Case Files
of Wake Forest Baptist Medical Center

Tell Me More About Your Abdominal Pain

Leslie Ellis, MD, Hematology and Oncology, Nkechinyere Emejuaiwe, MD, Rheumatology and Immunology, Jason Hopper, MD, Internal Medicine, Andrew Namen, MD, Pulmonary Critical Care, Allergy and Immunology, Chaudry Majeed, MD, Internal Medicine – Hospital Medicine, James Peacock, MD, Infectious Diseases

In **Case Files of Wake Forest Baptist Medical Center**, the clinical presentation of a real patient is described to a panel of experts in stages. The panel discusses the differential diagnosis, asks relevant questions, and explains their clinical thought process.

Case Presentation

Jason Hopper, MD

The patient is a 60-year-old African-American man who presented to Wake Forest Baptist Medical Center with abdominal pain and fever

Dr. Majeed The differential diagnosis should initially constitute a broad spectrum of possibilities in a patient with abdominal pain and fever. Information about anatomic location may help to narrow the possibilities. Pain in the right upper quadrant (RUQ) may indicate cholangitis, hepatitis, cholelithiasis, or pancreatitis. Diffuse abdominal pain can be caused by autoimmune diseases; for example, patients with microscopic polyangiitis can present with abdominal pain and fever. Autoimmune hemolytic anemia can also present in this manner. When pain is in the right lower quadrant, appendicitis is a common and easily correctable etiology. Other etiologies include nephrolithiasis or pyelonephritis. Pain in the left lower quadrant may indicate colitis, diverticulitis, or prostatitis. Lastly, many infectious diseases can present with abdominal pain and fever.

Dr. Namen Separating symptoms by quadrant is an excellent strategy for narrowing the differential diagnosis and guiding initial thoughts on treatment. In addition to the diagnoses mentioned, we want to include the most typical presentations. The most common cause of abdominal pain and fever is viral gastroenteritis which can be diffuse or focal in nature.[1]

Dr. Emejuaiwe I'd like to characterize the abdominal pain a little more. Is it acute in onset or is it a chronic process? Are there any precipitating factors? Is the pain intermittent or constant? Did the fever and abdominal pain begin simultaneously, or did one precede the other?

Dr. Peacock From an infectious disease standpoint, the focus should initially be on common etiologies like diverticular disease, appendicitis, or ruptured viscous tissue such as bowel, but more information is necessary.

The patient is a 60-year-old African-American man who presented with a chief complaint of bilateral lower abdominal pain. The pain began a few weeks ago and has worsened mildly. Associated symptoms included subjective low-grade fevers beginning at about the same time as his abdominal pain, exertional dyspnea, and unintentional weight loss spanning several weeks. There was no report of nausea or emesis, but he noted mild worsening of the pain after eating or drinking. There was no associated diarrhea or constipation. Several weeks preceding hospitalization, the patient had been seen in the emergency department and was diagnosed with diverticulitis. He was treated with ciprofloxacin and metronidazole orally with only mild improvement in symptoms. He presented a second time the week prior to admission and was given a second course of antibiotics, which again resulted in no significant improvement.

Dr. Peacock The fact that the pain is lower-abdominal rather than upper-abdominal immediately narrows the differential diagnosis considerably, as does the fact that it is bilateral. Many of the symptoms commonly associated with infectious gastrointestinal disease — such as nausea, vomiting, and diarrhea — were apparently not a component of this patient's initial presentation. It is noteworthy that he did have worsening of symptoms with eating. Exacerbation with eating might suggest that a gastrointestinal stimulus is producing or at least associated with his pain. The panel has alluded to the possibility of diverticular disease and diverticulitis, but the lackluster response to several courses of antibiotic therapy argues against those diagnoses.

Dr. Emejuaiwe The differential diagnosis needs to remain broad, but I agree that a telltale sign includes the lack of response to several courses of antibiotics, decreasing the likelihood of an infectious cause. The post-prandial pain may point to vascular compromise, especially given the patient's age (60). Common causes of vascular disease in the bowel include ischemic and autoimmune disease processes.

Dr. Namen Patients who have significant occlusion of the celiac artery or the inferior or superior mesenteric arteries can develop abdominal pain. One question is whether it was reproducible on palpation and whether the pain occurs after eating.

His abdominal pain after eating is in the same region, the lower abdomen, as his general complaint, but his pain is not exclusively associated with eating.

Dr. Namen His presentation of postprandial pain is unusual. Gastroenteritis or peptic ulcers are more common and may cause epigastric discomfort prior to eating, but when pain is localized to the lower abdomen, mesenteric vessel compromise via inflammation or occlusion is a primary concern.[2]

Dr. Majeed This is a patient with abdominal pain, fever, signs of shortness of breath or other pulmonary symptoms, and post-prandial pain. This constellation of symptoms may indicate a systemic process. The top of my differential diagnosis list includes multi-system inflammatory diseases like vasculitis or ischemic vascular disease with gastrointestinal complications.

The patient has a history of Hepatitis C spanning many years, but has never received treatment. He has no significant family history. He reports taking aspirin and ibuprofen intermittently for pain. He had a previous appendectomy. He is a current smoker with a 20 pack-year history. He denies current alcohol or drug use, but admits to using intravenous heroin roughly 20 years ago.

On physical exam the patient was afebrile, had a normal heart rate, was mildly tachypneic, and was mildly hypertensive. His abdominal pain was causing him a fair amount of distress. His head, eyes, ears, nose, and throat (HEENT) exam was within normal limits. He had a regular rate and rhythm on cardiovascular exam. Trace crackles were heard in the bilateral lung bases, but with normal respiratory effort. He had normo-active bowel sounds; there was tenderness in the bilateral lower quadrant. The tenderness upon palpation was mild compared to the degree of pain he reported and he showed no rebound or guarding. There was left-sided costo-vertebral angle (CVA) tenderness, but none on the right. He had no edema and no appreciable neurologic deficits.

Dr. Emejuaiwe Two things immediately stand out. We have an elderly patient with a history of hepatitis C infection. We know now that he has multi-system involvement; he has pulmonary symptoms, as well as abdominal pain with possible kidney processes. He has some constitutional symptoms with fever and weight loss. His vital signs show that he is hypertensive, which may hint that we are looking at a vasculitic process.

Dr. Namen One of the key features found on exam is crackles in the lung bases. Certain infectious disease of the lungs can often times be heard best in the upper lobes. Examples include atypical interstitial lung disease like pneumonitis or atypical fungal infection. When crackles are heard in the bases, the differential includes volume overload, infection, and inflammatory conditions such as interstitial lung disease. The vascular distribution is more prominent in the lower lobes of the lungs compared to the upper lobes. This patient exhibits an abdominal, pulmonary, and renal syndrome. What one kind of disease can connect all three organ systems? Inflammation from a vasculitic or infectious disease and malignancy are all possibilities. Bilateral basilar crackles fit the picture of a vasculitic process because the predominant vascular pedicle is in the lower lobes.

Dr. Peacock The predominance of signs still relate to the abdomen, so we must consider processes that target the bowel, perhaps in the left lower quadrant. This patient has hepatitis C, but abdominal pain is not a usual feature of this disease in its chronic phase. It is important to emphasize that vasculitis can occur as a consequence of hepatitis C, often related to some of the epiphenomena such as cryoglobulinemia. This may be a unifying theme in the search for an etiology of this multi-system disease process.

We will continue with the basic lab results for this patient obtained upon admission. Normal ranges are shown in parentheses. His metabolic panel showed no major abnormalities. Sodium was 135 mmol/L (135-146). Potassium was 3.6 mmol/L (3.5-5.3). Chloride was 97 mmol/L (98-110). CO2 was 21 mmol/L (21-33). BUN was 11 (8-24). Creatinine was 1.21 mg/dL (0.5-1.5). Calcium was 7.5 mg/dL (8.5-10.5). Protein was 7.7 g/dL (6-8.3). Albumin was low at 2.8 g/dL (3.5-5). Total bilirubin was elevated at 1.3 mg/dL (0.1-1.2). His alkaline phosphatase was elevated at 332 IU/L (25-125). He also had transaminitis, with an aspartate aminotransferase (AST) of 220 IU/L (5-40), and an alanine aminotransferase (ALT) of 106 IU/L (5-50). He had an elevated white blood cell (WBC) count at 19,100 (4,800-10,000). Hemoglobin was 11.6 g/dL (14-18) and platelets were 454,000 (160,000-360,000).

Dr. Namen Liver processes and common bile duct disease should be considered with this specific cluster of lab results. These numbers could more specifically be attributed to a viral illness, an inflammatory condition, or other etiologies. The elevated WBC count raises a red flag for an infectious etiology. However, the WBC count can be elevated in a number of inflammatory states as well, so it certainly does not exclude those conditions.

Dr. Majeed I agree that the liver function tests are concerning, and may indicate cholestatic pancreatitis, among other things. The alkaline phosphatase is more elevated than the AST and the ALT, which often indicates an obstructive process, such as ascending cholangitis. These numbers can be seen in hepatitis but are not consistent with primary hepatocellular disease. The AST is elevated more than the ALT, a finding usually associated with alcoholic hepatitis. Lastly, the decreased albumin may indicate chronic failure to thrive in this patient, due either to decreased appetite or as a direct result of his disease process.

Dr. Peacock The laboratory data clearly show that he does have inflammation, as reflected by the elevated WBC and platelet counts. The infectious or non-infectious nature of the disease remains to be determined. He does have hepatobiliary disfunction, but the specific features are rather ambiguous. There are some cholestatic features and some features that suggest hepatocellular dysfunction, but nothing provides directive information. Another interesting finding relates to his protein and albumin; his globulin fraction seems to be increased, an indicator that his illness has followed a chronic or subacute course. In addition to the things that have been discussed, we must consider biliary tree disease, sclerosing cholangitis, or an autoimmune biliary disorder. These biliary tree diseases are generally not associated with left lower quadrant pain, except in association with inflammatory bowel disease.

Student Do you make anything of the low lymphocyte count?

Dr. Ellis I don't, because it is a percentage. If you calculate 2% of the total leukocyte count (19,000), it is roughly 4, which is a normal absolute lymphocyte count. All this tells me is that the vast majority of cells are neutrophils, so the patient does not have an absolute lymphopenia, but the relative percentage is low. This is either a reactive inflammatory process or likely, based on the clinical presentation, a hyperactive bone marrow attempting to compensate for anemia. As the patient's bone marrow creates red blood cells in response to the anemia, one observes a secondary leukocytosis with a primary neutrophilia and thrombocytosis due to a shared hematopoietic predecessor.

We obtained an abdominal X-ray which showed no acute abnormalities. An abdominal CT was then obtained.

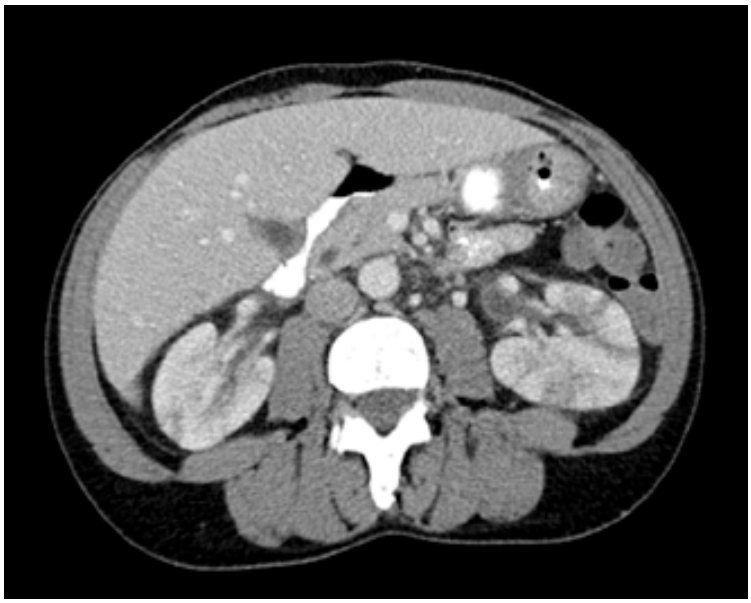

Image 1: Bilateral striated nephrograms consistent with pyelonephritis.

The radiologists saw bilateral striated nephrograms, which they thought were consistent with pyelonephritis. We subsequently performed bilateral renal ultrasound examinations, which showed the right kidney measuring 13.6 cm and the left measuring 12.5 cm, with no evidence of hydronephrosis and with bilateral increased echogenicity throughout. Further lab work included negative blood and urine cultures throughout the hospital stay. Urinalysis revealed mild proteinuria. Lipase was normal at 23 (11-82). Lactic acid was normal at .9 (0.5-2.2). Ammonia was 19 (11-35), and troponin was slightly elevated at .108(0-0.04). An electrocardiogram revealed sinus tachycardia without evidence of ischemic changes.

The patient was administered vancomycin and piperacillin/tazobactam in the Emergency Department for the presumptive diagnosis of pyelonephritis. He continued to have intermittent low-grade fevers over the next few days of his hospital stay. His condition worsened, with increasing leukocytosis (WBC – 26.4) on hospital day 4 despite antibiotic therapy and persistently negative cultures.

Dr. Emejuaiwe With an essentially unremarkable urinalysis and poor response to antibiotics, pyelonephritis becomes a less likely diagnosis. It would be helpful to know what the pathology within the kidney tissue would reveal; for example, whether there are ischemic changesor sequelae of an infectious process. The hypertension does not seem insignificant.

Dr. Majeed This patient's illness has been worsening for more than a month despite multiple attempts at empiric treatment. At this point it may be beneficial to investigate causes of a fever of unknown origin (FUO), focusing specifically on rheumatologic and oncologic factors. Given his subacute presentation, I would consider chronic myelocytic leukemia (CML) or perhaps mild acute myelocytic leukemia (AML). CML might be more likely, but the subacute presentation may suggest acute lymphoblastic leukemia (ALL). In the rheumatologic category, there are a host of autoimmune diseases that would need further workup, including anti-neutrophil antibody (ANA) and antibody testing.

Dr. Peacock What is the total duration of his fevers up to this point, and were they documented in the hospital?

He has had documented fevers of 100-101^{0}F for four weeks.

Dr. Peacock By definition, FUO is a fever which has persisted for an extended period of time, usually defined as 3 weeks, and has reached a magnitude of 101°F.[3] A FUO generally defies explanation via usual and routine tests, as seen in this patient.

Dr. Namen At this point, certain aspects help to narrow the differential diagnosis; for example, the lactic acid results are normal, which makes vascular catastrophe or ischemic colitis less likely. Is an ischemic or vascular cause completely ruled out? No, but a negative lactic acid finding suggests an alternative cause maybe more likely.

Dr. Peacock To summarize what has been said up to this point, we have a subacute, perhaps chronic disease process, some features of which are fever and a multiple other symptoms and exam findings that are fairly non-specific and non-localizing. Evidence of chronic inflammation and lack of response to broad-spectrum antibiotic therapy certainly directs us away from the more typical infections initially considered, including pyelonephritis and diverticular disease with complications. Assuming that this illness is not a chronic, subacute presentation of a rare and difficult-to-diagnose infection, other causes of inflammatory disease must be considered.

Dr. Ellis Oncologic or hematologic malignancy is less likely in this patient. Although we observe leukocytosis and thrombocytosis with anemia and an increase in neutrophilia, the peripheral blood of chronic myelocytic leukemia would show varied stages of neutrophil maturation, as typically found in the bone marrow. Assuming that the primary cells in this patient were mature neutrophils with neither metamyelocytes nor myeloblasts, the laboratory findings argue against CML. In acute leukemias, the WBC counts are elevated due to circulating blasts, which by definition are immature cells. One would not observe neutrophilia with leukocytosis and thrombocytosis in

an acute leukemia patient. The patient would have thrombocytopenia as the bone marrow is replaced by rapidly growing immature cells. Although you may see a mild reactive leukocytosis and thrombocytosis with solid tumors, I would certainly not expect the degree of elevation observed in this patient.

Dr. Majeed Another important aspect to consider is a travel history. Many insect-borne diseases have become more common in our area, and they can cause elevated liver enzymes and fever. One such illness that can present with multi-system complaints is ehrlichia. Do we know of recent travel or possible tick exposure?

There was no history of travel or exposure to ticks that he reported.

Dr. Ellis That is a good point to consider. We have at our disposal excellent antibiotics that simply don't provide universal coverage. Many broad-spectrum antibiotics have no efficacy for tick-borne illnesses and other less-common infections. Such rarities cannot be excluded based on an ineffectual response to antibiotic therapy.

We found nothing to suggest an atypical or tick-borne illness. We obtained further testing for fever of unknown origin, as suggested. Anti-neutrophil antibody (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) tests were negative. C3 was normal at 130 (79-152). C4 was 16 (15-70). C-reactive protein (CRP) was elevated at 156 (0-10) and the erythrocyte sedimentation rate (ESR) was >119 (0-20). His hepatitis C infection was found to be genotype 1a, and the viral load was elevated at 569,151. The abdomen was also reimaged via MRI, which again demonstrated striated nephrograms. Due to continued dyspnea, a trans-thoracic echocardiogram (TTE) was obtained, which demonstrated a reduced ejection fraction of 25% with global hypokinesia and no pericardial effusion or focal abnormalities.

Dr. Emejuaiwe In thinking about a possible diagnosis of vasculitis, we mentioned the patient had a history of hepatitis C infection, and we also mentioned the possibility of cryoglobulinemia associated with hepatitis C. This presentation is inconsistent with cryoglobulinemia, because the results do not show immune-complex deposition, as expected in a patient with cryoglobulinemic vasculitis. A vasculitis of some sort is still highly likely, and it would be useful to get more information about the histopathology of his blood vessels. His constellation of signs, symptoms, and lab tests point less towards a small-vessel vasculitis and more towards a medium-vessel vasculitic process, which could also explain the reduction in his ejection fraction.

Dr. Namen Most studies support that vasculitic processes, including thrombotic, would be accompanied by elevated lactic acid in most patients. However, some patients show false-negative results; these people have partial occlusions with some flow, but not complete obstruction. Patients with global hypokinesis and reduced ejection fractions tend to have more of these vascular changes, which may include mesenteric, coronary, or carotid arteries. That said, the negative ANCA and mildly elevated troponin suggests other vascular processes such as thrombosis or partial ischemia.

Dr. Emejuaiwe I would like to add a quick point about the ANCA result. ANCA negativity does not exclude a vasculitic process. Up to 30% of patients with systemic vasculitis, including granulomatosis with polyangiitis (GPA) or Churg-Strauss, have a negative ANCA result in the early stages of their disease process.[4] As the disease progresses, that ANCA then becomes positive; therefore, vasculitis cannot be ruled out on ANCA alone.

The patient underwent duplex ultrasound of his mesentery, which showed no major celiac or superior mesenteric stenosis. Doppler ultrasound of his renal vascular system showed 60% stenosis of the left renal artery and a normal right renal artery. We also did a CT angiogram of his chest showing trace pleural effusions, no pulmonary embolism, and normal abdominal aorta with patent branches. We then obtained an arteriogram of his left and right kidneys.

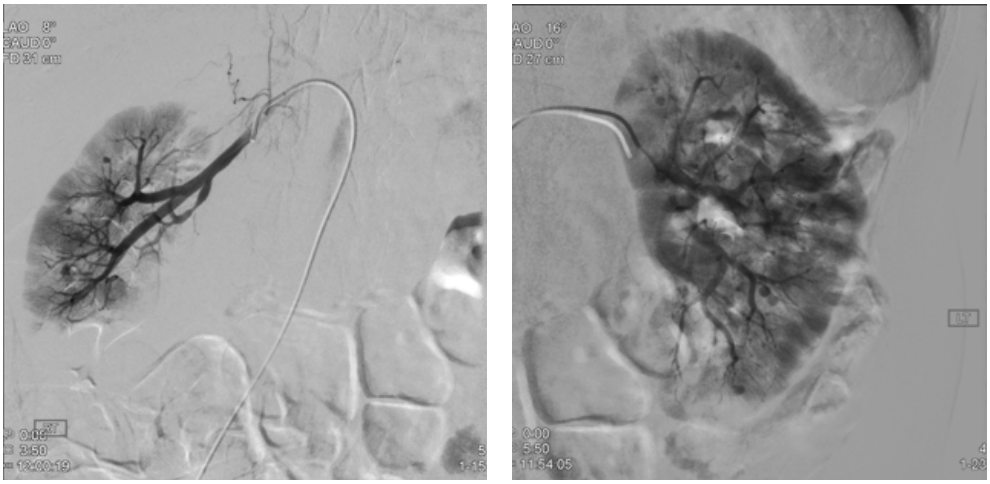

Image 2: Select arteriogram of the left renal artery and both right renal arteries demonstrates multifocal microaneurysms involving numerous subsegmental branches of both kidneys as well as subsegmental infarctions.

Rheumatology was consulted and the patient was diagnosed with medium-vessel vasculitis, namely polyarteritis nodosa (PAN). He was started on a three-day course of solumedrol and transitioned to oral prednisone. His abdominal pain improved with treatment and he was discharged home before being prescribed cyclophosphamide in the outpatient setting.

Commentary

Dr. Emejuaiwe The prototypical medium vessel vasculitides are PAN, Kawasaki's disease, and isolated central nervous system vasculitis. However as with all vasculitides, the differential diagnosis of medium-sized vessel vasculitis should remain broad. Mimics include:

Drug-associated vasculitis – Cutaneous and systemic PAN-like vasculitis may occur in association with use of medications like minocycline. Clinicians should consider the possibility of a drug-induced vasculitis in cases of medium-vessel vasculitis with atypical antineutrophil cytoplasmic antibody serologies or in patients with negative hepatitis B testing.[5]

Cholesterol embolization syndrome – This syndrome is typically seen in patients with advanced atherosclerosis after an endovascular procedure (but can occur spontaneously). They may have symptoms of multi-system disease with fever, weight loss, and fatigue. Clinically, ischemia of digits (an inflammatory response to the cholesterol crystals) can cause livedo reticularis and the classic "purple toe/finger" syndrome.

Thromboangiitis obliterans (Buerger's disease) – This is an inflammatory disease of small/medium arteries and veins caused by an inflammatory thrombus that generally spares the vessel wall. It is associated with tobacco use, although the role of this environmental factor in the pathogenesis of the disease is unknown.

Malignancy-associated vasculitis – This has been reported with both hematologic malignancies and solid tumors.[6] Other medium-vessel vasculitis mimics (depending on the clinical context) may include antiphospholipid antibody syndrome, endocarditis, Sweet's syndrome, atrial myxoma, calciphylaxis, fibromuscular dysplasia, endocarditis, drugs (cocaine, ergots, and amphetamines), and radiation.

In a patient with multi-system involvement, an overriding cause can be differentiated based on what organ systems are involved and the size of the vessels within those systems. If renal biopsies had been obtained, evidence of the involvement of medium-sized vessels, specifically transmural inflammation, would have been observed, reinforcing the diagnosis of PAN.

Dr. Peacock There is an association between chronic hepatitis and PAN, but it is typically associated with chronic hepatitis B. Up to 50% of patients with PAN have a concurrent hepatitis B infection. To my knowledge, this association occurs only rarely with hepatitis C, but in clinical medicine, rarity does not exclude possibility.

References:

1. Marsicao E, Vuong GM, Prather CM. Gastrointestinal causes of abdominal pain. Obstet Gynecol Clin.2014; 41(3):465-489.
2. Acosta S, Block T, Björnsson S, Resch T, Björck M, Nilsson T. Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. J Emerg Med. 2012;42(6):635-41.
3. Cunha BA, Lortholary O, Cunha CB. Fever of Unknown Origin: A Clinical Approach. Am J Med. 2015; 128 (10): 1138e1-1138e15.
4. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, et al. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med. 2015; 26(7): 545-553.
5. Kermani TA, Ham EK, Camilleri MJ, Warrington KJ. Polyarteritis nodosa-like vasculitis in association with minocycline use: a single-center case series. Semin Arthritis Rheum. 2012 Oct;42(2):213-21. doi: 10.1016/j.semarthrit.2012.03.006. Epub 2012 Jun 15.
6. Fain O, Hamidou M, Cacoub P, Godeau B, Wechsler B, et al. Vasculitides associated with malignancies: analysis of sixty patients. Arthritis Rheum. 2007 Dec 15; 57(8):1473-80.