosis of this zoonotic infection, thus decreasing the window period between empirical antimicrobial coverage and diagnostic confirmation.[6]

Leptospirosis is prevalent in tropical climates and has been associated with impoverished communities.[7] Urban slums, with poor sanitation and high rodent density, are an ideal environment for leptospirosis. The reported risk of infection in a Brazilian slum was as high as 3% per year.[8] Additionally, rodent sightings, as well as the presence of chickens, were risk factors for leptospirosis transmission in urban slums.[9] Correspondingly in this case, we hypothesize that the patient's interest in urban farming, specifically the chickens he kept, likely attracted the mice infected with leptospirosis. Urban chicken farming is becoming increasingly popular in the United States,[10] and may be a developing risk factor for human leptospirosis infection. Leptospirosis is one of many emerging zoonoses, such as avian influenza, tick-borne illness, and ebola, resulting from changing human ecology. Thus, when considering infectious etiologies, clinicians should ask patients about vocational and avocational exposures, including new trends such as urban farming, which may expose them to previously underappreciated illnesses.

TEACHING POINTS

1. Elderly patients with a FUO are more likely to be diagnosed with an underlying serious bacterial or viral infection when compared to a younger cohort of FUO patients.
2. The diagnosis of leptospirosis may initially be based on clinical suspicion in patients with classic features and exposures, noting the high specificity of

conjunctival suffusion, and initial titers may be nondiagnostic; therefore, empiric treatment should be considered when clinical suspicion is high.

3. Increased interest in urban chicken farming in the United States, with associated higher rodent density, may represent a newly recognized risk factor for human leptospirosis infection.

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