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TEMPO AND FRAME: CLINICAL PROBLEM SOLVING

Twists of Fate

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*In the **Tempo and Frame: Clinical Problem Solving** series, patient information is presented in sequential data blocks (bolded text) to a blinded expert clinician who interprets each segment and shares their diagnostic reasoning and management insights (regular text).*

CASE PRESENTATION

A 20-year-old man presented with one week of non-bloody, watery diarrhea associated with fatigue, malaise, and upper abdominal discomfort. He described 3-4 episodes daily of watery diarrhea which fluctuated in intensity. He also noted a feeling of malaise, which he initially attributed to food poisoning or viral gastroenteritis. However, as it persisted and later became associated with upper abdominal discomfort, he began to worry it was something more serious and sought care at the emergency department.

Acute diseases are often exposure-related and different when compared to chronic conditions. If the exposure is identified, then a trigger driving the underlying symptoms can be determined. Symptoms typically resolve with a combination of removal of the trigger, time, and if necessary, appropriate treatment. An acute onset of watery diarrhea is most often infectious. The exposure is most commonly food-related or secondary to contact with another infected individual. Most acute infectious diarrhea is self-limited and resolves within a week. Less commonly, the diarrhea can persist as in this case, and both benign and sinister diagnoses can be considered. One common explanation is a post-infectious state where diarrhea continues without active infection similar to persistent cough after the resolution of an acute viral respiratory infection. If not a direct consequence of the infection itself, ongoing exposure to the trigger or an exacerbating factor can be considered. This includes food-related intolerances such as lactose and/or toxic effects of ingestions, such as medication or alcohol. To determine whether further investigation should be pursued for acute diarrhea, better understanding of the patient's background, with particular attention to their immune status, is critical. If the host is immunocompromised (HIV/AIDS, autoimmune disease with use of specific medications, etc.), further investigation is warranted due to the potential for atypical presentations of common disease,

the higher risk of severe disease, and the increased incidence of less common diseases. Likewise, if the patient reports an unusual exposure, such as swimming in a freshwater lake or having unprotected sexual intercourse with new partners, this should prompt additional investigation. Although the patient's immunocompromised status is usually apparent from the medical history, a comprehensive social history is essential and must be obtained to assess a patient's risk for both common and atypical infections.

His medical history included Crohn's disease managed with infliximab infusions every eight weeks and seronegative rheumatoid arthritis with HLA-B27 positivity. His Crohn's disease had been diagnosed four years prior via colonoscopy when he developed eight weeks of non-bloody diarrhea. He was started on adalimumab initially, but due to inadequate symptom control, later transitioned to infliximab with resolution of symptoms. He had been in clinical remission for the past several years. He was not on any other medications, including herbs or supplements, and did not smoke, drink alcohol, or use recreational drugs. There was no recent travel, sick contacts, bites or scratches from insects or animals, or swimming in freshwater. He had lived in the Southeastern United States his whole life and was not sexually active.

Vital signs were notable for a normal temperature and blood pressure without tachycardia or tachypnea. The oxygen saturation was 98% on room air. The physical examination was notable for mild epigastric tenderness and a focal area of tenderness and fluctuance on digital rectal exam concerning for a perirectal abscess. The remainder of the physical examination was unremarkable.

Due to his immunosuppressed state, it is important to investigate for alternative diagnoses beyond simple viral or food-related gastroenteritis. These include common bacterial causes of diarrhea such as *Salmonella, Campylobacter, E. coli* and *Shigella*, which can be detected on stool microbial polymerase chain reaction (PCR) testing. *Clostridium difficile* infection, even in the absence of clear antibiotic exposure, must also be considered. Patients with inflammatory bowel disease, especially while on immunosuppression, have a higher risk of developing colitis from cytomegalovirus (CMV). This infection can mimic an inflammatory bowel disease (IBD) flare and present as severe or refractory colitis and should also be excluded.

In rare scenarios, certain conditions can mimic and mistakenly lead to a diagnosis of IBD. While his history, including the duration and quality of symptoms, colonoscopy findings, and response to standard treatment are strong evidence that his diagnosis is likely inflammatory bowel disease, this possibility should still be considered. Mimics of IBD include intestinal involvement of granulomatous infections, such as tuberculosis and endemic mycoses (especially histoplasmosis, which is the most likely to infiltrate the GI tract), autoimmune disorders such as intestinal vasculitis or Behcet's disease (which most commonly causes ileitis), toxic causes (such as NSAIDs and checkpoint inhibitors), and immunodeficiencies. If the initial investigation is unrevealing, or extra-luminal clues do not arise to guide further testing, these diagnoses can be pursued.

A perirectal abscess should be further investigated with incision and drainage, or if there is diagnostic uncertainty, cross-sectional imaging. If present, it could represent an infectious complication of the underlying symptom driver, a flare of his underlying Crohn's disease, or both.

Labs upon presentation are displayed in Table 1. Peripheral blood smear was without schistocytes or blasts. Viral respiratory panel, *C. difficile* stool testing, and blood cultures were negative. Testing for sexually transmitted infections, including HIV, gonorrhea, chlamydia, and syphilis, was negative. Toxicology screening in the urine and serum for illicit substances and alcohol was unrevealing.

The pattern of lab results can be interpreted in several ways. Hyponatremia, hypokalemia, and metabolic alkalosis suggest a dehydrated state, which clinically fits with his diarrhea. Anemia and thrombocytopenia in combination with the elevated C-Reactive protein, lactate dehydrogenase, and ferritin could correspond to an inflammatory illness with subsequent bone marrow suppression. Hemolytic anemia should be considered given the concurrent anemia and thrombocytopenia. Although the initial blood smear lacked schistocytes, this does not rule out an evolving thrombotic microangiopathy (TMA); therefore, ongoing vigilance for this life-threatening diagnosis is essential. In fact,

Table 1. Selected Laboratory Data

Test	Reference Range	Result
Sodium (mmol/L)	135-140	129
Potassium (mmol/L)	3.4-5.0	3.0
Chloride (mmol/L)	98-108	93
Carbon Dioxide (mmol/L)	23-32	30
Urea Nitrogen (mg/dL)	8-25	8
Creatinine (mg/dL)	0.6-1.5	1.0*
Glucose (mg/dL)	70-110	173
Calcium (mg/dL)	8.5-10.5	8.3
Total Protein (g/dL)	6.0-8.3	7.5
Albumin (g/dL)	3.3-5.0	3.6
Aspartate Aminotransferase (U/L)	10-40	1,206
Alanine Aminotransferase (U/L)	10-55	218
Total Bilirubin (mg/dL)	0-1.0	0.9
Alkaline Phosphatase (U/L)	45-115	165
White Cell Count (per µL)	4,500-11,000	6,600†
Hemoglobin (g/dL)	13.5-17.4	11.3‡
Platelets (per µL)	150,000-400,000	113,000
C-Reactive Protein (mg/dL)	<1.0	10.5
Ferritin (ng/mL)	30-100	2,107
Haptoglobin (mg/dL)	45-165	336
Lactate Dehydrogenase (U/L)	135-225	1,200

* Patient's baseline creatinine is 0.8 mg/dL
† Differential was 57% neutrophils, 28% lymphocytes, and 0% eosinophils
‡ Patient's baseline hemoglobin is 12.5 g/dL

most cases of TMA initially present as a flu-like prodrome or viral gastroenteritis, as seen in this case. Should the anemia and thrombocytopenia worsen, the peripheral smear and hemolysis studies should be repeated.

Elevated liver enzymes occur in acute hepatitis; however, values exceeding 1,000 U/L narrow the differential to infectious, ischemic, toxin-induced, and autoimmune hepatitis, as well as biliary obstruction. Testing for viral hepatitides, particularly A, B, and C, and also for viruses with hepatitis potential, including Epstein Bar Virus (EBV) and CMV, should be pursued. To exclude acute liver failure—a medical emergency—close evaluation of the coagulation cascade and the patient's mental status should also be performed.

An elevated aspartate aminotransferase (AST) out of proportion to the alanine aminotransferase (ALT) raises concern for the possibility of extra-hepatic drivers of AST elevation - rhabdomyolysis and hemolytic anemia. Given that his hemolytic workup was negative, the possibility of rhabdomyolysis looms large and a creatine kinase (CK) should be obtained.

Infectious causes of rhabdomyolysis are most commonly viral organisms such as influenza, SARS-CoV-2, and enterovirus. Common bacterial organisms can also be seen with rhabdomyolysis, such as staphylococcus and streptococcus, though are typically accompanied by positive blood cultures and sepsis with significant systemic inflammatory response syndrome (SIRS) criteria, both lacking in this patient. However, in immunosuppressed hosts such as this patient, typical SIRS criteria, even in the presence of bacteremia, may not be present. Therefore, empiric antibiotics for common organisms should be continued until further investigation is performed or a change in his illness course occurs. Finally, other rare causes of infectious rhabdomyolysis should be considered and include legionella and zoonotic/parasitic infections. Legionella classically presents as hyponatremia and rhabdomyolysis with elevated liver enzymes. Although pneumonia is the most common presentation, diarrhea can also be a prominent feature and testing should be pursued.

The combination of hyponatremia, thrombocytopenia, and elevated liver enzymes must also prompt consideration (and may sometimes be the only clue) of tickborne infections. Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis all occur in the Southeastern United States and patients often may not recall a tick bite. The absence of a rash does not exclude Rocky Mountain spotted fever as rare cases may be spotless. Although other classic features such as high fevers and arthralgia were not described by our patient, they may later come in his clinical course. Testing for these infections, along with empiric treatment with doxycycline, should be strongly considered.

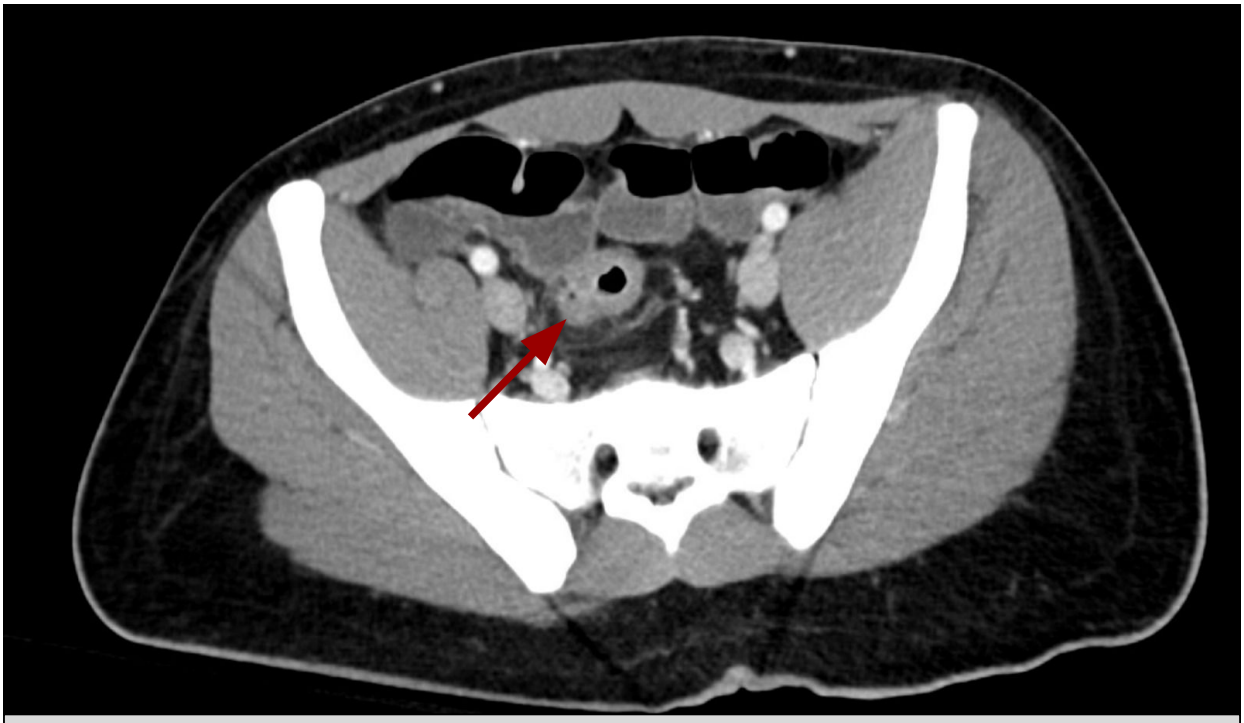

Figure 1. CT Abdomen and Pelvis with Contrast: In this selected axial image, sigmoid colitis with diverticulitis and a possible small focal abscess (arrow) is highlighted.

Toxic causes of rhabdomyolysis, including alcohol and recreational drug use, were appropriately excluded. Additional exposure history should also be obtained. Organophosphate poisoning, for example, can occur with a cholinergic toxidrome consisting of diarrhea and rhabdomyolysis, but the patient did not have additional suggestive features such as diaphoresis, bradycardia, or productive cough from bronchorrhea. There was no history of syncope or seizure to suggest sustained muscle contraction or immobilization as potential drivers. He had hypokalemia, but it was not sufficiently deranged to be implicated as the driver of the rhabdomyolysis. Other electrolytes, including magnesium and phosphorus, should be checked. If rhabdomyolysis is indeed confirmed, close monitoring for complications will be important, including local (compartment syndrome), metabolic (hypocalcemia, hyperkalemia, acute renal failure), and neurologic (encephalopathy, seizures, psychosis).

Magnesium and phosphorus levels were within normal limits. The CK level was 54,000 U/L. Legionella urine antigen testing was negative. The Rocky Mountain spotted fever IgG was elevated to 1:128; the IgM was non-reactive. Testing for Lyme disease, ehrlichiosis, and anaplasmosis was negative. Stool PCR testing for microbes including *Salmonella, E. coli, Shigella, Campylobacter,* and usual viruses was unrevealing. Serologies for hepatitis A, B, C, EBV, and CMV were negative. Coagulation studies were within normal limits. Contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed sigmoid colitis and diverticulitis with a suspected small focal abscess (Figure 1). The gluteal fold appeared inflamed at the location of the corresponding perirectal abscess on exam. These findings were interpreted as active inflammatory bowel disease with a possible superimposed infection. An incision and drainage was performed on the rectal abscess with resolution. No empiric glucocorticoids were given. His vital signs and mental status remained stable. Additional collateral history was obtained from his father and included the recent death of one horse and the ongoing febrile illness of another at the family stable. A diagnostic test was performed and empiric treatment was started.

The CT findings are consistent with a flare of inflammatory bowel disease, but the perirectal abscess

and diverticulitis cannot by themselves fully explain the patient's clinical picture, degree of inflammation, and profound laboratory abnormalities. Given the recent contact with a diseased horse, a transmissible zoonotic infection should be considered. Infections which are transmissible through horses include 1) *Rhodococcus equi* (usually presents with a cavitary lung lesion that can lead to bacteremia and abscesses), 2) common GI pathogens transmissible by animals including *Salmonella*, *E. coli* and C*ampylobacter*, 3) rodent-borne infections transmitted through horses including leptospirosis and tularemia, 4) soil-borne infections, such as anthrax, and 5) finally indirect transmission from horses through arthropod-borne infections such as *Bartonella vinsonii* subspecies *berkhoffii*, Eastern equine encephalitis virus, West Nile Virus, anaplasmosis, and Lyme disease. Reviewing the patient's clinical presentation and salient features, including the provided negative testing, leptospirosis is the most likely diagnosis in this patient. The combination of a flu-like illness accompanied by rhabdomyolysis, hyponatremia, thrombocytopenia, and transmission by horses is in keeping with the disease's illness script. This patient is most likely in the initial phase of leptospirosis, known as the leptospiremic phase, which typically lasts less than two weeks and in the majority of cases is a self-limited flu-like or GI illness. A subset of patients enter a secondary immune phase; this stage can lead to multi-organ dysfunction, typically affecting the renal, hepatic, pulmonary, and central nervous systems. Empiric initiation of doxycycline and close monitoring for symptom worsening is warranted and should not be deferred while awaiting the results of confirmatory testing.

Dr. Shen's Final Diagnosis: Leptospirosis

The patient's leptospirosis IgM came back positive with a high titer; concurrent IgG testing was negative, confirming a diagnosis of leptospirosis. He was treated with doxycycline and made a full recovery.

Final Diagnosis: Leptospirosis with concomitant Crohn's flare.

DISCUSSION

Leptospirosis is a globally distributed zoonotic disease caused by pathogenic gram-negative spirochetes. The estimated annual incidence is 1 million cases worldwide, though is likely underreported due to limitations in diagnostic access and inconsistent reporting mandates.[1-2] The approximate mortality rate is 6%.[3] The infection is most prevalent in tropical and subtropical regions with outbreaks following heavy rainfall and flooding. Transmission occurs through contact with water, soil, or food contaminated with urine from infected animals, including cattle, pigs, horses, dogs, and rodents.[1-4] The bacteria enter the human body through mucous membranes or abraded skin. Risk factors include recreational freshwater activities, occupational exposure to animals, and residence in areas with poor sanitation and rodent infestation. Climate change, increasing human-wildlife contact, and urban slum expansion are thought to be ongoing contributors to the emergence and spread of leptospirosis.[1-5]

The clinical presentation of leptospirosis is highly variable, ranging from asymptomatic infection to severe, life-threatening illness. The incubation period ranges from 2 to 30 days, with most cases occurring 5 to 14 days after exposure. While most symptomatic infections (90%) are self-limiting, 5–10% of patients develop severe multi-organ dysfunction.[2,3]

The classic disease pattern is biphasic. The acute septicemic (leptospiremic) phase lasts approximately 7 days and presents with nonspecific symptoms including fever, severe headache with photophobia and retro-orbital pain, myalgia (characteristically involving the calves and lower back), nausea, vomiting, diarrhea, abdominal pain, and cough. Conjunctival suffusion (red, injected eyes) is a characteristic though often inconsistent finding. Following this initial leptospiremic stage, a secondary immune phase begins, marked by rising antibody titers and the shedding of organisms in the urine. In patients progressing to severe disease, complications can include cardiac arrhythmia, hemodynamic collapse, hemorrhage, jaundice, liver failure, aseptic meningitis, pulmonary insufficiency, and renal failure. The pathophysiology is thought to be driven by a complex interplay between patient specific predisposition, high

bacterial burden, dysregulated immune responses (cytokine storm followed by immunoparalysis), and direct pathogen effects. The nonspecific clinical presentation makes leptospirosis challenging to distinguish from other tropical infectious diseases such as malaria, dengue, influenza, viral hepatitis, and yellow fever.[1-4]

Weil's disease, first described in 1886, represents the most clinically recognized and severe form of leptospirosis, characterized by jaundice and kidney failure.[1-3] The case-fatality rate for severe disease ranges from 5% to 15%, though those with pulmonary hemorrhage carry a particularly grave prognosis with mortality exceeding 50%. Poor prognostic indicators include older age, altered mental status, respiratory insufficiency, and oliguria.[2,4]

Laboratory confirmation is essential for diagnosis given the nonspecific clinical presentation, though the diagnostic approach depends critically on the timing of presentation relative to symptom onset. During the first week of illness, nucleic acid amplification tests such as PCR are most useful, as leptospires are detectable in blood during this septicemic phase. PCR can also be performed on cerebrospinal fluid in patients with meningeal signs and on urine after the first week of illness, though urinary shedding may be intermittent. However, PCR testing is often not readily available and culturing leptospires is difficult, requires specific culture media, and often takes weeks to grow, further limiting its utility.[2,4] Thus, serologic tests (IgM and IgG) are typically utilized. Although most useful for patients ten or more days into their clinical course, IgM antibodies typically appear 5 to 7 days after symptom onset and can be positive within the first week of infection. However, given the limited sensitivity in patients with acute symptomatic disease, paired acute (0-7 days) and convalescent (7-21 days later) samples should be obtained when possible, with a significant rise in titer (typically 4-fold or greater in the IgM sample) confirming the diagnosis.[1-6]

Current guidelines recommend initiating antibiotic therapy empirically as soon as leptospirosis is considered, prior to diagnostic confirmation, as early treatment may decrease disease severity and duration. For mild disease, doxycycline is the drug of choice, with ampicillin, amoxicillin, and azithromycin as alternatives. For severe leptospirosis, intravenous penicillin is recommended; ceftriaxone and cefotaxime are acceptable alternatives. Antibiotic treatment can precipitate the Jarisch-Herxheimer reaction in approximately 9% of cases. Although most commonly associated with syphilis, it can also be a feature of other spirochetal infections. This is characterized by fever, chills, and intensification of symptoms within 24 hours of treatment initiation, though this reaction is rarely fatal. While immunomodulatory therapies, including corticosteroids, have been proposed in the treatment of severe disease, current evidence is insufficient to support their routine use.[1-3,7]

In this immunosuppressed patient with Crohn's disease, acute diarrhea initially suggested common infectious etiologies or an inflammatory bowel disease flare. However, his unique exposure history and laboratory abnormalities suggested a systemic process, prompting a broader investigation into zoonotic and atypical pathogens that ultimately confirmed the diagnosis of leptospirosis. The coexistence of imaging findings consistent with active Crohn's disease also highlighted the potential for concurrent diagnoses rather than a single explanatory process. This case underscores the value of avoiding premature closure, integrating the host's unique vulnerability, reassessing new information as it emerges, and considering the possibility of multiple diagnoses—demonstrating the "twists of fate" that define complex clinical problem solving.

KEY TEACHING POINTS

- In immunosuppressed patients, symptoms such as acute diarrhea may warrant evaluation for atypical and zoonotic pathogens rather than assuming routine infectious or inflammatory etiologies. A thorough social history is important to identify the relevant differential diagnosis.
- The combination of clinical features including rhabdomyolysis, thrombocytopenia, elevated liver enzymes, and hyponatremia should prompt the consideration of systemic infectious processes, particularly zoonotic and tick-borne infections, including leptospirosis.
- Avoid premature diagnostic closure—concurrent conditions (leptospirosis and Crohn's flare) may coexist, particularly when host factors and exposure history point toward multiple processes.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. JS, AR, and AR were not involved in the review process or final editorial decisions per the Journal's Editor as Author policy. Alternative reviewers and independent oversight were utilized to ensure unbiased review, fairness, and adherence to quality standards.

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ETHICS STATEMENT

The authors obtained verbal informed consent, witnessed and documented in accordance with institutional guidelines, for publication of medical information and images.

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