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PHOTOCLINIC

Granulomatosis With Polyangiitis With Airway Compression

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A 12-year-old previously healthy boy presented to the emergency department with a 2-week history of headaches, malaise, and fever. During that time, the patient had been evaluated multiple times, with various diagnoses ranging from viral syndrome to acute otitis media and pneumonia. Despite treatment with amoxicillin, cefdinir, and azithromycin, his symptoms failed to improve. Additionally, the patient developed a nonproductive cough and decreased oral intake with a 1.4-kg weight loss. The patient had no significant past medical history, family history, or history of recent travel.

Physical examination. On the day of admission, laboratory test results showed an elevated C-reactive protein (CRP) level of 18.5 mg/dL (reference range, 0.08-3.1 mg/L), a white blood cell count of 11,000/µL (reference range, 45000-11,000/µL), a hemoglobin level of 12.1 g/dL (reference range, 14.0-17.5 g/dL), a hematocrit level of 36.1% (reference range, 41%-50%), and a platelet count of 538 × 10^3/µL (reference range, 150-350 × 10^3/µL). Urinalysis results

showed a trace level of protein. Results of a comprehensive metabolic panel were within normal limits, and chest radiographs showed a cavitary lesion in the right upper lobe **(Figure 1)**.

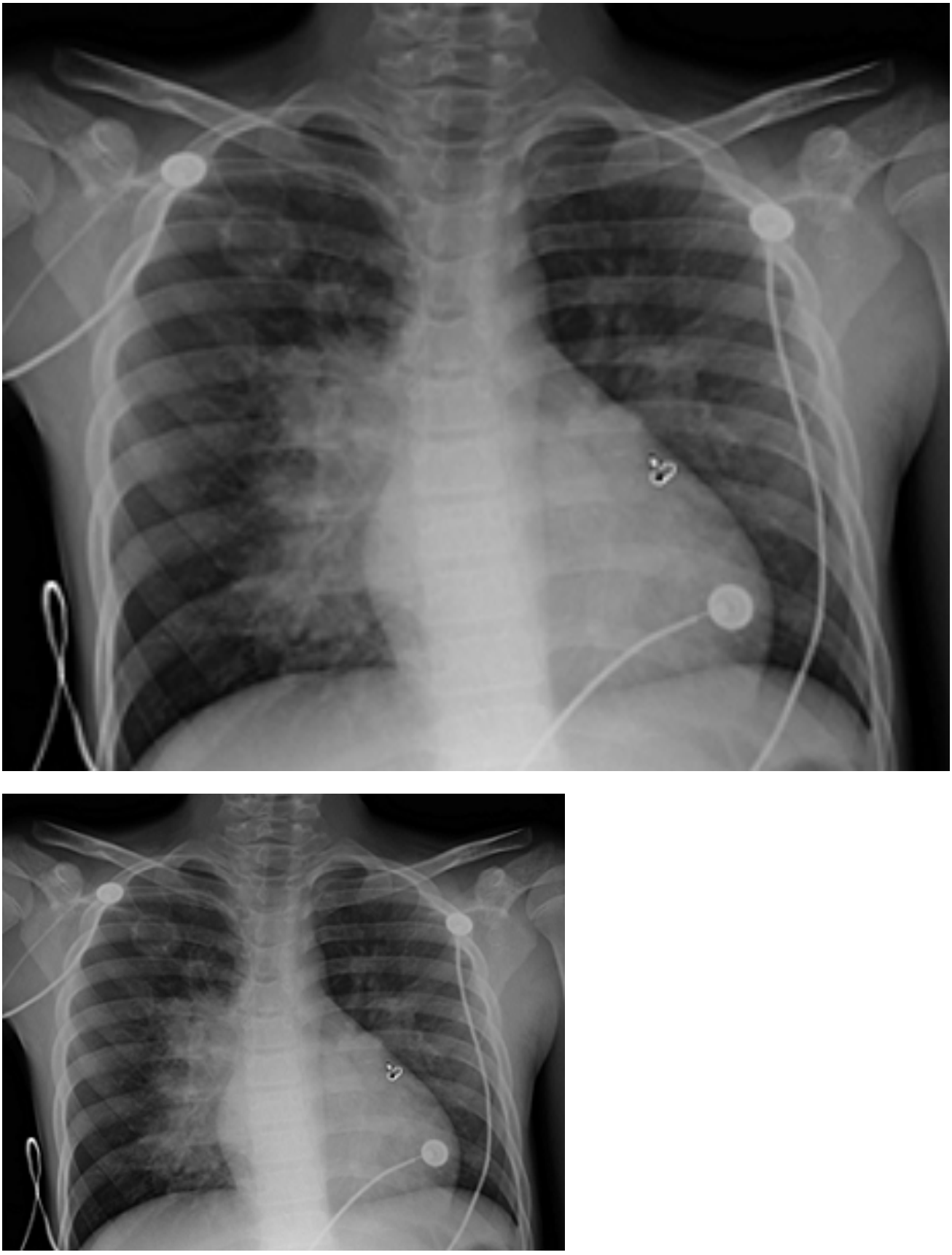
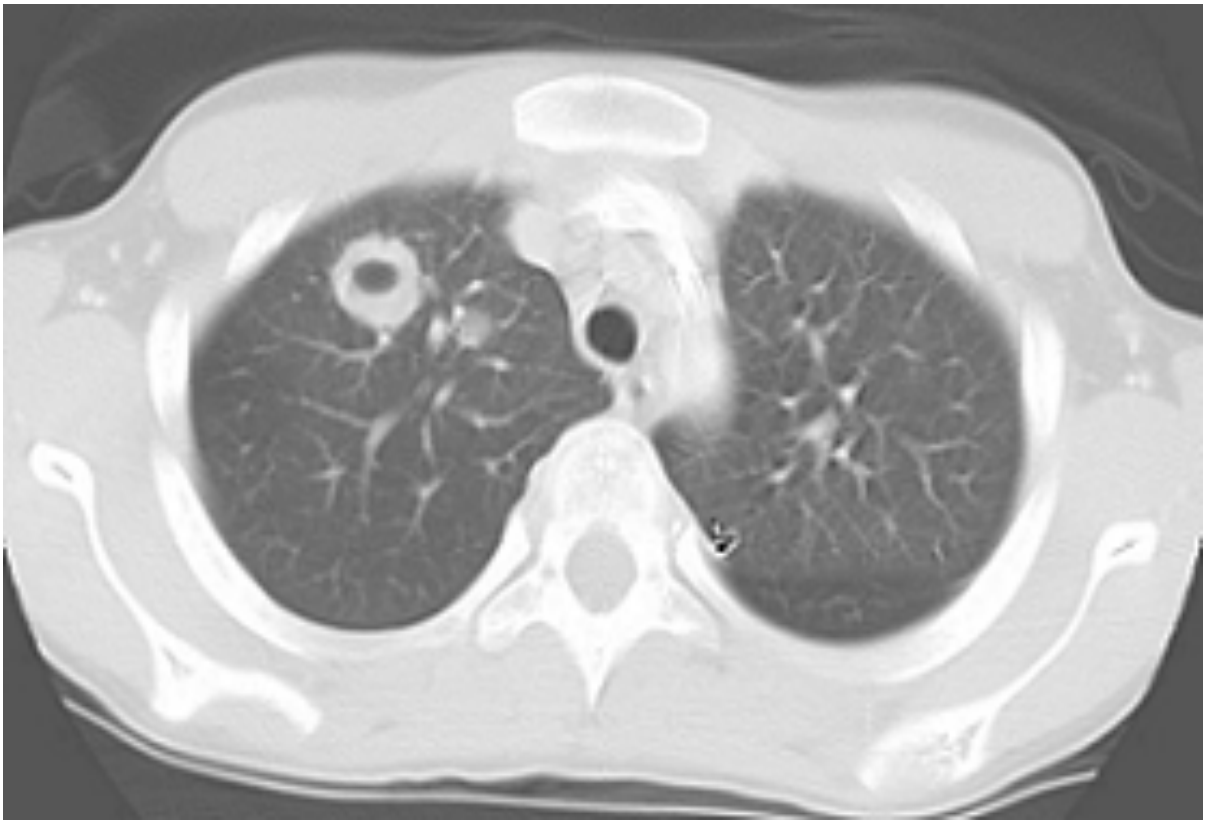
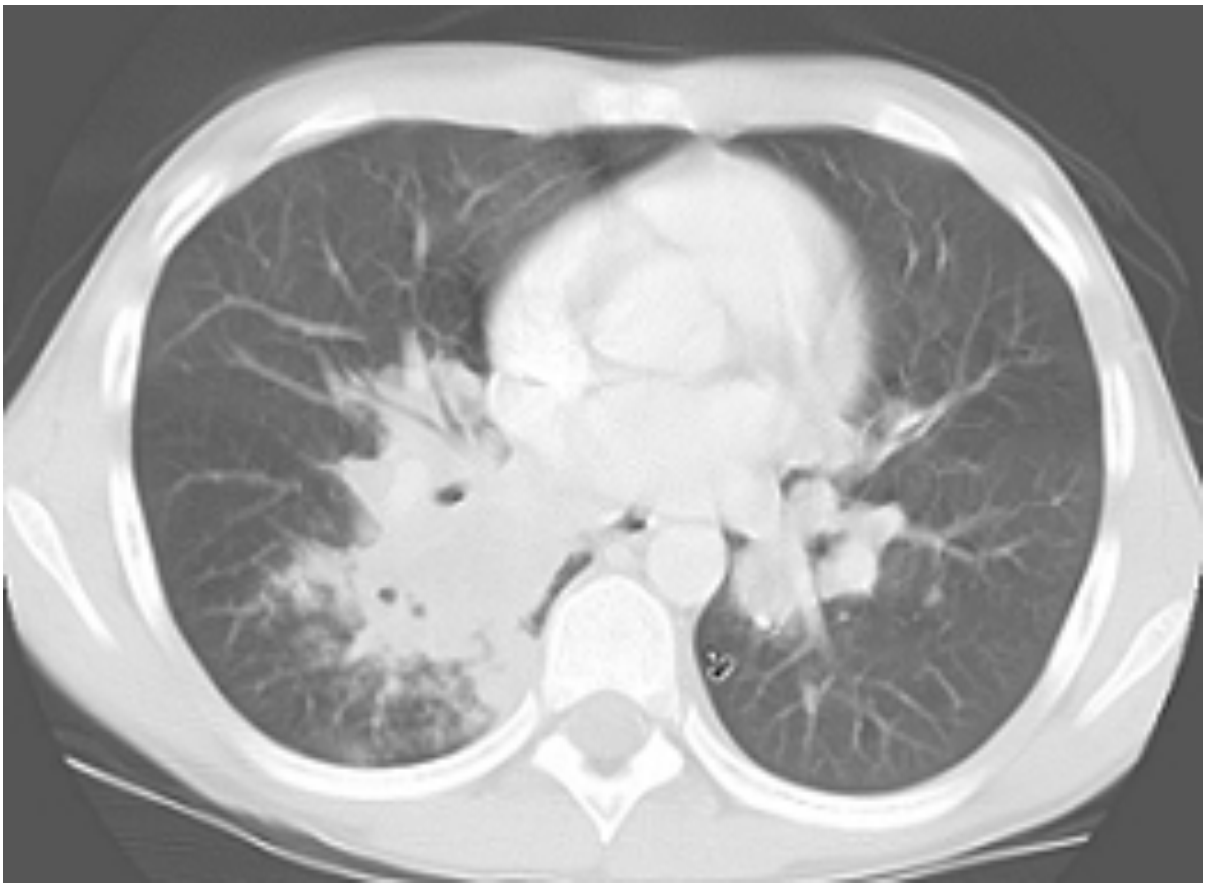


Figure 1. *A round cavitary lesion was visible in the right upper lobe.*

Initial vital signs included a pulse rate of 126 beats/min, a respiratory rate of 20 breaths/min, a blood pressure of 114/56 mm Hg, a temperature of 38.7°C, oxygen saturation of 94% on room air, and a weight of 37.1 kg. Pertinent findings on physical examination showed an ill but nontoxic–appearing boy with bilateral bulging tympanic membranes, diminished breath sounds in right middle lobe, and faint grade 2/6 systolic murmur at the left midsternal border. There was no evidence of rash or arthralgias.

Due to the characteristic cavitary lesion on chest radiographs, suspicion for *Staphylococcus aureus* pneumonia was high; hence, treatment with an intravenous (IV) vancomycin and IV cephalosporin was initiated. Several days of antimicrobial therapy resulted in no clinical improvement. A computed tomography (CT) scan of the thorax showed a large cavitary air-space opacity in the right lung and perihilar region, areas of necrosis and cavitation, and dense consolidation in right lower lung **(Figures 2a and 2b)**.





Figures 2a and 2b. *Thoracic CT scans showed a large air-space opacity and areas of necrosis and consolidation.*

An evaluation for fungal pneumonia and a purified protein derivative skin test for tuberculosis yielded negative results. The patient had no clinical changes after approximately 5 days in the hospital. However, this may have been attributed to subtherapeutic antibiotic levels. Nonetheless, the patient had developed new signs consisting of gingivostomatitis, hemoptysis, nasal discharge, and conjunctivitis. Given the patient's constellation of signs and symptoms and his failure to improve despite antibiotic therapy, a diagnosis of granulomatosis with polyangiitis (GPA) was considered and evaluated for.

Pending the results of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) testing, the patient developed acute renal failure overnight, with the creatinine level rising from 0.4 mg/dL to 1.8 mg/dL (reference range, 0.6-1.2 mg/dL).

The etiology of this acute kidney injury was believed to be multifactorial and included the dosage increase of the glycopeptide antibiotic and possible renal involvement in undiagnosed GPA. During the onset of acute renal failure, the patient appeared well-hydrated, and urinalysis results and urine output remained normal. The patient underwent a renal biopsy, along with bronchoscopy to evaluate hemoptysis and the airway. During the bronchoscopy, a 3.6-mm outer-diameter bronchoscope was unable to be advanced past the right mainstem bronchus

due to external compression **(Figure 3)**. In order to prevent possible bleeding, endobronchial biopsy and bronchoalveolar lavage were not performed.

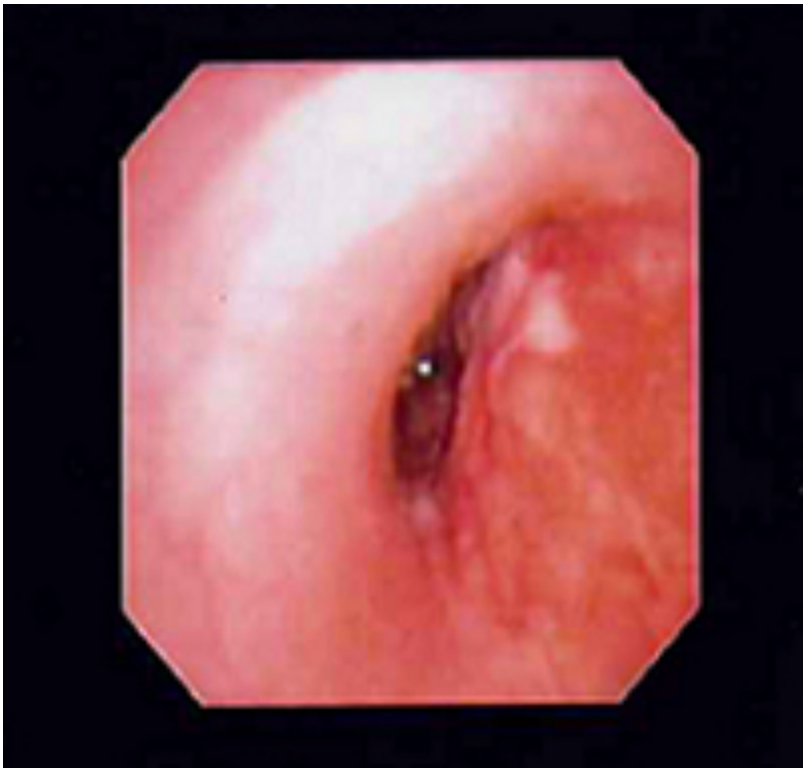


Figure 3. *Compression of right mainstem bronchus was noted during bronchoscopy.*

Acute kidney injury progressed to a peak creatinine level of 3.8 mg/dL. A unanimous decision was made to initiate high-dose IV steroids while awaiting c-ANCA results. The following day, positive c-ANCA results showed a value of 1209 AU/mL (≥26 AU/mL indicates a positive result) for serine protease 3 antibody. Dialysis was not required, and a gradual return to the baseline creatinine level occurred. The renal biopsy was limited for proper evaluation of kidney disease, since no glomeruli were present for evaluation on light microscopy sections.

The patient was continued on high-dose IV steroids for 3 consecutive days; then antibiotics were discontinued, and IV rituximab was initiated. The patient had a marked improvement of symptoms within a few days of treatment with IV steroids and was transitioned to daily oral prednisolone upon discharge home. The patient received IV rituximab weekly for 4 doses prior to follow-up imaging.

A chest radiograph performed 6 weeks after initiation of treatment showed complete resolution of the pulmonary cavitary lesion **(Figure 4)**.

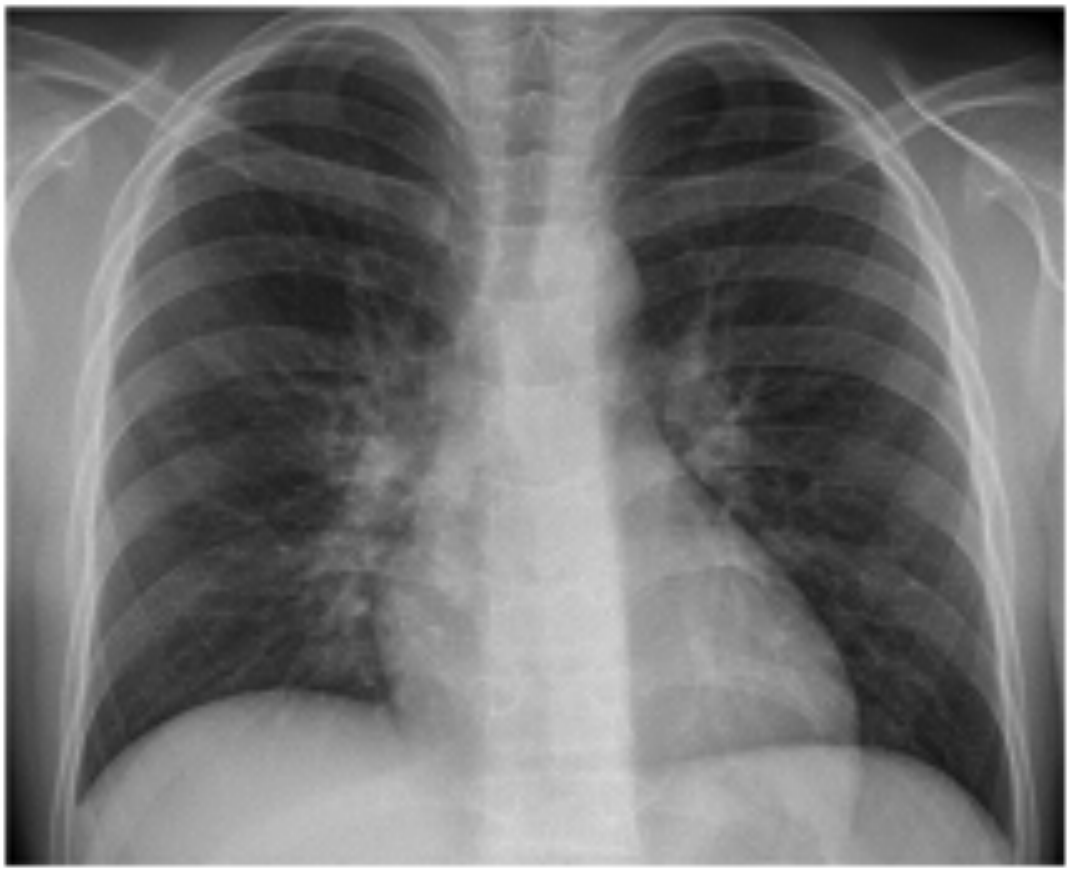


Figure 4. *A chest radiograph 6 weeks after initiation of treatment showed resolution of the right upper lobe cavitary lesion.*

Diagnosis. Our patient did not show clinical improvement despite broad-spectrum antibiotic coverage for what was thought to be pneumonia upon presentation. This, combined with new constellation of signs including gingivostomatitis, hemoptysis, nasal discharge, and conjunctivitis prompted investigation for alternate etiology. With literature review, we felt that the patient's signs and symptoms were consistent with GPA and worthy of evaluation for this diagnosis, despite knowledge of its rare incidence in the pediatric population.

Discussion. GPA, previously known as Wegener granulomatosis, is an autoimmune systemic disease that causes granulomatous inflammation of small and medium-sized blood vessels. Virtually every organ system may be affected, although the the upper and lower airways and the kidneys are most commonly involved. It is 1 of the 3 ANCA-associated vasculitides. The disease has a 100% mortality rate if left untreated.[1] The most common acute life-threatening causes are pulmonary hemorrhage, respiratory failure, acute renal failure, and rapidly progressing pauci-immune glomerulonephritis.[1]

GPA most frequently has an insidious onset of nonspecific symptoms, making it difficult to diagnose in a timely fashion. Diagnosis may be delayed by months or even years.[2] This may prove to be detrimental, since early diagnosis is vital for organ-sparing purposes.[2] Furthermore, although it has been reported in all age groups, the incidence of this rare disease in the

pediatric population is estimated to be less than 1 per 1 million annually.[3] Various reports have reported a delay in diagnosis of 2.7 months, 4.2 months, and 22 months, with a range of 0 to 49 months from onset of symptoms.[3-5] Therefore, the combination of vague, progressive, nonspecific symptoms plus the extreme rarity in pediatrics make the diagnosis of GPA very challenging.

This disease has characteristic granulomatous inflammation in small and medium-sized vessels occurring throughout various organs in the body. Pulmonary manifestations are common and include nodules, hemorrhage, and infiltrates.[1-3] However, external compression of a mainstem bronchus by a suspected granuloma, as in our patient's case, is exceedingly rare, and no such reports on pediatric review have been published to date.

Renal involvement is a common presenting symptom in 75% to 88% of cases, manifesting as proteinuria, hematuria, presence of casts, and/or acute renal failure. The hallmark renal biopsy yields pauci-immune glomerulonephritis. At presentation, our patient did not show renal involvement. However, acute kidney injury ensued over the course of less than 24 hours. Renal failure at presentation is a poor prognostic sign and is associated with a high risk of end-stage renal disease and death despite treatment.[1]

Laboratory evaluation findings often show normocytic normochromic anemia, thrombocytosis, an elevated erythrocyte sedimentation rate, and an elevated CRP level. Most importantly, studies for ANCA, which are commonly directed against serine proteinase 3, should be ordered. A positive result is present in 80% to 90% of the population with GPA.[4]

Treatment regimens for pediatric GPA vary and are derived from adult data. More commonly, the initial standard of care immunosuppressive therapy has been cyclophosphamide along with concomitant steroids. Although it has been shown to successfully induce remission, this regimen is not tolerated by all patients. Furthermore, a subset of patients are refractory to this treatment. This has led to various studies with the monoclonal antibody rituximab, which is directed against CD20 and leads to quick depletion of B cells.[6-8] In April 2011, the US Food and Drug Administration approved rituximab for treatment of GPA as an alternative to cyclophosphamide. The initial therapy choice is a topic of great debate and often depends on practitioner preference. In our patient's case, the potential negative impact of cyclophosphamide on fertility played a role in the decision, leading to rituximab as a more appropriate choice.

Conclusion. The symptoms of GPA may not occur in an insidious fashion, as is frequently reported. Severe symptoms such compression of the airway and renal failure may occur abruptly, as in our patient's case. Prompt diagnosis is key for organ-sparing purposes, and the treatment regimen should be carefully determined after review of each individual case to allow for remission while preserving quality of life acutely and in the future.

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