CLINICAL PRACTICE

*Exercises in Clinical Reasoning***Lessons Learned from a Middle-Aged Man with Testicular Pain: Exercises in Clinical Reasoning**

Brittany Payne, MD, MPH¹, Walter A. Brzezinski, MD², Amanda V. Clark, MD³,
Carlos A. Estrada, MD, MS^{4,5}, and Ryan R. Kraemer, MD^{1,4,5}

¹Tinsley Harrison Internal Medicine Residency Program, University of Alabama at Birmingham, Birmingham, AL, USA; ²Medical University of South Carolina, Charleston, SC, USA; ³Louis Stokes Cleveland VA Medical Center and Case Western Reserve School of Medicine, Cleveland, OH, USA; ⁴Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA; ⁵The University of Alabama at Birmingham, Birmingham, AL, USA.

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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.

CLINICAL INFORMATION

A 53-year-old man presented to the emergency department with progressively worsening bilateral testicular pain for 1 month. The pain was diffuse, sharp, and 10/10 in severity. It was associated with intermittent mid-to-lower abdominal pain, and was aggravated by food. There were no known alleviating factors.

The differential diagnosis for testicular pain is vast and includes malignant, infectious, vascular, and traumatic causes. The anatomic distribution is important, and etiologies that explain bilateral testicular pain are often different from those causing unilateral pain. Accordingly, the length of time helps to narrow the differential diagnosis, making systemic etiologies more common than traumatic causes. Testicular pain with associated abdominal symptoms causes one to question whether the abdominal pain is a referred symptom or whether there is a unique ongoing abdominal process.

Clinicians begin to formulate a differential diagnosis upon hearing the chief complaint, which gives a “first impression” and is one of the most important parts of the history. To formulate their differential, clinicians often begin with common causes of the chief complaint, as well as large categories of disease. With additional history, the clinician

begins to identify specific features of the symptom (bilateral vs. unilateral, 1 month vs. 1 week) that allow narrowing of the differential. Common causes of testicular pain include trauma, epididymitis, and testicular torsion, but notice that the clinician does not mention epididymitis or testicular torsion, since these diagnoses are usually unilateral and more acute in nature. He initially includes trauma on his differential, but recognizes that the length of time does not fit with a typical testicular trauma. Recognizing which features in the patient’s history do not fit a diagnosis is an integral part of the clinical reasoning process.

Upon review of systems, the patient described subjective fevers, chills, night sweats, 5-lb unintentional weight loss, lower extremity numbness and swelling, anorexia, bilateral joint pain, hand pain, and diffuse muscle aches. He denied dysuria, hematuria, trauma, penile discharge, melena, nausea, vomiting, chest pain, and dyspnea. He was previously diagnosed with bipolar disorder and hepatitis C virus infection. He had not undergone any surgeries. His family history consisted of diabetes mellitus, hypertension, and unknown psychiatric disorders. He had recently received a course of levofloxacin for presumed orchitis from a local urgent care center, without relief of his symptoms.

Constitutional symptoms, also known as B symptoms, include fever, drenching night sweats, and unintentional weight loss. These symptoms have diagnostic importance, as they may herald advanced, systemic disease rather than a local process. In particular, B systems are common with certain malignancies (e.g. Hodgkin’s lymphoma) and non-malignant conditions such as infectious (classically tuberculosis) and various inflammatory disorders.

The lack of response to oral antibiotics indicates either that he has an infection not sensitive to the particular oral antibiotic administered (e.g. quinolone-resistant bacterial infection or a fungal infection) or that he does not have infectious orchitis at all. Also, infectious orchitis alone would not account for many of his other symptoms such as lower extremity numbness and swelling, anorexia, bilateral joint pain, hand pain, and diffuse muscle aches.

The clinician avoids the cognitive heuristic of diagnostic momentum by questioning the accuracy of the previous diagnosis of orchitis. Diagnostic momentum occurs when a

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previous diagnosis is accepted and carried on without question;¹ in this case, the patient had a previous diagnosis of orchitis. Clinicians must be aware that incorrect diagnostic labels are often carried on without question, especially in the electronic medical record. In this case, the clinician recognizes that infectious orchitis should respond to levofloxacin, so either the patient does not have infectious orchitis, or he has infectious orchitis caused by a more unusual organism.

He lived in a friend's home and was unemployed. He smoked marijuana and tobacco. He had been intermittently imprisoned for the past 20 years, with his most recent release about 6 months prior to presentation. He had a history of intravenous drug use and alcohol abuse, with his last use about 10 years earlier. He denied recent sexual activity.

Certain chronic health conditions, such as mental health and substance abuse problems, are more common in the penal system than in the community. Persons incarcerated within the federal system are more likely to suffer from HIV, for instance, where the risk of infection is as much as five times that in the general population. His history of intravenous drug use also places him at increased risk for HIV as well as other blood-borne infections such as hepatitis B.

Our patient has subacute onset of numerous systemic symptoms that make one disease process most likely; however, if he had an immunocompromising condition (such as HIV), he could have multiple diagnoses.

The clinician still has three large categories of diseases on his differential—infectious, malignant, and inflammatory—but begins to question whether one or multiple diseases are to blame. Occam's razor—also called diagnostic parsimony—is a problem-solving principle that encourages one to find the least number of diseases to explain the constellation of symptoms. The counterargument to Occam's Razor is called Hickam's dictum, which states that “patients can have as many diseases as they damn well please,” and affirms that oftentimes multiple disease processes are present to explain the entire clinical picture.² At some point during every presentation with multiple complaints or findings, physicians must ask themselves whether there is one unifying diagnosis or whether there could be multiple disease processes present.

The patient's physical examination showed a temperature of 98.4 °F, blood pressure of 134/71 mmHg, heart rate of 90 beats per min, and respiratory rate of 18 breaths per min. He was in distress due to pain. He had no lymphadenopathy. His abdominal exam revealed positive bowel sounds and diffuse tenderness to deep palpation, but was non-distended, without rebound or guarding. He had no hepatosplenomegaly. His extremities displayed a full range of motion upon flexion and extension. He had normal muscle tone and bulk. There were no bony joint deformities, swelling, or tenderness. His lower extremities showed 1+ pitting edema to the knees. His genitourinary exam showed bilateral varicoceles, an uncircumcised phallus, and severe diffuse tenderness upon palpation of both testicles. The pain was unrelieved with lifting the testicles. The right testicle was abnormal, with irregular consistency.

A varicocele is an abnormal swelling or enlargement of the venous system that drains the scrotum. The left testis is more

likely to have idiopathic varicoceles, as the left testicular vein connects directly to the renal vein, causing increased venous pressure (while the right testicular vein drains directly into the inferior vena cava). The swelling in the lower extremities, in conjunction with the bilateral varicoceles, points towards a dysfunction or obstruction in the venous system, whether physiologic or structural. Portal hypertension from cirrhosis, among volume overload states, may lead to increased swelling in the genital area and peripheral edema.

Initial laboratory values included sodium 135 mmol/L, potassium 4.0 mmol/L, chloride 99 mmol/L, bicarbonate 28 mmol/L, blood urea nitrogen 17 mg/dL, creatinine 1.0 mg/dL, white blood count 12 cells/cm, hemoglobin 13 g/dL, platelets 164,000/cm, total protein 8.6 g/dL, albumin 3.0 g/dL, total bilirubin 0.7 mg/dL, aspartate aminotransferase 64/L, alanine amino transferase 50/L, alkaline phosphatase 135/L, prothrombin 14.5 s, and activated partial thromboplastin 30 s. Amylase, lipase, and lactic acid were within normal limits. Urinalysis was within normal limits.

The most striking feature of the laboratory data is the globulin gap, also known as the paraprotein gap. In this patient, the difference between the total serum protein concentration and the serum albumin concentration is greater than 5.5 g/dL. This paraprotein gap is caused by excess elevation of non-albumin serum proteins, which can be either polyclonal or monoclonal. This patient has hepatitis C, which can cause a polyclonal gammopathy and may help explain this laboratory finding. Alternatively, there could be a monoclonal cause such as a hematological dyscrasia, multiple myeloma, or monoclonal gammopathy of unknown significance. Serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) would be helpful for differentiating between a monoclonal and polyclonal gammopathy.

At this point, the patient has a large number of symptoms, physical exam findings, and laboratory anomalies. The cognitive load for the clinician (the total amount of mental effort being used in the working memory) is quite high.³ This places the clinician at risk of making a clinical reasoning error by losing track of some of the “pieces to the puzzle” as he reasons through the case.

One technique for reducing the effects of high cognitive load is the problem representation. A problem representation is a construct that summarizes the key features of the presentation, findings, and context utilizing semantic qualifiers—opposing, abstract descriptive terms that can be used to compare and contrast clinical presentations (e.g., acute vs. chronic, diffuse vs. localized, mild vs. severe).⁴ For this patient, the problem representation could be: “A middle-aged man with a history of bipolar disorder, hepatitis C, and IV drug use presents with subacute B symptoms, diffuse abdominal pain, lower extremity numbness/swelling, musculoskeletal pain, and bilateral varicoceles with significant testicular pain and an elevated protein gap.” By stepping back and summarizing the case, and thinking in terms of semantic qualifiers, clinicians may be able to improve their diagnostic reasoning.⁴

A testicular ultrasound revealed bilateral varicoceles as well as three well-circumscribed lesions on the right

testicle (Fig. 1). The lesions contained small amounts of calcifications. The left testicle on ultrasound was normal. Computed tomographic angiography of the abdomen and pelvis (Fig. 2) revealed multiple hypoattenuating lesions in the pancreas (tail, body) and spleen. The kidneys had multiple linear and wedge-shaped lesions. Multiple small, non-pathologically enhancing lymph nodes were also noted.

Additional studies revealed C-reactive protein 74 mg/L, erythrocyte sedimentation rate 100 mm/h, and low complement levels. The HIV 1 and 2 antibodies, urine chlamydia and gonorrhea, serum beta-human chorionic gonadotropin, and alpha fetoprotein studies were within normal limits. However, hepatitis BsAg, anti-hepatitis Bc IgM, and anti-hepatitis C antibody serology test results were positive.

Given the ultrasound results, the suspicion of malignancy as the underlying diagnosis is now even greater. However, primary testicular cancer is a relatively uncommon disease. While it can occur at any age, it is most commonly seen in younger males, aged 15–35 years old. In men over the age of 50 years, testicular masses are usually not caused by primary testicular cancer. Lymphoma would be more likely, especially given the above stated B symptoms. We must also consider metastatic cancer involving the testis. In this case, the best avenue for diagnosis is surgical, either testicular biopsy or unilateral right-sided orchiectomy.

At this point, the clinician reasons that the testicular lesions are likely a result of malignancy. He abandons infectious and inflammatory causes and begins to speculate on the type of malignancy that the patient may have. He has fallen prey to a common cognitive bias known as the “anchoring” heuristic. Anchoring occurs in the diagnostic process when a clinician “zones in” on a single feature of the presentation, sometimes ignoring other information.⁵ Anchoring can lead a clinician down the wrong diagnostic path. Here, the clinician zones in on the lesions in the left testicle, pancreas, and spleen. He narrows his differential diagnosis to the category of malignancy, and does not account for several findings including low complement levels, new diagnosis of hepatitis B, and wedge-shaped kidney lesions (a sign of vascular involvement with infarction). It is likely that the high cognitive load has caused the clinician to lose track of these “pieces to the puzzle.” Perhaps cognitive debiasing approaches such as revising the problem representation, a diagnostic time

out, or a diagnostic checklist could have helped him avoid this error.⁶

The clinician does recognize, however, that the next most important step is a testicular biopsy. In the workup of complex patient presentations, there is often significant diagnostic uncertainty. Clinicians must decide which test is most likely to generate the diagnosis while causing the least risk of harm to the patient. Knowledge of the performance characteristics of various diagnostic testing modalities, in addition to consideration of many patient and contextual factors, plays a role in this important decision. Expert clinicians are adept at determining the most effective diagnostic study, which can often be more important than determining the correct diagnosis based on history and physical exam alone.

The patient underwent a right orchiectomy 2 days after admission; the testicle measured 4.5 × 4.0 × 2.5 cm. The pathologic exam revealed multifocal, segmental testicular infarctions and ischemic changes in small and medium-sized arteries (Fig. 3). Upon magnification, perivascular necrotizing inflammation with fibrinoid necrosis and pleomorphic cell infiltration without granuloma formation was visualized. The surgical specimen confirmed the final diagnosis. Given the presence of hepatitis B, testicular vasculitis, and multiple organ involvement, the final diagnosis of polyarteritis nodosa (PAN) was established.

In the postoperative period, medicine, rheumatology, and infectious diseases services were consulted. The patient underwent plasmapheresis (five cycles) and received methylprednisolone and tenofovir for treatment of hepatitis B. His clinical status improved, and he was discharged home on prednisone and tenofovir.

DISCUSSION

Clinicians complete a number of clinical reasoning tasks in the course of evaluating patients and making diagnoses. Goldszmidt et al.⁷ recently compiled a list of 24 clinical reasoning tasks during clinical encounters derived from 27 international experts in clinical reasoning. In this exercise in clinical reasoning, our clinician was faced with a complex patient presenting with a rare diagnosis. He completed many clinical reasoning tasks, including identifying active issues (testicular pain, B symptoms, lower extremity numbness, etc.), considering alternative diagnoses (his differential included three main categories of disease: malignant, infectious, inflammatory), determining the most likely diagnosis (he decided on malignancy after the ultrasound showed the testicular masses), and selecting a diagnostic investigation (testicular biopsy). Despite the wrong diagnosis leading his differential, he correctly identified the appropriate next diagnostic step, a biopsy of an affected organ, which ultimately led to the correct diagnosis of PAN. After the final diagnosis was revealed, our clinician could complete two additional clinical reasoning tasks: (1) identifying knowledge gaps and establishing a personal learning plan; and (2) considering cognitive and personal biases that may influence reasoning.⁷

Self-reflection and identifying personal learning needs has long been considered an important component of building expertise.⁸

Fig. 1 Testicular ultrasound. Right, demonstrates three solid lesions (arrows point to two).

Fig. 2 Computed tomography angiography of the abdomen and pelvis. **Panel A:** Bilateral kidney multiple wedge-shaped hypodense areas. **Panel B:** Multiple hypoattenuating lesions on spleen and body/tail of pancreas (arrows).

Our clinician could reflect on the diagnosis of PAN and seek to understand why it was not on his differential for this patient. Perhaps the clinician's illness script for PAN was incomplete. For instance, it may not have included neuropathy or testicular lesions/pain (present in only 20 % of PAN cases). In this case, the clinician could review the features of PAN to expand his illness script for the disease. Alternatively, the clinician may realize that his illness script for PAN was relatively complete, but that he did not connect his illness script with the patient's presentation. In this case, the clinician could reflect upon his clinical reasoning. Upon reflection, our clinician may find that once he recognized that the cognitive load of the case was high, he could have perhaps taken a diagnostic time out.⁹ During this time out, he could have asked himself several questions, including: "What might this be other than malignancy?" and "What features of the case can I not explain from a diagnosis of malignancy?" He could consider listing all of the patient's symptoms/findings or forming a problem

representation to bring to mind an alternative diagnosis. Stepping back and reflecting on the plausibility of a working diagnosis is an important tool for managing the cognitive load of complex cases and avoiding diagnostic error.⁹ In fact, knowing when to slow down has been associated with expert decision making.¹⁰ Through self-reflection on both made and missed diagnoses, clinicians can sharpen this vital skill.

After identifying a cognitive error, our clinician could seek a strategy for avoiding this error in the future. Numerous interventions for reducing diagnostic error have been proposed.¹¹ Perhaps the clinician would benefit from reviewing the cognitive debiasing strategies proposed by Croskerry⁶ or Trowbridge's "Twelve tips for teaching avoidance of diagnostic error."¹² Through regular self-reflection and familiarity with interventions for reducing common diagnostic errors, clinicians can aim to increase their diagnostic accuracy and minimize future diagnostic pitfalls.

Fig. 3 Testicular pathologic exam. Multifocal testicular infarctions and ischemic changes in medium-sized arteries. Perivascular necrotizing inflammation with fibrinoid necrosis and pleomorphic cell infiltration. **Panel A:** Area of infarction with associated ischemic changes in a testicular artery (arrow). **Panel B:** Magnified view of panel A, further emphasizing the perivascular necrotizing inflammation and pleomorphic cell infiltration.

CLINICAL TEACHING POINTS

1. The most common causes of scrotal pain include testicular torsion, epididymitis, orchitis, malignancy, trauma, and inguinal hernia. Vasculitis is a rare etiology for testicular pain.
2. Polyarteritis nodosa (PAN) is a rare type of inflammatory vasculitis affecting medium-sized vessels, causing segmental necrotizing lesions that lead to blood vessel aneurysms and tissue ischemia with infarctions.¹³ PAN is most often idiopathic, but has been associated with active hepatitis B, hepatitis C, or both. A diagnosis of PAN should be initially suspected based on a combination of characteristic symptoms, physical exam findings, and compatible laboratory tests; however, there is no diagnostic laboratory test for PAN. Manifestations of PAN may include malaise/weight loss, neuropathy, arthralgia/myalgia, renal disease, new-onset hypertension, gastrointestinal symptoms, testicular symptoms (unilateral or bilateral), and various cutaneous manifestations (including livedo reticularis). Many of these findings are included in the American College of Rheumatology classification criteria, which can serve as a guide for clinicians but were not intended for diagnostic purposes.¹³
3. Given the potential morbidity associated with PAN treatment, the diagnosis should be confirmed prior to starting treatment. Biopsy of an affected organ is the preferred method. In cases where biopsy is not possible or would be associated with substantial risk of morbidity, imaging (angiography showing typical aneurysms) can serve as an alternative means to confirm the diagnosis.¹⁴
4. Treatment for PAN is dependent on severity and underlying etiology. In cases where the etiology is idiopathic, steroids are often the cornerstone of therapy for mild disease. Additionally, immunosuppressant agents such as cyclophosphamide are added for moderate to severe disease.¹⁴ In cases associated with hepatitis B, the most effective treatment involves combined therapy with corticosteroids, antiretrovirals, and plasmapheresis.¹⁵

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Corresponding Author: Ryan R. Kraemer, MD; The University of Alabama at Birmingham, 734 Faculty Office Tower, 510 20th Street South, Birmingham, AL 35294-3407, USA (e-mail: rkraemer@uabmc.edu).

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