

A 14-Year-Old Boy With Sore Throat and Tea-Colored Urine

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KEY WORDS

Wegener granulomatosis, vasculitis, rheumatology, glomerulonephritis, palatine tonsil

ABBREVIATIONS

ANCA—antineutrophil cytoplasmic antibody
APSGN—acute poststreptococcal glomerulonephritis
ELISA—enzyme-linked immunosorbent assay
GPA—granulomatosis with polyangiitis
PR3—proteinase 3

Dr Cooper reviewed the patient's case, performed the literature review, and drafted the initial manuscript; Dr Rakheja provided and interpreted the histopathologic images and revised the manuscript; Dr Punaro critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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www.pediatrics.org/cgi/doi/10.1542/peds.2013-0466

doi:10.1542/peds.2013-0466

Accepted for publication Oct 21, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

abstract

Granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis) is a rare, multisystem, necrotizing granulomatous vasculitis that classically affects the upper and lower respiratory tracts and kidneys but can have diverse clinical features. The clinical course is often rapidly progressive, and without appropriate treatment is almost universally fatal. Early symptoms are often nonspecific and a high index of suspicion is needed to recognize this serious disease, particularly in the absence of overt pulmonary or renal manifestations. Because initial symptoms can mimic those of infection, patients often present first to the general pediatrician. We present a case of pediatric GPA in a 14-year-old boy who initially presented with constitutional symptoms, sore throat, and hematuria, and then developed grossly necrotic-appearing tonsils before rapid deterioration requiring intensive life-saving measures. We review the common manifestations of GPA, including those that may be unique to the pediatric population, and emphasize the importance of early diagnosis and intervention in preventing devastating outcomes from this disease. *Pediatrics* 2014;133:e1377–e1380

Granulomatosis with polyangiitis (GPA) is a necrotizing granulomatous vasculitis with widespread systemic features. Anti-neutrophil cytoplasmic antibodies (ANCA), specifically in the cytoplasmic staining pattern directed against proteinase 3 (PR3), are present in most patients with active disease and probably play a role in disease pathogenesis.¹ The upper and lower airways and kidneys are the primary sites of disease involvement in GPA, but many other organ systems can be involved. Head and neck symptoms, including lesions of the oral cavity, nasal cavity, sinuses, larynx, and trachea are common, and when seen in combination with nephritis or lower airway disease should raise suspicion for GPA.

PATIENT PRESENTATION

A 14-year-old previously healthy African American male presented to the inpatient general pediatrics unit with a 2-week history of myalgias, fatigue, subjective fever, sore throat, and a 14-pound weight loss over 10 days. On the day of admission, he developed tea-colored urine. Physical examination was initially unremarkable. Laboratory studies revealed an elevated erythrocyte sedimentation rate of 85 mm/hour, a normal white blood cell count of 5.5×10^3 per mm^3 with normal differential (67% neutrophils, 26% lymphocytes, 6% monocytes, 1% eosinophils), a normocytic anemia with a hemoglobin of 8.5 g/dL, and a normal platelet count of 354×10^3 per mm^3 . Additional laboratory tests revealed a mildly elevated creatine kinase but otherwise normal muscle enzymes and a low albumin of 3.3 g/dL. Routine urinalysis was remarkable for 15 red blood cells per high power field and 2+ protein; however, the microscopic examination was free of casts. Serum creatinine at presentation was 1 mg/dL (normal: 0.3–1 mg/dL), and serum urea nitrogen was 17 mg/dL (normal: 6–20 mg/dL). Initial infectious studies were negative, including throat, blood, and urine cultures; *Mycoplasma*

pneumoniae antibodies; Epstein-Barr virus; cytomegalovirus polymerase chain reaction; QuantiFERON Gold tuberculosis test (QIAGEN, Valencia, CA); HIV enzyme-linked immunosorbent assay (ELISA); and quantitative real-time polymerase chain reaction. Chest radiograph and renal ultrasound were unremarkable. Complement component 3 (C3) level was 192 mg/dL (normal: 70–206 mg/dL), complement component 4 (C4) level was 21.4 mg/dL (normal: 11–61 mg/dL), and serologic examination for antinuclear antibody was negative.

On hospital day 4, new painful swelling of the left tonsil with ulceration and purulent-appearing discharge was noted. Evaluation by otolaryngology revealed a necrotic-appearing left tonsil and purulent drainage from the right tonsil, without other oral lesions. Renal biopsy and bilateral tonsillectomy were performed the following day.

Histologic examination of the tonsils revealed lymphoid follicular hyperplasia. The right tonsil showed foci of superficial epithelial necrosis and neutrophilic inflammation, and the left showed frank ulceration with necrosis, neutrophilic inflammation, vascular congestion, and hemorrhage (Fig 1). Aerobic, anaerobic, and fungal cultures showed only mixed oropharyngeal flora. Renal biopsy revealed focal necrotizing glomerulonephritis with

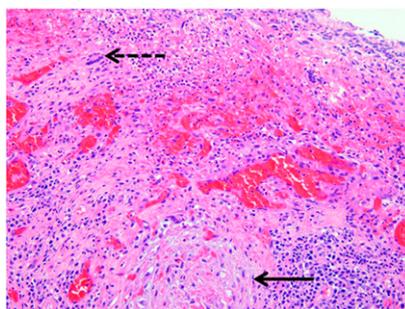


FIGURE 1
Photomicrograph of left tonsillectomy specimen shows ulceration (top) with fibrinopurulent exudate, hemorrhage, vascular congestion, and a multinucleated giant cell (dashed arrow) in the ulcer bed. A vein with an occlusive thrombus (solid arrow) is seen at the bottom. Hematoxylin and eosin stain; original magnification $\times 100$.

crescent formation by light microscopy (Fig 2). The tissue lacked significant staining for immunoglobulins or complement components by immunofluorescence microscopy or electron-dense immune complex deposits on electron microscopy (Fig 3) and was thus classified as a “pauci-immune” glomerulonephritis.

The serum ANCA was detected on immunofluorescence in the granular cytoplasmic pattern at a titer of 1:2560 (normal: $<1:20$) and was specific for serine PR3 by ELISA. On the basis of the patient’s positive PR3-ANCA, abnormal urinalysis, upper airway (tonsillar) involvement, and pauci-immune glomerulonephritis, a diagnosis of GPA was made.

In the postoperative period, the patient developed new-onset respiratory distress and hypoxia, then further decompensated, developing hemoptysis and requiring intubation and mechanical ventilation. Bronchoscopy revealed numerous areas of active bleeding consistent with diffuse alveolar hemorrhage, and bronchoalveolar lavage fluid cultures were negative.

The patient was treated with steroids and oral daily cyclophosphamide for GPA and with trimethoprim-sulfamethoxazole for prevention of *Pneumocystis* infection. Given his critical respiratory status and ongoing pulmonary hemorrhage, he underwent 7 rounds of plasma exchange. He responded well to these interventions, and a repeat bronchoscopy showed no active bleeding. He was subsequently

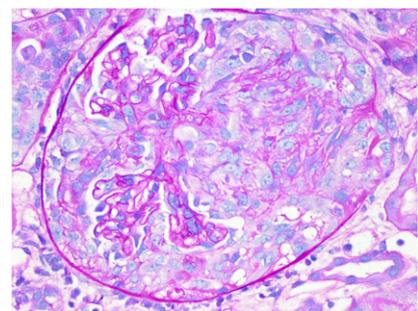


FIGURE 2
Photomicrograph of kidney biopsy shows extracapillary proliferation (cellular crescent) with compressed glomerular capillary tuft. Periodic acid Schiff stain; original magnification $\times 400$.

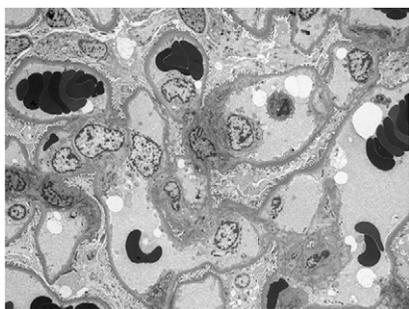


FIGURE 3

Electron micrograph of kidney biopsy showing glomerular capillaries with normal glomerular capillary basement membranes and podocyte foot processes. No electron-dense deposits are noted in the glomerular capillary walls or the mesangium. Original magnification $\times 700$.

extubated and eventually discharged from the hospital for outpatient care. Although he responded well to the initial treatment, his long-term prognosis remains guarded given the high risk of disease relapse and serious infections in patients with GPA.

DISCUSSION

Granulomatous vasculitis of the upper and lower airways and pauci-immune necrotizing glomerulonephritis encompass the classic triad of manifestations of GPA and often are directly related to the high morbidity of the disease. It is well recognized, however, that a much broader clinical spectrum of disease exists in both adults and children.

In 2010, the European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society proposed the first validated criteria for the classification of childhood vasculitides, which require the presence of 3 of the following 6 criteria for the diagnosis of GPA:

- granulomatous inflammation on biopsy;
- upper airway involvement, including chronic nasal or sinus symptoms;
- laryngo-tracheo-bronchial involvement;
- pulmonary involvement (chest radiograph or computed tomography

showing nodules, cavities, or fixed infiltrates);

- ANCA positivity by immunofluorescence or ELISA; and
- renal involvement including proteinuria, hematuria, or pauci-immune glomerulonephritis on biopsy.²

The study and characterization of pediatric-onset GPA is particularly challenging given the rarity of the disease in this age group. In the largest cohort of pediatric GPA to date involving 65 patients, the most common manifestations at presentation were nonspecific constitutional symptoms including fever, fatigue, and weight loss (89%); ear, nose, and throat complaints (80%); and pulmonary (80%) and renal (75%) disease.³ The nonspecific nature of early symptoms demands a high index of suspicion for early recognition of the disease, because, as this case shows, rapid progression to life-threatening status can occur in patients with GPA, even in the midst of a timely workup.

The tea-colored urine in this case suggested the possibility of glomerulonephritis. The most common cause of glomerulonephritis in childhood is acute poststreptococcal glomerulonephritis (APSGN), a self-limited condition. The onset of APSGN classically follows a pharyngitis infection by 1 to 2 weeks (or streptococcal skin infection by 3 to 6 weeks) and is associated with serologic evidence of recent group A streptococcal infection and depressed serum C3 levels. In adolescents, another common cause of glomerulonephritis is immunoglobulin A nephropathy, characterized by macroscopic hematuria coincident with symptoms of pharyngitis and normal complement levels. Additional causes of GN in this age group include Henoch-Schönlein purpura, membranoproliferative glomerulonephritis, systemic lupus erythematosus, Alport syndrome, Goodpasture syndrome, and the ANCA-associated vasculitides GPA and microscopic polyangiitis.

Features atypical for APSGN should raise suspicion for a less common etiology and prompt additional laboratory testing and early renal biopsy to establish an accurate diagnosis.⁴ Measurement of complement levels is helpful because hypocomplementemia is present in cases of lupus, APSGN, or membranoproliferative glomerulonephritis. Renal biopsy in GPA classically shows a necrotizing pauci-immune crescentic glomerulonephritis. The morphologic features of necrotizing crescentic glomerulonephritis may also be seen in immune complex-mediated glomerulonephritides such as lupus and immunoglobulin A nephropathy. The immune complex-mediated glomerulonephritides show glomerular deposition of immunoglobulins and/or complement on immunofluorescence microscopy and electron-dense immune complex deposits on electron microscopy. In contrast, the renal biopsy in ANCA-associated vasculitides shows neither significant staining for immunoglobulins or complement components by immunofluorescence microscopy nor electron-dense immune complex deposits by electron microscopy.⁴

If GPA is suspected clinically, evaluation for the presence of ANCA should be performed. In the proper clinical context, ANCA positivity can be extremely helpful in establishing a diagnosis. In a cohort of 60 pediatric GPA patients used to validate the recently developed classification criteria for pediatric GPA, the high sensitivity and specificity of ANCA detected by immunofluorescence (84% and 91%, respectively) and of PR3 by ELISA (69% and 96%, respectively) led to the inclusion of ANCA positivity by either method in the GPA criteria.²

Although laboratory testing and early biopsy are critical to diagnosis, careful attention to historical clues and physical examination findings can help guide the diagnostic evaluation. In 1 study, pediatric patients with a prolonged disease course (>12 months)

before diagnosis were more likely to have predominantly ear, nose, and throat and dermatologic involvement without renal manifestations.³ This finding implies that patients without critical organ involvement at disease onset may be more difficult to recognize and correctly diagnose. Familiarity with the spectrum of disease manifestations that can occur in GPA can aid in rapid recognition of this disease.

The presence of upper or lower airway disease in combination with glomerulonephritis should always raise suspicion for GPA. Upper airway involvement including laryngo-tracheo-bronchial stenoses and other head and neck symptoms are unique features of GPA. Children are more likely than adults to develop upper airway stenosis during the course of their disease.⁵⁻⁷ The nose and paranasal sinuses are the most commonly affected sites in the head and neck.⁸ In an archive of 65 pediatric GPA patients, 60% reported sinusitis as a manifestation of disease.³ Nasal symptoms range from nonspecific signs such as epistaxis or purulent discharge to septal perforation

or saddle nose deformity, complete collapse of the nasal bridge from cartilage destruction.

Involvement of the oral cavity is less common but well described, occurring in 6% to 13% of patients in adult studies.⁹ The classic oral finding is strawberry gingivitis, a hyperplastic red to purple gingival lesion with numerous petechiae. Strawberry gingivitis has occasionally been reported as the initial presenting sign of disease, including 1 case in a 6-year-old child.¹⁰ The largest pediatric cohorts have reported oral ulcers occurring at a frequency of 9% to 32% during the disease course.^{3,6,7,11} Oral lesions can mimic infection, particularly fungal disease, which must be considered in the differential diagnosis.⁹ The tonsillar necrosis that our patient developed was a helpful clue in the identification of his diagnosis. Although tonsillar involvement has typically been described in the literature in the context of extensive oral involvement, the presence of this midline necrotizing lesion in a systemically inflamed patient with glomerulonephritis, normal comple-

ment levels, and a positive PR3-ANCA further raised suspicion for GPA, even before the diagnostic renal biopsy.¹²

With the currently available treatment modalities, the outlook for patients with GPA has improved from near-total fatality to a >90% 5-year survival, although the relapse rate remains high. Successful treatment currently remains largely dependent on early aggressive initiation of steroids and cyclophosphamide. More recently, studies using the anti-CD20 chimeric monoclonal antibody rituximab for induction of remission have been encouraging, and further trials are underway.¹³

CONCLUSIONS

GPA is a rare disease, particularly in the pediatric population, and can have devastating consequences if not diagnosed promptly and treated aggressively. The general pediatrician plays a key role in the early recognition of GPA given the broad spectrum of clinical manifestations that may accompany or precede the classic lesions of the airways and kidney.

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DOI: 10.1542/peds.2013-0466 originally published online April 21, 2014;

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DOI: 10.1542/peds.2013-0466 originally published online April 21, 2014;

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