CLINICAL PRACTICE

Exercises in Clinical Reasoning

Exercise in Clinical Reasoning: *Trust but Verify*

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In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (italics) is integrated throughout the discussion.

A 56-year-old man presented with a 1-day history of left-sided flank pain and hematuria. He had a history of Crohn's disease (on mesalamine) and two previous hospitalizations for kidney stones. He stated that the pain is sharp, 8/10 in severity with radiation to his left groin. He additionally noticed dark red urine without clots or associated dysuria coinciding with his back pain. Ibuprofen did not relieve the pain. He denied nausea, vomiting, abdominal pain, subjective fever, chills, rigors, melena, hematochezia, history of lower back trauma, or neurologic deficits. He had a kidney stone (calcium oxalate) 2 years prior with successful lithotripsy. The calcium oxalate stones were thought secondary to his Crohn's disease.

Patients with Crohn's disease have an increased risk of kidney stones, especially those with a prior history of bowel surgery.[1] This small intestine disease increases oxalate absorption which then binds to calcium and, thus, elevated calcium oxalate that precipitates as stones in the urinary tract. This patient's presentation (flank pain, hematuria without infectious signs/symptoms) suggests a recurrent kidney stone; however, I would like more information on the primary diagnosis of Crohn's given its presumed etiology for the stones.

The discussant asks for more information about the Crohn's diagnosis, wanting to understand the context of the Crohn's. Her reasoning lays out the illness script for Crohn's and kidney stones. An illness script provides a mental summary of expected features of a disease. Thus, she wants to compare her illness script for Crohn's and subsequent kidney stones with more information about both Crohn's and the kidney disease. She wonders if this could be a presentation of diagnostic momentum (i.e., once someone labels the patient with a diagnosis, we often assume that diagnosis without re-examination).

He was discharged from the armed services 30 years prior to the current admission with a diagnosis of ulcerative colitis. We have no details about this diagnosis. A clinician changed the diagnosis 10 years later to the current Crohn's disease diagnosis based on an episode of diarrhea with abdominal pain, but without gastroenterology evaluation. Ten years after receiving the revised diagnosis, he had a presumed inflammatory bowel disease (IBD) flare treated with mesalamine and prednisone with resolution of his pain. During that admission, an abdominal CT showed thickening of the terminal ileum and proximal colon. A colonoscopy performed 3 years previously found a normal-appearing ileum to 20 cm, a single polyp (< 5 mm) in the ascending colon, and non-specific erythema of the rectum without mucosal edema, friability, or ulceration. These endoscopic findings suggest that the patient did not have active disease. He also had multiple biopsies at that time with no abnormalities on pathology. He reported no additional flares since that admission (1–2 bowel movements per day, no hematochezia/melena, visual changes, arthralgias, or abdominal pain).

Based on this patient's past medical history, the primary diagnosis of Crohn's is questionable. No tissue diagnosis supported the original diagnosis; he had not needed surgery, nor did he have a history of fistulas. The lack of previous surgery, absence of fistulas, and multiple negative biopsies make the diagnosis of Crohn's highly unlikely. His colonoscopy that showed no active endoscopic or histologic pathology further supports our suspicion that he may not have a small bowel disease. Thus, we need further investigation to understand why this man has recurrent kidney stones.

Here, the discussant tries to match the patient's problem representation with her illness script for Crohn's disease. As she does not find a match, she considers Crohn's now a previously presumed diagnosis that is most unlikely and thus requests more data. Implicitly, she invokes diagnostic momentum and wants to investigate alternative possibilities to explain the kidney stones.

On presentation, he was in no acute distress. He has normal conjunctiva and no oral ulcerations, visual field

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deficits, alopecia, or facial rash. His cardiopulmonary exam is unremarkable. He has left-sided flank tenderness but no abdominal pain, tenderness to palpation, or hepatosplenomegaly. Musculoskeletal exam reveals no joint swelling, erythema, or tenderness to palpation. His initial laboratory testing revealed a white blood cell count of 4.6 × 10^9/L, hemoglobin of 15.3 g/dL, platelets of 216 × 10^9/L, BUN of 36 mg/dL with creatinine of 3.5 mg/dL (1.7 mg/dL in 2014), and calcium of 13.4 mg/dL (8.4–10.2 mg/dL) with an albumin of 4.6 g/dL. The remainder of his metabolic panel was normal. On chart review, the calcium level had been mildly elevated for 5 years and previously attributed to drinking 1 gallon of milk each week with no calcium carbonate intake or vitamin D supplementation. No previous lab testing for a cause of hypercalcemia appeared in the chart.

This patient had a worsening of his prior known baseline creatinine and persistently elevated calcium. Hypercalcemia often causes volume contraction by causing a nephrogenic diabetes insipidus. I would first order aggressive intravenous fluids and then recheck the creatinine. Since hypercalcemia does cause kidney stones, I would do an extensive hypercalcemia evaluation. Laboratory testing should include PTH, PTHrp, vitamin D levels (both 25 and 1-25), TSH, and SPEP. I would reassess the history, better quantitate the milk intake, and determine if the patient is also ingesting calcium carbonate.

Now, the discussant focuses on the hypercalcemia as the cause of the kidney stones. Diagnostic momentum no longer dominates her thinking. She now has a new pivot—hypercalcemia, a laboratory finding that has a defined differential diagnosis. Collecting data can help us narrow potential diagnoses that could cause the patient's hypercalcemia. This process involves type II thinking, that is developing a differential diagnosis and working through that differential with careful history, targeted physical examination, and appropriate testing. Knowing that one should engage in this process is the skill and experience of understanding that we need to focus on discovering a diagnosis that is not immediately obvious.

Given his hypercalcemia on the initial metabolic panel, additional lab work was obtained. The patient's parathyroid hormone level was 2.6 pg/mL (range: 15–65 pg/mL), parathyroid hormone-related protein was 17 pmol/L (range: 14–27 pmol/L), thyroid-stimulating hormone was 2.11 mIU/L (within normal limits), serum protein electrophoresis showed no M-spike, vitamin A level was 49 mcg/dL (within normal limits), and 25-hydroxyvitamin D level was 18.6 pg/mL (range 30–100 pg/mL). The patient's 1,25-dihydroxyvitamin D level was 71 pg/mL (range: 18–72 pg/mL).

The parathyroid hormone is low, suggestive of a PTH-independent process. Laboratory testing excludes many causes for the persistent hypercalcemia: multiple myeloma (SPEP results), squamous cell carcinoma (low-normal PTHrP), hyperthyroidism (normal TSH level), increased vitamin D intake (low 25-hydroxyvitamin D), and increased vitamin A intake (normal vitamin A level). The 1-25-dihydroxyvitamin D is high normal suggesting the possibility of increased metabolism of 25-hydroxyvitamin D as seen with some granulomatous diseases. Common granulomatous causes of hypercalcemia include sarcoidosis, tuberculosis, and lymphoma.

Now, the discussant steps through the laboratory testing making sense of each result, and thus excluding many possibilities in her differential diagnosis. Laboratory test interpretation involves understanding the context of the laboratory test. Here, the 1,25-dihydroxyvitamin D level is high normal but should be low in the presence of hypercalcemia. Normal ranges for many tests are developed from patients without disease. Understanding when test results should be low and thus interpreting a high-normal result as likely abnormal given the context demonstrates skilled interpretation.

On imaging, his abdominal CT reveals an 8-mm calculus in the right renal pelvis and a 5-mm non-obstructing right renal calculus. By the second day, the patient no longer had left flank pain and believed he had passed his stone. Reviewing the abdominal CT scan the day after admission, the radiologist notes the calculi and then mentions significant mesenteric adenopathy not previously noted (Fig. 1). Given these findings, we reviewed his previous abdominal CT. On that review, the current radiologist disagreed with the original report of thickening of the terminal ileum and proximal colon. To avoid confirmation bias, we then had the most experienced radiologist in the department review the film without providing history. He also read the previous CT as unremarkable showing no thickening of the terminal ileum or proximal colon. We then reviewed his chest X-ray, which showed bilateral hilar fullness. A review of a chest CT from 4 years previously showed mediastinal adenopathy with a suggestion from radiology to consider sarcoidosis. That image was ordered following a report from the earlier abdominal CT of mediastinal and hilar adenopathy. Further laboratory testing included an angiotensin-converting enzyme (ACE) level of 111 nmol/mL/min (normal less than 40 nmol/mL/min).

A review of the imaging clarifies the diagnostic delay. The inaccurate read of the previous abdominal CT supported the stated diagnosis of Crohn's disease, leading to persistent diagnostic momentum. Despite the chest CT suggesting sarcoidosis, further evaluation did not occur. The original abdominal CT report did not mention the adenopathy. Spending time with the radiologists and reviewing both new and older films clarify our understanding of the likely diagnosis and the reasons for diagnostic delay.

The discussant mentions multiple causes of diagnostic delay. The previous CT read of a thickened terminal ileum presents a classic example of confirmation bias. The request for the CT included a history of diarrhea in a patient with Crohn's disease. Given that background, radiologists look harder for radiological evidence of Crohn's. The clinicians who seemingly ignored the suggestion of sarcoidosis on chest CT likely did so because that suggestion seemed out of context,

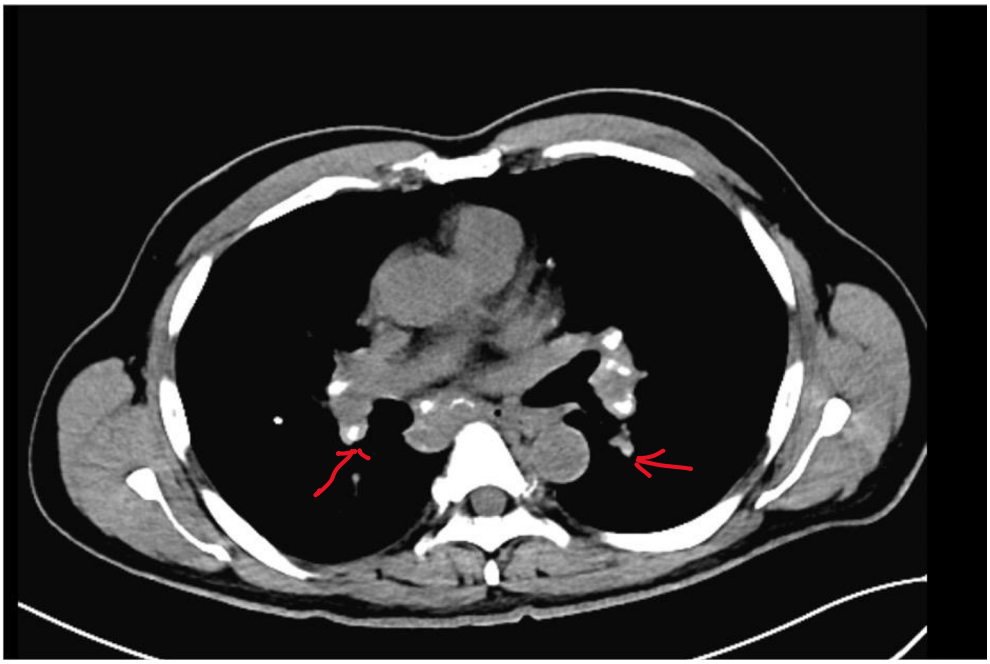

Fig. 1 Abdominal CT scan showing adenopathy.

and they did not consider sarcoidosis as an etiology for abdominal pain because of diagnostic momentum. At that time, there was no clinical suggestion for that diagnosis. This is a common cause of radiologic diagnostic errors, as conversations with clinicians are rare, and the clinical information provided is often scant. This aliquot demonstrates the value of reviewing the patient's images with the radiologist. Conversations with radiologists can help expand or contract the differential diagnosis. Because differentials are often broad in the absence of clinical information, context allows for a more accurate and targeted diagnosis.

Given his high-normal 1,25-dihydroxyvitamin D (with significant hypercalcemia), angiotensin-converting enzyme level, widespread abdominal adenopathy, chest imaging with hilar adenopathy, and lack of any evidence for Crohn's disease, a presumptive diagnosis of sarcoidosis is made. A biopsy of an abdominal nodule revealed non-caseating granulomas consistent with sarcoidosis, adding a pathologic specimen to confirm the new diagnosis.

Abdominal sarcoidosis is uncommon and, thus, an often-unrecognized disease. This patient had lymphadenopathy in the mesentery and hilar adenopathy, which were both previously missed. The markedly increased ACE level while not definitive does increase the diagnostic probability of sarcoidosis. While abdominal sarcoidosis is usually asymptomatic, when it involves the small bowel, it can cause symptoms which occur with luminal narrowing, such as nausea, vomiting, abdominal pain, obstruction, etc. Lymphadenopathy is often asymptomatic unless it begins to cause a mass effect on surrounding organs. Awareness of intra-abdominal sarcoidosis imaging findings would help diagnose unrecognized disease.

The discussant reflects on the difficulty of diagnosing a rare disease until someone questions the presumed diagnosis. When the pivot switched to hypercalcemia, a series of steps led to the clinicians gathering more data and finally focusing on an unsuspected diagnosis. The key factor was the willingness to reject diagnostic momentum and reconsider a long-held diagnosis, as our discussant suggests in the first aliquot.

DISCUSSION

Many physicians have noted that once a patient's health care record includes a chronic disease, subsequent physicians tend to accept that diagnosis (i.e., diagnostic momentum). That tendency probably explains the long diagnostic delay in this patient.

Skepticism about listed diagnoses (or admission diagnoses) leads to reconsidering those diagnoses.[2] The process involves knowing the illness script for the chronic disease and comparing that to the patient's course. Our discussant signaled the importance of diagnostic questioning in the first aliquot.

Klein described the importance of the pre-mortem exam.[3] We can apply this procedure to medical decisions. When physicians consider a diagnosis, they should mentally imagine the clinical implications of using that diagnosis. An incorrect diagnosis can have two potentially negative implications: The patient will likely get treated for the wrong diagnosis, and the proper diagnosis will have a significant delay resulting in possible adverse impact for the patient. Once physicians considered these implications of the presumed diagnosis, they abandoned diagnostic momentum, restarted the diagnostic process, and arrived at the new diagnosis.

There had been several opportunities to discard the diagnosis of Crohn's disease earlier and consider the possibility of a different diagnosis. Having an unremarkable colonoscopy could have stimulated a diagnostic reconsideration. The only evidence for Crohn's was the incorrect reading of an abdominal CT scan that was read as thickening of the ileum during a diarrheal episode. The patient had recurrent kidney stones and hypercalcemia, yet the hypercalcemia was not evaluated, and physicians continued to assign the kidney stone risk to the presumed Crohn's disease. Diagnostic excellence requires reassessment of a proposed diagnosis and asking if missing an alternative diagnosis might have untoward consequences.

When the latest clinicians reconsidered the diagnosis, they reassessed the evidence—no fistula history, no evidence of inflammation, no GI surgeries, and a normal colonoscopy—and concluded that they could no longer trust that diagnosis.

"Trust but verify." Ronald Reagan made this proverb well known after learning it from an advisor, Suzanne Massie. It comes from Russian—*Doveryay, no proveryay*. While the proverb is an oxymoron, it does describe perfectly our responsibility as physicians. In this case, the proverb pertains to the original Crohn's diagnosis, as well as radiology reports that were originally read with limited clinical information provided by the ordering physician and with a prior abdominal pathology previously erroneously assigned.

We sometimes assume that radiology reports are truth. However, the radiology literature is replete with articles about diagnostic errors.[4,5] Again, we have a responsibility to "trust but verify." Working with radiology to review films and adding in the current context of the patient often allow correction of those errors. As internists, we should review images with radiologists to add clinical context and thus decrease biased interpretation. Better interdisciplinary communication between internists and radiologists can improve patient care by facilitating more informed image interpretation. The patient often benefits from these conversations with our radiology colleagues, because we are more likely to reach the correct diagnosis and a more informed reading of the images.

CLINICAL TEACHING POINTS

1. Hypercalcemia deserves evaluation, even when it is modest.[6] An earlier diagnosis of the cause of hypercalcemia can result in treatment that will decrease complications. Physicians sometimes overlook modest elevations of laboratory data. In this patient, even a modest elevation deserved investigation because of the context of recurrent kidney stones.
2. Clinicians should consistently review radiology reports and images. When possible, review the images with a radiologist. Radiologists make the same types of diagnostic errors as internists. Viewing the images as a team, with additional clinical information, can reduce such errors.
3. Sarcoidosis can have varied presentations. While abdominal sarcoidosis is uncommon, in this case, a chest CT suggesting an evaluation for sarcoidosis could have led to an earlier diagnosis.
4. Hypercalciuria occurs in approximately 2/3 of patients with sarcoidosis, with a much lower percentage of patients having hypercalcemia. We should always consider the possibility of sarcoidosis in patients with calcium oxalate kidney stones. Since the hypercalciuria occurs due to increased 1,25-dihydroxyvitamin D, we should specifically test these levels as 25-hydroxyvitamin D levels will usually be decreased.[7]

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