



Submitted on: 05/10/2020

Approved on: 18/11/2020

CASE REPORT

Childhood granulomatosis with polyangiitis: the experience of a tertiary referral center in Ceará, Brazil

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Keywords:

Granulomatosis with polyangiitis, Anti-neutrophil cytoplasmic antibody-associated vasculitis, Pediatrics, Glomerulonephritis, Systemic vasculitis, Respiratory Tract Diseases.

Abstract

Granulomatosis with polyangiitis (GPA) is an ANCA-associated necrotizing granulomatous vasculitis. It is rare in the pediatric population and predominantly affects small and medium-sizes blood vessels; it preferentially involves the kidneys and the upper and lower respiratory tract. This retrospective case series looked into the medical charts of children and adolescents aged up to 18 years diagnosed with the condition based on the EULAR/PReS criteria in the period ranging from 2014 to 2019. It describes clinical characteristics, laboratory findings and treatment options, along with the progress of GPA in children. In our series, GPA predominantly affected females (80%) and the median age at diagnosis was 11.1 years. The classic clinical triad comprising granulomatous inflammation, pauci-immune necrotizing glomerulonephritis, and upper and lower respiratory tract involvement, was highly prevalent, and delays in diagnosis occurred particularly in individuals with mild kidney or lung involvement. Laboratory findings included elevated erythrocyte sedimentation rate, anemia, and hematuria; alterations included sinus disease, pulmonary infiltrates, nodules, and cavitation seen on CT scans of the head and chest, all of which are key diagnostic elements. All patients were treated with glucocorticoids and cyclophosphamide. Morbidity remained significant and unchanged throughout the course of the disease. Clinical and laboratory findings and prescribed treatments were consistent with the literature. Given its severity, this disease requires early recognition, aggressive initial treatment, and long-term patient follow-up.

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis that predominantly affects small and medium-size blood vessels, usually associated with antineutrophil cytoplasmic antibodies (ANCA)¹. The spectrum of involvement ranges from localized disease, without renal impairment, to multisystem dysfunction²⁻⁴. Although it may affect any organ, it is mainly seen in the form of granulomatous inflammation of the upper and lower respiratory tract and pauci-immune necrotizing glomerulonephritis³⁻⁹. Incidence in pediatric populations is estimated to range from 0.02 to 6.4 per 100,000 people a year⁵. Although rare, it can produce devastating outcomes.

This retrospective case series was based on the review of the medical charts of children and adolescents aged up to 18 years seen from 2014 to 2019, who met at least three of the following six criteria: 1) histopathology findings (granulomatous inflammation); 2) upper airway involvement; 3) laryngotracheobronchial involvement; 4) lung involvement; 5) ANCA positive; 6) kidney involvement. This study describes the clinical characteristics, laboratory findings, and treatments administered to children diagnosed with GPA, and the development of the disease. The Research Ethics Committee of our institution approved the study. Data were expressed as absolute numbers, frequencies/proportions, medians, and ranges (minimum-maximum).

RESULTS

Four female and one male were included in the study. The median age and time to diagnosis were 11.1 years (9.1-12.3years) and 12.7 months (1-26.3months), respectively. Delays in diagnosis were observed particularly in individuals with mild kidney or lung involvement. All patients required hospitalization and the median length of stay was two months (1.2 - 4.2 months).

Acute symptoms were seen in 40% of the patients (Table 1). Every patient had upper airway involvement at the time of diagnosis, with sinus disease as the main manifestation. None of the patients had laryngotracheobronchial involvement, and only two were ANCA-positive at diagnosis.

All patients in this study had renal involvement, with hematuria as the earliest sign of disease. Three children had a glomerular filtration rate of less than 15 ml/minute/1.73m², of which two had rapidly progressive glomerulonephritis with glomerular crescents and progressed to end-stage renal disease requiring renal replacement therapy. Since they did not recover kidney function, the patients underwent renal transplantation. Indirect immunofluorescence with a pauci-immune pattern was observed in all cases.

Although only three patients had pulmonary symptoms at presentation, all had alterations on chest CT scans. Three patients had fixed pulmonary infiltrates, two had nodules, and one had cavitation (Table 2).

Table 1. Initial signs and symptoms, progression, complications, and treatment administered to patients with granulomatosis with polyangiitis.

Patient	Sex	Age (years)	Early symptoms	Progression	Treatment
1	M	11.5	Headache, cough, dyspnea, epistaxis, weight loss >5%	Sinusitis, hematuria, proteinuria, hemoptysis, ARF, seizures	Pulse therapy with methylprednisolone; CT + CP; AZA
2	F	11	Headache, abdominal pain, myalgia, arthritis, hematuria	Sinusitis, AOM, Proteinuria, SH, subcutaneous nodules	Pulse therapy with methylprednisolone; CT + CP; MTX + CT; AZA + MTX + CT
3	F	12.3	Headache, fever, cough, myalgia, arthritis, epistaxis, weight loss >5%	Anemia, hematuria, proteinuria, dyspnea, hemoptysis, SH, AKI	Pulse therapy with methylprednisolone; CT + CP; RTX + CP; Ig; AZA+ CT; MMF + AZA
4	F	9.1	Fever, hematuria, proteinuria	Sinusitis, cough, AOM, dyspnea, SH, AKI, RRT	Pulse therapy with methylprednisolone; MMF; CP + CT; Ig + methylprednisolone; MMF; Tacrolimus, MFS
5	F	10.2	Headache, myalgia, arthralgia, weight loss >5%, abdominal pain, epistaxis, hematemesis, hematuria	bilateral AOM, mastoiditis, SH, AKI, RRT, seizures, hypertensive encephalopathy	Pulse therapy with methylprednisolone; CP + CT; RTX; Ig; MMF; Tacrolimus, MFS

F: female; M: male; ARF: acute respiratory insufficiency; AKI: acute kidney injury; AOM: acute otitis media; SH: systemic hypertension; RRT: renal replacement therapy; CT: corticoid; CP: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; RTX: rituximab; MMF: mycophenolate mofetil; MFS: mycophenolate sodium; Ig: immunoglobulin.

Table 2. Laboratory, imaging, and histopathology test results of patients with granulomatosis with polyangiitis (N = 5).

Patient	ESR (mm/h)	Hb (g/dL)	Hematuria (p/c)	ANCA	Chest HRCT	CT of the sinuses
1	100	6.9	+++ >40	Negative	Areas of trapped air in the upper and middle segment with mosaic thickening of the interlobar septa, and cavitation in the right upper lobe and ground-glass areas to the left	Ethmoid sinus and bilateral sphenoidal sinus disease
2	59	11.6	+++ 50	Negative	Nodules in the lower segment of the middle lobe of the right lung	Lobulated mucous thickening on the floor of the maxillary sinuses. Bilateral ethmoid and maxillary sinusitis
3	110	6.4	+++ 30	1:160	Ground glass areas in left lower lobe and halo sign	Ethmoid sinus disease
4	68	8.4	++++ >40	Negative	Diffuse bronchial parietal thickening, suggestive of bronchopathy	Ethmoid, sphenoid, frontal, and maxillary sinus disease
5	60	8.7	33	1:80	Bilateral ground-glass opacity in upper lobes and nodules with a halo measuring 0.6 cm in middle lobe of the right lung and posterior basal lobe of the left lung	Left sphenoid sinus disease + mastoiditis on the right

ESR: erythrocyte sedimentation rate; Hb: hemoglobin; ANCA: antineutrophil cytoplasmic antibodies; P: perinuclear pattern; mm/h: millimeters per hour; g/dL: grams per deciliter, mg/24h: milligrams in 24 hours; c/f: cells per field; HRCT: high resolution computed tomography.

Four children had central nervous system (CNS) involvement at presentation, with headaches as the chief complaint. Two children had gastrointestinal symptoms, including abdominal pain and diarrhea as initial symptoms.

A marked elevation in erythrocyte sedimentation rates and anemia were observed initially, which gradually improved upon the commencement of treatment.

All patients were given glucocorticoids as induction therapy and steroid pulse therapy with methylprednisolone (30 mg/kg with a maximum of 1 gram per day for 3 days), followed by gradual weaning with oral prednisone 2 mg/kg (up to 60 mg). Initially, four patients were given six cycles of cyclophosphamide (600mg/m² in the first month and 700mg/m² every three weeks for up to six months), except for one, who had induction therapy with mycophenolate mofetil (500-1,500 mg/day). In addition, three patients were prescribed intravenous immunoglobulin (2g/kg) and two were given rituximab (375 mg/m² once a week for 4 weeks) due to unimproved or worsening kidney function.

The indications for the five patients given cyclophosphamide were as follows: alveolar hemorrhage (N = 1); and kidney failure with an eGFR <50 mg/dl (N = 4).

During follow-up, one patient had an audiogram showing conductive hearing loss. One had a saddle nose as a result of nasal cartilage obliteration.

Three achieved remission with low-dose steroids in combination with glucocorticoid-sparing agents, and one

achieved remission on azathioprine alone (2 mg/kg/day). Of these, two achieved remission after kidney transplantation. Time to remission was 12.3 months (10-16 months).

Two patients did not achieve remission and remained on long-term maintenance treatment on account of persistent kidney dysfunction.

Five children had to be readmitted for the following reasons: infection (N=2); hypertensive urgency (N=1); dialysis catheter malfunction (N=2); and renal transplantation (N=2).

None of the patients on follow-up relapsed or died.

DISCUSSION

GPA occurs rarely in children, with few cases described in Brazil. The five cases diagnosed at a single tertiary center within approximately five years motivated this study. Females were predominant in our cohort with 80% of the cases, as similarly described in other series¹⁻⁵.

The median age at diagnosis in our cohort was 11.1 years, as also reported in other recently published pediatric series^{3-5,10,11}. The median time to diagnosis was 12.7 months, a period longer than that of the 3 to 5 months (1.5 – 8 months) published in five other studies^{3-5,10,11}. The disparity between onset of disease and diagnosis may indicate difficulties related to the disease's unspecific presentations and insidious onset seen in 60% of the patients in our series. Low ANCA positivity (40%) may have occurred due to the difficulties faced locally

in performing tests with ELISA kits. Although the presence of antibodies is not required for purposes of diagnosis, it is still a useful indicator to corroborate diagnosis¹²⁻¹⁴.

The children with GPA in our series had multisystem involvement, although a study published in 1993 suggested that GPA in children presents more often as a localized or limited disease¹¹. The reason for the high prevalence of generalized disease in our study is not entirely clear, but it is likely due to the fact that our hospital is a referral center for pediatric rheumatology in the state.

Regarding the clinical findings described in our series, upper respiratory tract involvement was the main finding in children with GPA, as also reported in the literature^{1,7-10}. Previous studies found that the most common complication in the pediatric form of the disease is subglottic stenosis^{10,14}. Although no patient in the present study had laryngotracheobronchial involvement, subglottic stenosis may narrow the diagnostic hypotheses when compared to other respiratory tract manifestations.

Unlike previous studies,¹⁻⁶ all patients included in our series had kidney disease. In our experience, recovery from kidney disease is a rare event.

Kidney biopsies were crucial for the diagnosis of GPA, as they showed pauci-immune glomerulonephritis in all patients. They also provided important prognostic information, in that patients with crescentic glomerulonephritis progressed rapidly to end-stage renal disease.

In our series, pulmonary involvement was as common as kidney disease. Imaging findings in our population were comparable to those reported in other pediatric series, although with a higher proportion of anomalies^{5,14}. The importance of obtaining chest CT scans in patients with persistent airway disease cannot be emphasized enough.

In agreement with recent literature^{3,5}, gastrointestinal and neurological manifestations were common in our group and often preceded the diagnosis of GPAws.

Altered laboratory test results, except for the absence of ANCA positivity seen in 60% of the patients, were common in our population and were all well described.

Prescribed treatments were consistent with the EULAR and SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) recommendations, with steroid induction therapy being the most prescribed protocol⁶⁻⁸. Although rituximab has been the medication of choice in recent studies for providing the same therapeutic response as cyclophosphamide with fewer side effects, our series showed no such predilection¹⁵. As for remission maintenance treatment, international recommendations over doses and length of treatment were followed.

The impact on morbidity in our cohort was significant both at presentation and during disease progression, as evidenced by the need for hospitalization at diagnosis (100%), frequent hospital readmissions, high prevalence of chronic

kidney disease (60%), saddle nose deformities (20%), and hearing loss (20%).

Most children achieved remission at least once and are still being treated and kept on outpatient follow-up. Unlike our study, most longer-term studies reported both recurrence and death, which indicates that longer patient follow-up is needed¹⁻⁵.

CONCLUSION

Children with GPA often presented with the systemic form of the disease. Timely diagnosis is of the essence, given the increased morbidity associated with multisystem involvement. The risks of chronic organ damage confirm the severity and difficulty of treating the disease, reinforcing the need for early recognition, aggressive initial treatment, and long-term patient follow-up.

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