CLINICAL PRACTICE
Clinical Reasoning

The Writing on the Wall: An Exercise in Clinical Reasoning

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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 25 year-old woman with a history of gastroesophageal reflux disease (GERD) presented to her primary care physician with a 2-week history of daily 9/10 right upper quadrant (RUQ) stabbing pain without radiation. The pain started after lifting heavy boxes, was intermittent throughout the day, occurred at rest and with activity, and worsened when running or walking for long distances. She had no relief with naproxen, warm compresses, or massage. She denied fever, nausea, vomiting, diarrhea, weight loss, or anorexia. She had experienced intermittent constipation for 1 year. On exam, the vital signs were normal. She had tenderness in the RUQ, and the pain was reproduced with full forward flexion at the hips. Her physician diagnosed a muscle strain and prescribed tramadol.

Common causes of right upper abdominal pain include cholecystitis, choledocholithiasis, and hepatitis. The lack of fever and time frame renders acute infection less likely. GERD is a conceivable cause of her pain, although the association with activity is not characteristic. The working diagnosis of muscle strain was reasonable given the association with hip flexion, but muscle injuries are usually relieved with analgesics and rest. Constipation causes abdominal discomfort and may be prominent in irritable bowel syndrome (IBS) but can also be a symptom of hypothyroidism or hypercalcemia. However, isolated RUQ pain worsened by movement is not characteristic of constipation. Ectopic pregnancy should be excluded.

The discussant combines regional anatomy in the abdomen and epidemiology to generate a differential diagnosis. The patient's age, pain with mechanical stress, and absence of signs of systemic inflammation dissuade him from examining serious processes including ischemia, obstruction, perforation, or organ-based infection or inflammation, although a few plausible causes from the latter category were mentioned.

The patient returned to see her primary care physician (PCP) 3 months later. During those 3 months, she had chills, nausea, vomiting (2–3 times per day), and drenching night sweats without fevers. The pain remained severe, worsened with movement, and had not improved with daily tramadol. She had an unintentional 15-pound weight loss. She denied dysphagia, odynophagia, heartburn, early satiety, or pain related to meals. There was no hematemesis, melena, hematochezia, diarrhea, vaginal discharge, or suprapubic discomfort. She had not been sexually active for the past 3 years. Her menstrual cycles were irregular since menarche at age 12. Menses would last up to 2 weeks followed by amenorrhea for several months. Her last menses was 4 months earlier.

Medications included omeprazole, naproxen, and tramadol. She smoked 3 cigarettes a day since the age of 18. She had been employed as a retail clerk but had stopped working because of the pain. She lived with her parents in rural southern New Mexico and denied illicit drug or alcohol use. She had no family history of gastrointestinal or autoimmune disease. She had not traveled outside of the state recently.

The complete records from that visit were unavailable but the patient reported marked tenderness in the right upper quadrant during the examination. She was advised to seek care at an emergency department.

The 15-pound weight loss, drenching night sweats, and chills suggest inflammation, which may arise from infection, autoimmunity, or malignancy. Nausea and vomiting point toward a gastrointestinal or hepatobiliary disease rather than a musculoskeletal source of pain. Autoimmune hepatitis could explain her systemic symptoms extending over months. Biliary colic may account for episodic nausea, vomiting, and pain

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but is not accompanied by night sweats or weight loss. Early pregnancy could explain recent menstrual irregularities, abdominal discomfort, weight loss, nausea, and emesis. Subacute infections such as Fitz-Hugh-Curtis syndrome or hepatic abscess are plausible. Malignancies such as leukemia and lymphoma can present with abdominal pain and fevers and are more likely at her age than hepatocellular carcinoma (HCC) or cholangiocarcinoma. Muscle strain is a reasonable explanation for the initial pain from lifting heavy boxes but is an insufficient explanation for the systemic symptoms.

The clinician identifies two elements that substantially lower the probability of muscle wall strain: evidence of inflammation and vomiting. A third factor (although not specifically mentioned) is the mismatch between the illness script for a muscle strain and pain extending over months.

The patient presented to the local emergency department (ED) 2 weeks after the evaluation by her PCP. She was in moderate distress with worsening RUQ discomfort. Vital signs were normal. Her abdomen was non-distended with normal bowel sounds; the patient had central adiposity. There was severe tenderness to light palpation with guarding of the right upper quadrant. There was no jaundice or stigmata of chronic liver disease. Rectal and pelvic exams were normal. Testing for sexually transmitted infections was not performed. A urine pregnancy test was negative.

Each presentation should be evaluated both in isolation and in the context of her subacute illness. NSAID-induced peptic ulcer disease (PUD) may account for her unremitting pain, although her naproxen use began after the RUQ pain; furthermore, marked tenderness and night sweats are discordant with uncomplicated PUD.

The discussant entertains multiple causes of abdominal pain but does not comment on the "severe tenderness to light palpation." Signal detection theory describes how decision-makers determine whether information is meaningful for solving a problem ("signal") or will have no bearing on the solution ("noise").[1] *It is likely that clinicians categorize data points as signal when they match features held in relevant illness scripts or help discriminate among illness scripts. It is possible that the discussant has not articulated a problem representation that includes the superficial tenderness because that finding does not map to a diagnosis in his library of illness scripts, and therefore, he perceives the finding to be "noise." Confirmation bias—only paying attention to data points that fit a pre-existing hypothesis—is a conceivable explanation for overlooking the superficial tenderness but is less likely because the discussant has not elaborated a leading hypothesis yet.*

A complete blood count, metabolic panel, serum cortisol, liver function tests, lipase, urinalysis, and serum pregnancy test were normal. A right upper quadrant ultrasound and a CT scan of the abdomen and pelvis were normal. The patient was treated with intravenous analgesics and anti-emetics and was discharged home. Her daily pain continued.

Six months later, she experienced an acute episode of severe generalized abdominal pain and returned to the local ED. Laboratory tests were normal. CT of the abdomen revealed a 7-cm left ovarian cyst without torsion; the cyst was not seen on the previous CT scan. She underwent a laparoscopic left ovarian cystectomy with diminution of her abdominal discomfort.

One week later, her abdominal pain, nausea, and vomiting recurred. She was hospitalized multiple times thereafter over the next 3 months for RUQ pain with exquisite tenderness, vomiting, and anorexia. She lost an additional 15 pounds (now total 30 pounds). A third CT of the abdomen and pelvis during this time was normal. Her pain, nausea, and vomiting improved with analgesics and anti-emetics, and she was discharged home.

She has had an interval gynecologic condition superimposed on her chronic abdominal pain syndrome; treatment of the former did not mitigate the latter, and the two are unlikely to be related. The left-sided ovarian cyst would not explain the right-sided abdominal pain or the chronic night sweats, weight loss, or vomiting. The exquisite tenderness to light palpation of the RUQ remains unexplained. The normal third CT excludes a complication of ovarian cystectomy, such as small bowel obstruction or post-operative abscess. The immediate improvement in pain after surgery may be related to the effects of anesthesia and analgesics.

The differential diagnosis for her recurrent nausea and vomiting includes cyclic vomiting syndrome (CVS), cannabinoid hyperemesis syndrome (CHS), gastroparesis, inflammatory bowel disease (IBD), IBS, or PUD. CVS usually has asymptomatic interludes, whereas she has been persistently symptomatic for months. She denied cannabinoid use, lacks the bloody diarrhea characteristic of IBD, and has no risk factors (e.g., diabetes) for gastroparesis. Her pain, nausea, and constipation are consistent with IBS, but the night sweats and 30-pound weight loss are incompatible. Chronic intestinal ischemia could explain her pain and weight loss, but arterial insufficiency is rare at her age.

When abdominal pain (with or without vomiting) persists for this duration without an anatomic correlate on imaging, rare conditions like acute intermittent porphyria, familial Mediterranean fever, heavy metal poisoning, and polyarteritis nodosa warrant consideration. Endoscopy and angiography are indicated at this point.

The discussant's consideration of an expanding list of diagnostic possibilities reflects uncertainty regarding the boundary of possible solutions. When a clinician is unaware of plausible solutions, sorting data into signal or noise is difficult. Instead of being able to establish a single problem representation and using that as a filter to strive for diagnostic parsimony, the clinician must resort to taking different combinations of the dataset—recurrent nausea and vomiting, right-sided abdominal pain, night sweats, and weight loss—and lurch from one

candidate diagnosis that explains one subset of the data to another diagnosis that explains a different subset.

Thirteen months after the onset of pain, the patient presented to the local ED again due to pain and was instructed to drive to a tertiary care center for further evaluation. She was tearful and unable to move or eat consistently due to worsening right upper quadrant pain that radiated to her back. She reported ongoing vomiting, persistent night sweats, and chills. Her temperature was 36.1 °C, heart rate 90 bpm, and blood pressure 129/77 mmHg. She had exquisite RUQ tenderness to light palpation with a normal skin exam. The remainder of her physical exam was normal. The leukocyte count was 20,000/mm^3 (77% neutrophils, 13% lymphocytes, 8% monocytes, 1% eosinophils, 1% basophils). Hemoglobin was 16.7 g/dL (12–16 g/dL) and platelets were 369/mm^3 (150–400/mm^3). The mean corpuscular volume was 93 fL (81–101 fL). Cell morphology on the peripheral blood smear was normal. The chemistry panel, liver function tests, lipase, iron, ferritin, international normalized ratio, lactate, urinalysis, and thyroid-stimulating hormone were normal. Her erythrocyte sedimentation rate was 40 mm/h (0–21 mm/h) and C-reactive protein was 13.1 mg/dL (< 0.3 mg/dL). Hepatitis virus serologies were nonreactive. Blood cultures were negative. The antinuclear antibody (ANA) was normal. Pregnancy test was negative.

Electrocardiogram, troponin, and chest X-ray were normal. Abdominal ultrasound showed a normal liver, gallbladder, and common bile duct. Esophagogastroduodenoscopy (EGD) showed mild esophagitis and duodenitis with small superficial duodenal erosions. Endoscopic retrograde cholangiopancreatography, hepatobiliary iminodiacetic acid (HIDA) scan, and colonoscopy were normal. A 1-week trial of amitriptyline for neuropathic pain was ineffective.

There is no evidence for a luminal or hepatobiliary disorder (the mild esophagitis and duodenitis on EGD are unlikely to be responsible for her severe symptoms). The leukocytosis may signal an infection but could be explained by a stress reaction or severe dehydration from nausea and vomiting. The modest elevation in CRP and ESR are not suggestive of systemic inflammation. The elevated hemoglobin likely represents hemoconcentration. The endoscopies, imaging, and peripheral smear render a neoplasm unlikely. Autoimmune hepatitis is improbable given the normal ANA and lack of liver abnormalities on labs or imaging.

Musculoskeletal injury to the lower thoracic or lumbar spine could cause neuropathic pain with radiculopathy, but not the systemic symptoms; furthermore, treatment directed at neuropathic pain was ineffective.

Having reached the bounds of my experience (5 years in practice) and knowledge, I would need to search for additional information to solve this specific problem: a young woman with a history of GERD with 1 year of chronic, intermittent, superficial abdominal pain, persistent emesis, chills, night sweats, leukocytosis, and unintentional weight loss with repeatedly normal abdominal imaging (except for the ovarian cyst).

The discussant continues to consider abdominal pain syndromes that may originate from the abdominal wall, viscera, or nerves. He recognizes the limit of his knowledge and experience. Regardless of whether the discussant turns to colleagues or the literature to help him solve the problem, he recognizes he has to name the problem explicitly, and he does so by articulating a problem representation which characterizes the who, what, and when of this clinical conundrum—Who is this patient? What is the syndrome she has? How long has it been going on?

A review of the medical literature for causes of chronic, superficial abdominal pain was conducted. Candidate diagnoses included slipping rib syndrome (SRS), thoracic nerve radiculopathy, abdominal wall tear, desmoid tumor, and abdominal cutaneous nerve entrapment syndrome (ACNES).

SRS occurs when the medial fibrous connections of the 8th, 9th, or 10th rib become weak and the ribs slip and impinge the intercostal nerve; pain ensues with movement (e.g., bending). Thoracic radiculopathy arises when a disc herniation or degenerative spine disease entraps an abdominal wall intercostal nerve. Abdominal wall tears can develop with strenuous exertion and exacerbate with repetitive abdominal flexing (e.g., in hockey players). Desmoid tumor is a rare superficial connective tissue mass most often seen in young women that causes localized abdominal pain. ACNES arises when a cutaneous abdominal nerve becomes entrapped within the rectus abdominus muscle, commonly by injury, causing intermittent, localized discomfort. Ongoing pain leads to a heightened sensitivity to touch and worsening pain.

Except for radiculopathy, I have never encountered any of these diagnoses (or perhaps I missed them) and I must compare the literature-based descriptions with this patient's presentation.

An abdominal wall tear can develop and progress with repetitive motion over months to years, but in her case, there was only one episode of overexertion when the pain began. Several abdominal examinations and CT scans did not reveal a superficial mass pointing to a desmoid tumor. It is conceivable that a disc herniation from her original lifting episode could have triggered thoracic radiculopathy. SRS is possible, but less likely given that the pain with SRS is mostly associated with movement (e.g., twisting, bending, lifting) and this patient has pain both with and without movement. A nerve entrapment with the original lifting episode may have led to unremitting neuropathic pain from ACNES. None of these diagnoses is characterized by leukocytosis, night sweats, or weight loss however.

Having defined the problem and reviewed the relevant literature search results, the discussant is able to replicate the standard clinical reasoning process step of comparing the problem representation with the candidate illness scripts

which are comprised of textbook knowledge and real-world experience. However, for rare conditions which the clinician has no direct patient care experience with (e.g., SRS), the comparison is limited to the "textbook" description in the literature.

Superficial palpation in the right upper quadrant over the right rectus and oblique musculature reproduced the pain. The patient experienced RUQ discomfort when raising both legs with the knees fully extended (Carnett's sign). Ultrasound-guided bupivacaine and dexamethasone injection delivered subfascially to the aponeurosis of the rectus abdominus led to instantaneous and complete resolution of her pain. Her nausea, vomiting, and night sweats resolved within 1 day of the injection. Her white blood cell count normalized after IV hydration. ACNES was diagnosed. Six months after the injection, she remained pain-free without additional weight loss. She returned to the ED 1 year later with moderate RUQ pain and was discharged without a prescription and has not returned to the pain clinic where she received her original injection.

COMMENTARY

There are two dimensions of uncertainty in medicine—aleatoric uncertainty (due to random variation in biologic and other systems) and epistemic uncertainty (due to the limitations of medical knowledge).[2] That latter arises from the boundaries of existing scientific knowledge or from limitations in the ability of a clinician to possess, access, or process existing scientific knowledge. The discussant navigated epistemic uncertainty throughout the case, using anatomy, epidemiology, and imaging to trigger an extensive library of illness scripts to explain abdominal pain but was unable to find a suitable match.

When a clinician is unable to reach a diagnosis, they may ponder where the answer to the case lies—or if a definitive answer exists at all. Questions they may ask themselves include the following:

(1) Have I reached the limit of my knowledge but not that of my colleagues?
(2) Have I reached the limits of my local network's knowledge but not that of another physician or team elsewhere?
(3) Have I reached the limits of medical knowledge (i.e., there is no known answer to the problem)?

Efficiently searching the medical literature, which is one approach to answering these questions, is challenging. Cook et al. interviewed 50 family medicine and internal medicine physicians to examine barriers to answering questions that arise at the point of care.[3] They found that clinicians must decide whether to search the particular issue, when to search (e.g., before, during, or after the clinical encounter), and what resource to use (e.g., colleague or computer).

The proliferation of information sources (journals, blogs, social media) not only increases the chances of finding an answer but also makes the decision to embark more daunting and makes the endpoint ambiguous. The question of "when to stop" is particularly relevant before concluding that a phenomenon is truly idiopathic or unanswered by medical science. Medical librarians are experts at navigating the literature. In one study, a librarian consultation service provided answers in real time to primary care clinical questions submitted via smartphone.[4]

In this case, search results yielded a diagnosis (ACNES). However, this conclusion shifted the focus to a new issue of epistemic uncertainty: were the weight loss and night sweats part of ACNES, or did they point to an unrelated second process? The literature on ACNES did not suggest the former. One hypothesis is that the severe pain triggered an autonomic response which mediated anorexia, nausea, vomiting (with associated weight loss), and night sweats. This analogical reasoning is based on the association between night sweats and gastrointestinal disorders such as GERD.[5, 6] However, that line of reasoning remains speculative. For now, no one—not even the literature—knows the answer to that question.

TEACHING POINTS

(1) Superficial abdominal pain syndromes should be considered when patients present with severe pain and tenderness upon light palpation.
(2) ACNES arises when myofascial structures entrap or irritate an abdominal cutaneous nerve. Pregnancy, obesity, and surgery may be precipitating factors.
(3) Many patients with ACNES have instantaneous and lasting relief following a trigger point injection with an anesthetic, which is sometimes accompanied by a corticosteroid.[7–9]

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