CLINICAL PRACTICE

*Exercise in Clinical Reasoning***When the Past Informs the Present:
An Exercise in Clinical Reasoning**

Reza Manesh, MD¹, Rabih M. Geha, MD^{2,3}, Gurpreet Dhaliwal, MD^{2,3}, Joseph Heng, MD¹,
Lois J. Arend, MD, PhD⁴, Derek M. Fine, MD⁵, and Allan C. Gelber, MD⁶

¹Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ²Medical Service, San Francisco Veterans Affairs Hospital, San Francisco, CA, USA; ³Department of Medicine, University of California San Francisco, San Francisco, CA, USA; ⁴Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁵Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁶Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

J Gen Intern Med 35(3):922–7

DOI: 10.1007/s11606-019-05491-9

© Society of General Internal Medicine 2019

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 24-year-old man presented to the emergency department (ED) with 2 weeks of left-sided flank pain. One week before admission, he developed fevers, chills, and a productive cough. He did not have dyspnea, chest pain, hemoptysis, gross hematuria, or dysuria.

Genitourinary (e.g., nephrolithiasis) and musculoskeletal disorders (e.g., intercostal muscle strain) often account for flank pain. Occasionally, the character of the discomfort may suggest a thoracic radiculopathy, as may arise from herpes zoster. Left-sided flank pain may reflect splenic infarction or congestion. The development of fevers and cough with left flank pain could point to a lower lobe pneumonia. Life-threatening causes of flank pain include rupture of an abdominal aortic aneurysm and adrenal hemorrhage, but the 2-week time course is inconsistent with these diagnoses.

Two years prior, he presented with right facial droop, right arm and leg weakness, and expressive aphasia. A left middle cerebral artery stroke, right lower extremity deep venous thrombosis (DVT), right subsegmental pulmonary embolism, thrombocytopenia, and microangiopathic hemolysis were identified. An ADAMTS13 (a metalloproteinase which cleaves von Willebrand multimers into shorter strands) activity level of 9% (normal, 70–150) confirmed the diagnosis

of thrombotic thrombocytopenic purpura (TTP). He improved with plasmapheresis, glucocorticoids, and anticoagulation but had mild residual right-sided weakness. Anticoagulation was discontinued after 6 months; he remained on levetiracetam for seizure prophylaxis. There was no family history of hematologic or autoimmune conditions. He did not use illicit drugs, alcohol, or tobacco.

The combination of microangiopathic hemolysis, thrombocytopenia, and thrombosis is sufficient to initiate treatment for TTP. Improvement with plasma exchange and glucocorticoids supports the diagnosis of TTP; a reduced ADAMTS13 activity level is confirmatory. Triggers are identified in half of cases and include infections (e.g., human immunodeficiency virus [HIV]), autoimmune disease (e.g., systemic lupus erythematosus [SLE]), and pregnancy. These conditions may accentuate a previously subclinical deficiency of ADAMTS13 by increasing von Willebrand factor levels. A recurrence of TTP with visceral thrombosis could account for his flank pain (e.g., splenic infarct, renal vein thrombosis). Alternatively, an underlying precipitant for the original episode of TTP, such as undiagnosed HIV or SLE, could be responsible for the current presentation.

Verifying past diagnoses is important to avoid propagating a diagnostic error. In this case, the match between the clinical features, diagnostic testing, and response to treatment is sufficient to verify the previous diagnosis of TTP. The discussant's review of TTP's clinical features and pathophysiology prompts him to consider whether the current illness is a recurrence of TTP, a reflection of an underlying precipitant (previously undiagnosed) of TTP, or a mechanistically related phenomenon (a new autoimmune or thrombotic disease.)

His temperature was 38.1°C, heart rate 91 beats per minute (bpm), blood pressure 143/86 mmHg, and respiratory rate 18 with an oxygen saturation of 97% while breathing room air. He appeared comfortable. Jugular

Received February 22, 2019

Revised September 3, 2019

Accepted October 4, 2019

Published online December 17, 2019

venous pressure (JVP) was normal. His cardiac exam was normal. There were no stigmata of cirrhosis. He had crackles in the left lung base and mild pitting edema to the mid-shins. There was no costovertebral angle tenderness or rash. The abdomen was soft and nontender with no hepatosplenomegaly. He had unchanged mild right-sided upper and lower extremity weakness.

Cardiac, hepatic, and renal diseases account for the majority of systemic causes of bilateral lower extremity edema. The absence of signs of cardiac dysfunction (e.g., elevated JVP) or liver disease (e.g., ascites, jaundice) heightens the likelihood of a nephrogenic cause, which usually lacks unique physical exam findings. Inferior vena cava thrombosis is a rare cause of lower extremity edema, but is plausible in a patient with a history of DVT. Venous stasis is uncommon in this age group but may have developed as a sequela of his prior venous thrombosis.

Fever, cough, and crackles are suggestive of pneumonia although the duration of symptoms raises the possibility of an indolent infection (e.g., tuberculosis) or an inflammatory pulmonary syndrome (e.g., cryptogenic organizing pneumonia).

The absence of signs implicating the heart or liver along with the patient's history of hypercoagulability prompts the discussant to consider less common causes of bilateral edema. Spontaneous inferior vena cava thrombosis or bilateral venous insufficiency could only be justifiably entertained in a 24-year-old because of his history of extensive thromboembolic disease.

The white cell count was 4400 per cubic millimeter, with 68% neutrophils and 17% lymphocytes, hemoglobin 10.7 g/dL, mean corpuscular volume 78 fL, and platelet count 268,000 per cubic millimeter. Peripheral blood smear showed neutrophils with toxic granulations and microcytic erythrocytes without fragmentation. Serum ferritin was 426 ng/mL (normal, 30–400). The creatinine was 2.9 mg/dL (baseline, 1.1). The aspartate aminotransferase was 41 U/L (normal, 0–37), alanine aminotransferase 41 U/L (normal, 0–40), total bilirubin 0.4 mg/dL, alkaline phosphatase 178 U/L (normal, 30–120), albumin 2.5 g/dL (normal, 3.5–5.3), total protein 6.6 g/dL, creatine kinase 558 U/L (normal, 24–195), and lactate dehydrogenase (LDH) 228 U/L (normal, 118–273). The total cholesterol was 146 mg/dL (normal, < 200).

Prothrombin time, international normalized ratio, and activated partial thromboplastin time were normal. Respiratory virus panel was negative. Urinalysis revealed 3+ protein and 2 red blood cells (RBC) and 27 white blood cells (WBC) per high-power field. The spot urine protein-to-creatinine ratio was 4 (normal, 0–0.19).

Chest x-ray demonstrated opacification of the left lower lung and large left pleural effusion (Fig. 1a). Computed tomography scan of the chest without contrast demonstrated consolidation in the left upper and lower lobes with

air bronchograms (Fig. 1b) and mild splenomegaly in the caudal images.

Marked proteinuria, hypoalbuminemia, hyperlipidemia, and edema constitute the nephrotic syndrome. Primary kidney diseases that cause nephrotic syndrome in adults include focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease. Secondary causes of nephrotic syndrome include infections (e.g., HIV), autoimmune diseases (e.g., SLE), malignancies (e.g., colon cancer), drugs (e.g., nonsteroidal anti-inflammatory drugs), and amyloidosis. Although diabetic nephropathy frequently causes nephrotic range proteinuria (i.e., protein excretion > 3.5 g over 24 h), nephrotic syndrome is seen in a minority of these patients.

Nephrotic syndrome is often associated with normal glomerular filtration, particularly early in its course. Thus, causes of acute kidney injury (AKI), such as acute tubular injury from sepsis, should be considered in parallel with causes of nephrotic syndrome. Pyuria and a low-grade fever may reflect a urinary tract infection or interstitial nephritis (e.g., HIV-associated nephropathy). A renal biopsy could elucidate the causes of nephrotic syndrome and AKI.

The fever, cough, toxic granulations, and alveolar consolidation are sufficient to preliminarily diagnose bacterial pneumonia and initiate antimicrobial therapy, even though other causes of pneumonitis (e.g., diffuse alveolar hemorrhage) remain under consideration. Renal immunoglobulin and antithrombin III wasting in nephrotic syndrome may render him immunocompromised and hypercoagulable, respectively. Consolidation in the upper lobes raises the possibility of tuberculosis, which may also disseminate to the kidneys. Hypercoagulability may lead to pulmonary embolism. A renal vein thrombosis with a large clot burden may contribute to AKI.

Concurrent pulmonary and kidney disease commonly arises from pre-renal AKI from decreased oral intake in the setting of pneumonia, or pulmonary edema from AKI-mediated hypervolemia. A pulmonary-renal syndrome such as anti-neutrophil cytoplasmic antibody-associated vasculitis and anti-glomerular basement membrane (GBM) disease (Goodpasture's syndrome) may also result in concomitant lung and kidney injury.

The fever, productive cough, flank pain, and multilobar consolidation can be explained by a bacterial pneumonia. However, acute kidney injury and history of TTP (an autoimmune illness) prompt the discussant to also consider rare disorders such as pulmonary-renal syndromes.

He was treated with ceftriaxone and azithromycin for community-acquired pneumonia. The fever, flank pain, and cough improved. Creatinine decreased to 2 mg/dL following intravenous hydration. Twenty-four-hour urine protein was 10,176 mg (normal, 0–100). A renal biopsy was performed. He was discharged with a renal clinic appointment in 5 days.

Figure 1 (a) Chest x-ray demonstrates opacification of left lower lung. There is a large left pleural effusion. The left hemidiaphragm and left heart border are obscured. (b) Computed tomography scan of the chest without contrast demonstrates consolidation in the upper and lower left lobes, left hemidiaphragmatic elevation, and pleural effusion.

Two days later, he returned to the ED with cough, fever, and dyspnea. Blood and sputum cultures from the previous hospitalization were sterile. Temperature was 39.2°C, heart rate 132 bpm, blood pressure 160/82 mmHg, respiratory rate 22 breaths per minute, and oxygen saturation 95% on 2 L of oxygen. He was using accessory muscles to breathe. Breath sounds were diminished in the left lower base. Aside from tachycardia, his cardiovascular exam was normal.

Hemoglobin was 10.4 g/dL, white cell count 14,700 per cubic millimeter with 83% neutrophils and 10% lymphocytes, and platelet count 359,000 per cubic millimeter. Serum creatinine was 2.4 mg/dL, erythrocyte sedimentation rate (ESR) 114 mm/h, C-reactive protein 17 mg/dL (normal, < 0.5), troponin I 0.06 ng/mL (normal, < 0.04), and LDH 353 U/L. HIV antibody was nonreactive as were hepatitis C antibody and hepatitis B surface antigen. Peripheral blood smear revealed reactive leukocytosis and no schistocytes.

CT scan of the chest, abdomen, and pelvis without contrast demonstrated interval development of patchy consolidations in left upper and right lower lobes, increased left pleural effusion with total left lower lobe collapse, and partial left upper lobe collapse, and a small right pleural effusion.

The recurrent symptoms, new right lower lobe infiltrate, and enlarging left-sided pleural effusion suggest incomplete treatment or recurrence of the pleuropulmonary inflammatory process; whether it is infectious remains uncertain. Oropharyngeal aspiration, immunodeficiency, and impaired mucociliary clearance (e.g., chronic bronchitis or obstructing mass) are common causes of recurrent or refractory pulmonary infections. Given that the cough, fever, and pulmonary infiltrates have not resolved with antimicrobial therapy, pulmonary hemorrhage or pneumonitis due to SLE or other pulmonary-renal syndromes (ANCA-mediated or GBM-mediated) continue to warrant consideration.

Tachycardia and acute kidney injury are likely contributors to the minimally elevated troponin, but a new pulmonary embolism merits consideration owing to the history of a prior pulmonary embolism and the pleural effusion. The combination of anemia, AKI, and LDH elevation prompts consideration of recurrent TTP, but the lack of schistocytes on peripheral blood smear and a normal platelet count exclude a microangiopathic hemolytic anemia.

Signal detection theory describes how decision-makers determine whether a data point is relevant (“signal”) or unrelated (“noise”) to the final solution.¹ The trivial troponin elevation is suspected to be noise, but the history of a thrombotic tendency prompts the clinician to consider if it is signal (for pulmonary embolism). Similarly, elevated LDH is likely an epiphenomenon of the lung injury, but the history of TTP triggers the discussant to consider if it is signal, i.e., reflecting a recurrence of TTP-related hemolysis. To help determine whether an abnormal finding is signal or noise, other aspects of the patient’s course must be considered. In this case, the lack of schistocytes and normal platelet count led the discussant to exclude TTP and interpret the LDH as noise, despite the accompanying anemia.

Further exploration of the medical history identified no prior or current alopecia, rash, pericarditis, arthritis, or mucosal ulcers. ANA titer was $\geq 1:640$ (speckled pattern). C3 and C4 complement levels were normal. Rheumatoid factor, anti-double-stranded DNA antibody, and anti-mitochondrial antibody were negative. Anti-ribonucleoprotein (RNP) and anti-Smith antibodies were negative (without further quantification in the hospital laboratory). Renal biopsy demonstrated a focal proliferative glomerulonephritis (GN) with endocapillary and extracapillary proliferation, fibrinoid necrosis, and fibrin thrombi. There was concomitant histologic evidence of membranous glomerulonephritis. Immunofluorescence microscopy revealed immune deposits along capillary walls and in the

mesangium and focal granular tubular basement membrane staining (Fig. 2). Electron microscopy demonstrated subepithelial electron-dense, deposits characteristic of membranous nephropathy.

The high titer ANA, positive anti-Smith antibody, and concomitant proliferative GN and membranous nephropathy are diagnostic of SLE; RNP seropositivity is also characteristic of SLE. Autoimmune serositis is the likely cause of the pleural effusions. Pulmonary parenchymal involvement in SLE may reflect diffuse alveolar hemorrhage or an acute interstitial pneumonitis. The possibility of a superimposed bacterial infection warrants empiric antibiotics, bronchoscopy or thoracentesis for microbiologic samples, and close monitoring following initiation of immunosuppressive therapy. SLE is a risk factor for thromboembolism, so pulmonary embolism remains an important consideration.

Intravenous vancomycin, cefepime, and azithromycin were administered. A chest tube drained bloody pleural fluid which had 85,000 RBC per cubic millimeter (normal, 0–99) and 1094 WBC per cubic millimeter (normal, 0–499) with a lymphocytic predominance, pH 7.41, glucose 99 mg/dL, LDH 751 U/L, and protein 4 g/dL. The serum protein was 5.9 g/dL. Multiple sputum stains were negative for acid-fast bacilli. He continued to have fever, dyspnea, and hypoxemia.

The pleural fluid-to-serum ratios of LDH and protein are consistent with an exudative pleural effusion. The lymphocytic predominance, normal pH, negative Gram stain, and normal

glucose exclude empyema, although an uncomplicated parapneumonic effusion is plausible. Malignancy is the most common cause of an atraumatic bloody pleural effusion, but a cancer was not evident on chest and abdominal imaging. A pulmonary embolism would account for his symptoms and bloody pleural effusion. Antiphospholipid syndrome is the most common thrombotic condition linked to SLE.

CT scan with contrast revealed segmental pulmonary emboli in the right middle and lower lobe, persistent patchy consolidation involving both lungs with an increase in the right lower lobe consolidation, decreased left pleural effusion, and occlusive thrombosis of the left renal vein with edema of the left kidney (Fig. 3). Lupus anticoagulant, beta-2 glycoprotein antibody, and anticardiolipin antibody were negative.

The fever, pulmonary infiltrates, exudative pleural effusion, pulmonary and renal vein thromboses, and histologic evidence of active glomerulonephritis are all compatible with a new diagnosis of systemic lupus erythematosus. In hindsight, the precipitant for the episode of TTP 2 years earlier may have been unrecognized SLE. Initiation of immunosuppressive therapy is imperative.

He was treated with heparin, prednisone, mycophenolate mofetil, and hydroxychloroquine. After diminution in pleural fluid output, the chest tube was removed. Because a large occlusive renal vein thrombosis may induce renal engorgement and cause AKI, the interventional radiology

Figure 2 (a) Hematoxylin and eosin stain demonstrates mild endocapillary proliferation, segmental fibrinoid necrosis, and a fibrin thrombus (arrows). (b) Silver stain shows irregularities in the glomerular basement membranes including holes and occasional spikes. (c) Pronounced IgG immunofluorescence staining along capillary walls and in the mesangium is demonstrated. (d) Electron microscopy demonstrates subepithelial, intramembranous, and subendothelial electron-dense deposits and endothelial tubuloreticular inclusions.

Figure 3 Computed tomography with contrast demonstrates right segmental pulmonary embolism in the right middle lobe (a, arrow) and an occlusive thrombosis of the left renal vein (b, arrow).

service performed a left renal vein thrombectomy. His tachycardia, fever, and hypoxemia resolved within a few days. Blood, sputum, and pleural fluid cultures were sterile. Antibiotics were discontinued after 5 days. His creatinine decreased from 2.9 to 1.7 mg/dL after 9 days of immunosuppression and anticoagulation. His renal function returned to normal over the subsequent 2 weeks.

Two years after his hospitalization, he has no recurrence of disease activity in the kidney, hematologic, or neurologic systems while continuing therapy with hydroxychloroquine, mycophenolate mofetil, and warfarin and gradual reduction of his prednisone dose. He is exercising regularly and working full-time.

Commentary

In this case, establishing a new diagnosis of SLE involved not only analyzing new data as the case unfolded but also weighing the prior episode of TTP. This element of the patient's medical history (PMH) caused the discussant to consider the validity of TTP as a diagnosis, its manifestations and pathophysiology, and its potential mechanistic link to the evolving problem representation at nearly every stage of the case.

TTP is a thrombotic microangiopathic disorder resulting from profoundly suppressed levels of ADAMTS13, an enzyme that cleaves von Willebrand factor.² Low enzyme activity arises from an ADAMTS13 autoantibody inhibitor or, rarely, from an inherited mutation of the ADAMTS13 gene.

Figure 4 This chain of reasoning illustrates how the history of TTP influenced the discussant's analysis of fever, cough, and flank pain.

Autoimmune disease, most commonly SLE, is identified in up to 20% of patients during their initial episode of TTP.² Furthermore, 10% of patients diagnosed with idiopathic TTP subsequently develop an autoimmune disease, mostly commonly SLE.³ The mechanistic underpinnings of an association between SLE and TTP include the propensity for autoantibody formation to ADAMTS13 as well as the increased levels of von Willebrand factor that accompany most inflammatory disorders.²

The diagnosis of SLE came into focus as the initial manifestations—fever, cough, flank pain—were joined by pulmonary infiltrates, exudative pleural effusion, pulmonary artery and renal vein thromboses, AKI, and the nephrotic syndrome.^{4–7} The history of TTP was not essential to making the diagnosis, but the association between SLE and TTP added coherence to the conclusion. However, TTP, with its autoimmune nature, legacy of thromboses, and potential for recurrence, also triggered several alternative hypotheses. These theories warranted close consideration given the associated morbidity and highly specific treatments (e.g., immunosuppression for ANCA-related vasculitis, plasma exchange for recurrent TTP, or anticoagulation alone for recurrent thrombosis).

Often the PMH forces the clinician to consider multiple hypotheses simultaneously by asking if today's presentation (e.g., an acute headache) is a recurrence of the past (e.g., recurrent migraine), a related-but-distinct phenomenon (e.g., medication overuse headache), or an unrelated event (e.g., acute subarachnoid hemorrhage). In this case, the past episode of TTP, rather than unambiguously increasing the probability of SLE, forced the clinicians to engage in a complex chain of causal reasoning (Fig. 4) that triggered multiple candidate diagnoses that otherwise may not have been considered. Ultimately, this proved to be a case where the past informed the present.

Teaching Points

- 1 Nephrotic syndrome results from renal disorders which enhance permeability of the glomerulus. It is characterized by nephrotic range proteinuria (> 3.5 g/dL in 24 h), peripheral edema, hyperlipidemia, and hypoalbuminemia (< 3 g/dL).
- 2 Secondary causes of membranous nephropathy include systemic lupus erythematosus (SLE), hepatitis B infection, and medications.
- 3 Autoimmune diseases, particularly SLE, are identified in 20% of patients during an index presentation of TTP.² In patients with an initial diagnosis of idiopathic TTP, 10% subsequently develop another autoimmune disease.
- 4 Hypercoagulability associated with SLE and the nephrotic syndrome may result in pulmonary embolism and renal vein thrombosis.

Acknowledgments:: Dr. Manesh is supported by the Jeremiah A. Barondess Fellowship in the Clinical Transaction of the New York Academy of Medicine, in collaboration with the Accreditation Council for Graduate Medical Education (ACGME).

Corresponding Author: Reza Manesh, MD; Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA (e-mail: rsedigh1@jhmi.edu).

Compliance with Ethical Standards:

Conflict of Interest: Dr. Dhaliwal reports receiving honoraria from ISMIE Mutual Insurance Company, Physicians' Reciprocal Insurers, and GE Healthcare. All the remaining authors declare that they do not have a conflict of interest.

REFERENCES

1. Gupta N, Feingold K, Dhaliwal G. Stressing Signal Versus Noise: An Exercise in Clinical Reasoning. *J Gen Intern Med* 2017;32:122–126.
2. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood*. 2017;129:2836–46.
3. Jonsson OG, Fink CW. Systemic lupus erythematosus presenting as thrombotic thrombocytopenic purpura. *J Rheumatol* 1990;17:973–4.
4. Lisnevskaja L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet* 2014; 384: 1878–88
5. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365:2110–21.
6. Pines A, Kaplinsky N, Olchovsky D, Rozenman J, Frankl O. Pleuropulmonary manifestations of systemic lupus erythematosus: clinical features of its subgroups. Prognostic and therapeutic implications. *Chest*. 1985;88(1):129–35.
7. Keane MP, Lynch JP 3rd. Pleuropulmonary manifestations of systemic lupus erythematosus. *Thorax*. 2000;55(2):159–66.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.