MAYO CLINIC

58-Year-Old Man With Eosinophilia, Lymphadenopathy, and Proteinuria

Stephanie A. Williams, MD; Thomas G. Cotter, MD; and Christopher M. Wittich, MD, PharmD

A 53-year-old man with a history of hyperlipidemia presented to the emergency department with abdominal pain of 4 days' duration. He also described frothy urine, drenching night sweats, and a 4-kg unintentional weight loss. His recent medical history was remarkable for recurrent episodes of respiratory symptoms manifesting as nonproductive cough and shortness of breath with associated wheezing that had occurred over the preceding year. His symptoms were typically responsive to albuterol. His last episode was 3 weeks before the current presentation and required a short course of prednisone. Outpatient evaluation included normal findings on spirometry; however, this test was performed shortly after the prednisone course. Overall, a clinical diagnosis of asthma was made on the basis of his symptomatology and response to treatment.

His only medication was the recently initiated albuterol inhaler. He used over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) for occasional joint pain. He was a nonsmoker, did not routinely consume alcohol, and had never used illicit drugs. He had no history of recent travel or other exposures. He had no family history of asthma, atopy, or autoimmunity.

On presentation to the emergency department, the patient was in no acute distress. His vital signs were within normal limits, apart from mild sinus tachycardia (heart rate, 104 beats/min). Physical examination findings were notable for painless cervical, right axillary, and supraclavicular lymphadenopathy. He had bilateral 2+ pitting edema in the lower extremities to the knees. Respiratory tract examination revealed mild scattered polyphonic wheezes bilaterally. Abdominal, cardiovascular, and cutaneous examinations yielded normal results.

Laboratory testing revealed the following notable results (reference ranges provided parenthetically): white blood cell count, 12.2×10^9/L ($3.5\text{-}10.5 \times 10^9$/L); eosinophils, 2.10×10^9/L($0.05\text{-}0.50 \times 10^9$/L; the eosinophil count was 1.43×10^9/L 3 months previously); hemoglobin, 13.7 g/dL (13.5-17.5 g/dL); platelet count, 151×10^9/L ($150\text{-}450 \times 10^9$/L); internationalized normalized ratio, 1.3 (0.0-1.1); sodium, 136 mmol/L (135-145 mmol/L); potassium, 3.4 mmol/L (3.6-5.2 mmol/L); serum urea nitrogen, 58 mg/dL (8-24 mg/dL); creatinine, 1.3 mg/dL (0.8-1.3 mg/dL); albumin, 2.9 g/dL (3.5-5.0 g/dL); and C-reactive protein, 66.2 mg/L (≤8.0 mg/L). His liver chemistry and lipase test results were normal. Urinalysis revealed protein 3+, ketones 1+, bilirubin 2+, and no blood, nitrates, or leukocytes. A subsequent 24-hour urine collection revealed proteinuria (protein, 5 mg/dL).

Chest radiography revealed bibasilar opacities concerning for infiltrates that had not been present on previous imaging over a year prior. Computed tomography of the neck, thorax, abdomen, and pelvis revealed prominent cervical, axillary, mediastinal, periportal, and retroperitoneal lymphadenopathy. There was mild atelectasis or scarring in the lung bases with a tiny pleural effusion in the right lung. Also noted was periduodenal retroperitoneal fluid with mild circumferential duodenal wall thickening concerning for duodenitis.

1. **Given this clinical presentation, which *one* of the following is the *most likely* cause of this patient's overt proteinuria and associated eosinophilia?**
   a. Acute interstitial nephritis
   b. Analgesic nephropathy
   c. Secondary glomerulopathy due to a systemic process
   d. Cholesterol embolization syndrome
   e. Anti–glomerular basement membrane (anti-GBM)–mediated disease

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo Clinic School of Graduate Medical Education, Rochester, MN (S.A.W., T.G.C.); Advisor to residents and Consultant in General Internal Medicine, Mayo Clinic, Rochester, MN (C.M.W.).

Acute interstitial nephritis is unlikely, despite the risk factor of recent NSAID use, as it does not usually cause this degree of proteinuria. The classic triad of acute interstitial nephritis—fever, rash, and eosinophilia—occurs in only 10% of cases.[1] Patients with acute interstitial nephritis occasionally present with active urinary sediment with white blood cells, white blood cell casts, and red blood cells, which were not present in this case. Analgesic nephropathy is unlikely because it is a renal disease characterized by papillary necrosis and chronic interstitial nephritis.[2] This patient's eosinophilia also predated the NSAID use by 3 months. Further, it is typically caused by a more long-term consumption of analgesic agents.[3]

This patient's nephrotic-range proteinuria is most likely due to secondary glomerulonephropathy in the setting of a multisystemic disease process. Glomerular disease can be classified as primary or secondary to an underlying disease. Mechanisms of proteinuria can generally be divided into glomerular, tubular, or overflow. Nephrotic-range proteinuria indicates a urinary protein level greater than 3.0 to 3.5 mg/dL. Daily protein excretion of more than 4.0 g indicates a glomerular etiology, between 2.0 g and 4.0 g is usually glomerular, and between 0.15 g and 2 g is often tubular or overflow.[4]

Cholesterol embolization syndrome may cause multisystem involvement associated with eosinophilia, but this process is generally precipitated by an invasive procedure, such as percutaneous coronary intervention. Anti-GBM disease is also unlikely because it classically presents with pulmonary-renal syndrome (pulmonary hemorrhage and acute renal failure with nonnephrotic-range proteinuria and nephritic urinary sediment).

Given this patient's clinical presentation and concerning diagnostic findings, he was admitted to the general medicine ward for further evaluation and care. Additional laboratory testing revealed no abnormalities for the following: vasculitis screen (including myeloperoxidase, proteinase 3, antinuclear antibody, and anti-GBM antibody), human immunodeficiency virus, cytomegalovirus, syphilis, blood cultures, and fungal screening were also negative. He had had normal findings on a tuberculin test 7 months earlier, and QuantiFERON-TB results during the current admission were negative.

2. At this stage in this patient's work-up, which *one* of the following is the *best* next step in management?

a. Lumber puncture
b. Renal biopsy
c. Fine-needle aspiration of lymph node
d. Excisional lymph node biopsy
e. Duodenal biopsy

Lumbar puncture is unlikely to be beneficial given the absence of central nervous system symptoms. Renal biopsy, although a consideration in view of the patient's nephrotic proteinuria, is associated with up to a 13% risk of complication[5] and in this case may provide limited diagnostic information in the setting of a presumed systemic illness. Further scenarios in which renal biopsy is contraindicated include isolated glomerular hematuria, nonnephrotic proteinuria, or acute renal failure.[6]

The differential diagnosis for this patient with generalized lymphadenopathy was broad, including neoplastic, infectious, hypersensitivity, and reactive processes. Given the peripheral eosinophilia and the extent of constitutional symptoms reported, malignant processes such as leukemia and lymphoma needed to be out ruled. Fine-needle aspiration cytology is inappropriate when lymphoma is a consideration as it does not provide information on tissue architecture that is required for both lymphoma diagnosis and cytogenetic testing.[7] Only a complete excisional lymph node biopsy is appropriate to provide enough tissue for histologic, immunologic, and molecular assessment to differentiate lymphoma from a reactive process. Considering the patient's imaging findings, a duodenal biopsy may identify an eosinophilic infiltrate. However, it would not elucidate the etiology of his symptoms and thus is not the best next step in management.

Excisional biopsy of the right axillary lymph node was performed and revealed follicular and paracortical hyperplasia with an immunoblastic reaction, slightly increased Epstein-Barr virus—positive cells, and scattered eosinophils. Flow cytometry on the lymph node tissue did not reveal a monoclonal B-cell or T-cell population or aberrant expression of T-cell or NK-cell markers. Peripheral blood flow cytometry results were also normal.