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

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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 (3.5-10.5 × 10^9/L); eosinophils, 2.10 × 10^9/L(0.05-0.50 × 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 (150-450 × 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.

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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.

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Given the ongoing concern for an underlying eosinophilic clonal disorder (such as chronic myeloid leukemia, chronic eosinophilic leukemia, mast cell disorder, or hypereosinophilic syndrome), a bone marrow biopsy was performed, which revealed moderately hypercellular bone marrow (80%) with moderately increased eosinophils and no clonal abnormality. Findings on fluorescence in situ hybridization for *FIP1L1*, *CHIC2*, and *PDGFRA* regions were within normal limits. There were no morphologic or immunophenotypic features of mastocytosis. Further, the serum tryptase levels were normal, which is typically the initial diagnostic test to distinguish between cutaneous and systemic mastocytosis.

Our patient began to experience new symptoms 1 week after hospital admission. A new petechial rash developed on the bilateral pretibial areas. This symptom was accompanied by an increasing creatinine level, which peaked at 1.6 mg/dL, and a progressive increase in eosinophil count, which peaked at 56% of the leukocyte differential. He also had 2 episodes of supraventricular tachycardia that required intensive care unit admission for rate control and monitoring. Transthoracic echocardiography revealed a calculated ventricular ejection fraction of 65%, normal left ventricular wall thickness and chamber size, and no severe valvular abnormalities. At this point, empirical glucocorticoid therapy was considered given the progressive multisystem involvement with increasing peripheral eosinophilia.

3. In this patient, which *one* of the following is *most important* to rule out before initiation of corticosteroid therapy?

a. Strongyloidiasis
b. Histoplasmosis
c. Cryptococcosis
d. Blastomycosis
e. Aspergillosis

Most helminthic infections can cause eosinophilia. Strongyloidiasis can cause both eosinophilia and gastrointestinal tract symptoms, as in our patient. Importantly, strongyloidiasis has a risk of hyperinfection syndrome in the setting of immunosuppression. This risk is due to parasitic dissemination, which can be potentially fatal and has been described even after short courses of corticosteroid therapy.[8] Prophylactic ivermectin is advised before initiation of corticosteroid treatment if the clinical presentation is suspicious for strongyloidiasis. In our patient, histoplasmosis, cryptococcosis, blastomycosis, and aspergillosis should be excluded, but strongyloidiasis is most important to rule out before initiation of corticosteroid therapy to prevent hyperinfection.

The diagnostic work-up continued. Skin biopsy of the petechial rash revealed perivascular and interstitial mixed dermal inflammation with numerous eosinophils and nonspecific immunofluorescence results. No vasculitis was noted. During this time, a sensorimotor peripheral neuropathy developed in a glove-and-stocking distribution, and empirical high-dose prednisone was administered. After corticosteroid therapy, his elevated eosinophil count resolved, proteinuria decreased substantially to 3 g after the first dose, his creatinine concentration returned to baseline, and constitutional symptoms dramatically improved.

4. At this point, which *one* of the following is the *most likely* diagnosis?

a. Addison disease
b. Eosinophilic granulomatosis with polyangiitis (EGPA)
c. Hypereosinophilic syndrome (HES)
d. Henoch-Schönlein purpura
e. Systemic lupus erythematosus

Addison disease can be associated with eosinophilia but usually not to the degree seen in our patient. Further, he has no other features (hypotension, abdominal symptoms, or skin pigmentation) suggestive of Addison disease. The clinical diagnosis in this case is antineutrophil cytoplasmic antibody (ANCA)—negative eosinophilic granulomatosis with polyangiitis (EGPA), previously termed *Churg-Strauss syndrome*. Eosinophilic granulomatosis with polyangiitis is a clinical diagnosis and supported by histology. American College of Rheumatology guidelines for diagnosis for EGPA include having all 3 of the following: asthma, eosinophil count higher than 1.5×10^9/L, and vasculitis. The following factors are also suggestive: eosinophils more than 10% of the total white blood cell count, peripheral neuropathy, nonfixed pulmonary infiltrate, paranasal sinus abnormalities,

and histiologic evidence of extravascular eosinophils. Our patient fulfilled these criteria in terms of asthma, eosinophilia, petechial rash, peripheral neuropathy, transient pulmonary infiltrate, and extravascular eosinophils on skin biopsy. Asthma was not documented on spirometry, but recent corticosteroid use could have confounded the results. Although our patient had no documented vasculitis on skin biopsy, histologic evidence can be particularly difficult to obtain because the vasculitis and extravascular necrotizing granulomas typically seen in EGPA can be fleeting. Further, EGPA typically responds quickly to corticosteroids. Overall, given the aforementioned reasons and because our patient had a profound corticosteroid response both clinically (constitutional symptoms, lymphadenopathy) and biochemically (eosinophilia, inflammatory markers), it was believed that EGPA was the most likely diagnosis.

Hypereosinophilic syndrome is defined as persistent unexplained eosinophilia (eosinophil count, >1500/mm^3) of at least 6 months' duration that leads to end-organ damage, fulfilling Chusid diagnostic criteria.[9] It is a diagnosis of exclusion. For all patients presenting with chronic eosinophilia for which an underlying disease cannot be identified, the diagnosis of HES or EGPA is suggested. With HES, almost any organ can be involved but most commonly the heart, skin, nervous system, and gut. Asthma is more uncommon in HES, but pulmonary infiltrates can occur. Some patients with HES are resistant to corticosteroid treatment or respond only to a high dose of corticosteroids.[9]

Henoch-Schönlein purpura is an ANCA-negative vasculitis that affects children more often than adults. It commonly presents with abdominal pain, arthralgia, purpuric rash, and glomerulonephritis. Predominance of IgA deposition on biopsy characterizes Henoch-Schönlein purpura, unlike this patient's skin biopsy results. Our patient did not meet the 4 of the 11 American College of Rheumatology criteria required for diagnosis of systemic lupus erythematous.

Antinuclear antibody test results were also negative. Both renal and nerve biopsies were considered by the treatment team. Given the normalization of the patient's glomerular filtration and response to therapy, the risks were deemed higher than the potential benefit. The patient asked the clinical team about his prognosis.

5. Which *one* of the features of this patient's clinical presentation is *most* predictive of a poor clinical outcome?

a. ANCA-negative test results
b. Age greater than 55 years
c. Renal inefficiency
d. Rash
e. Asthma symptoms

The role of ANCA itself in predicting outcome in patients with EGPA is unknown.[10] Clinical manifestations of EGPA tend to segregate into 2 subsets—those with predominantly vasculitic features or predominantly eosinophilic manifestations. ANCA-positive patients more frequently have peripheral neuropathy, renal involvement, and purpura due to small-vessel vasculitis, whereas cardiac involvement and lung infiltrates prevail in ANCA-negative patients.[10-12]

The Five-Factor Score has been used to predict survival in patients with vasculitis, including EGPA. It was validated in 1996 in patients with polyarteritis nodosa, granulomatosis with polyangiitis, and EGPA. Criteria include cardiac involvement, gastrointestinal tract disease (bleeding, perforation, infarction, or pancreatitis), renal insufficiency (plasma creatinine concentration, >1.6 mg/dL), proteinuria (urinary protein, >1 g/d), and central nervous system involvement.[13]

This scoring system was revisited in 2009 by Guillevin et al,[13] who found that the following factors were associated with higher 5-year mortality: age more than 65 years, cardiac symptoms, gastrointestinal tract involvement, and renal inefficiency. Ear, nose, and throat symptoms in patients with EGPA were associated with lower risk of death. According to this revised scoring system, those with scores of 0, 1, and 2 or higher had a 5-year mortality rate of 9%, 21%, and 40%, respectively. The Five-Factor Score can only be used for prognosis at diagnosis of vasculitis. It is not validated for use during a vasculitis flare. Therefore, our patient's renal insufficiency—not his age, rash, or asthma symptoms—is most predictive of a poor clinical outcome.

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The patient is currently doing well, with improvement in all symptoms and normalization of both renal function and inflammatory markers while receiving mycophenolate mofetil and undergoing corticosteroid taper. Mycophenolate mofetil was initiated rather than methotrexate in light of new symptoms of neuropathy.

DISCUSSION

Eosinophilic granulomatosis with polyangiitis is a multisystemic disease classified among the ANCA-associated vasculitides. However, ANCA positivity is detected in only 40% to 60% of patients, making ANCA-negative EGPA a diagnostic challenge. Patients who are ANCA-negative tend to have more sinusitis or rhinitis and conductive or sensorineural hearing loss as part of their presentation. Patients with EGPA often have an established diagnosis of asthma (classically, they are taking leukotriene inhibitors when EGPA develops).[9-11]

In regard to epidemiology, the mean age at EGPA diagnosis is 48 years; the sex ratio is approximately 1:1.[9] Clinically, the foundation for diagnosis is constitutional and pulmonary symptoms. Interestingly, the disease can often develop through 3 stages. First, there is a prodromal phase that can precede the diagnosis from months to years (on average, 8 to 10 years).[9] This stage typically consists of allergic rhinitis symptoms followed by asthma symptoms, which are usually corticosteroid dependent. Second is the eosinophilic phase, which is characterized by both blood and tissue eosinophilia during which eosinophilic pneumonia or gastroenteritis may develop. The third phase is described as a systemic vasculitis phase.[14]

This case highlights the multisystemic disease progression of EGPA. Our patient experienced prodromal respiratory and constitutional symptoms for a number of months before the current presentation. Subsequently, prominent eosinophilia developed, and he required treatment for tachycardia and had abdominal pain with evidence of duodenal inflammation on computed tomography. Entering the third vasculitic phase, a stereotypical rash and peripheral sensorimotor neuropathy developed.

Other potential organs affected in EGPA include the kidneys, heart, and neurologic system. Renal involvement in EGPA ranges from necrotizing crescentic glomerulonephritis to eosinophilic interstitial nephritis or mesangial glomerulonephritis and focal segmental glomerulosclerosis, which can lead to nephrotic-range proteinuria. In patients with endomyocardial involvement, biopsy typically reveals an eosinophilic infiltrate rather than a vasculitis and endomyocardial involvement is present in about 30% of cases.[9] Supraventricular arrhythmias, as occurred in our patient, can be due to infiltration into the conduction system. Neurologic involvement including mononeuritis multiplex is observed in 50% to 75% of patients.[9] Overall, approximately 75% of deaths are directly attributable to vasculitis manifesting as a cardiac source.[9] It is important to note that in our patient, no vasculitis was proven on tissue biopsy; yet, several surrogate clinical markers (eosinophilia, nephrotic-range proteinuria, pulmonary opacities, new neuropathy, systemic and multiorgan involvement) point toward the vasculitis diagnosis.

In regard to management, corticosteroids are the mainstay and produce remission in more than 80% of cases.[9] However, relapses can occur often without maintenance therapy. Further, cyclophosphamide should be considered as first-line treatment for severe forms of EGPA. Rituximab is also used as induction therapy for treatment of severe organ manifestations of EGPA. Azathioprine is often used for maintenance therapy in conjunction with a glucocorticoid taper.

As demonstrated in this case, EGPA requires a multidisciplinary approach to diagnosis and management. Our patient's care involved numerous specialties including internal medicine, infectious disease, hematology, and rheumatology. Follow-up usually requires several months or years because patients may experience relapse requiring immediate medical care and further immunosuppression.

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CORRECT ANSWERS: 1. c. 2. d. 3. a. 4. b. 5. c.