Global Pediatric Health
Volume 4: 1–4
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2333794X17733860
journals.sagepub.com/home/gph
SAGE

Unilateral Periorbital Swelling in Two Previously Healthy Females

Amanda R. Schlefman, DO[1], AnneMarie C. Brescia, MD[1], Maureen G. Leffler, DO[1], and Carlos D. Rosé, MD[1]

Received July 3, 2017. Accepted for publication August 21, 2017.

Case Report

Patient 1

This previously healthy 6-year-old girl presented to our children's hospital after being diagnosed and treated for blepharoconjunctivitis with preseptal cellulitis of her left eye. Symptoms of swelling and redness failed to improve and subsequent magnetic resonance imaging (MRI) identified an orbital mass. An eyelid biopsy was obtained revealing histiocytes with central punctuate necrosis, multinucleated giant cells, and vasocentric inflammatory infiltrate with some cells within the vessel wall (Figure 1A). Simultaneously she was found to be anemic (nadir 4.3 g/dL) with thrombocytosis (905 000/μL) and elevated acute phase reactants (erythrocyte sedimentation rate 139 mm/h, C-reactive protein 5.4 mg/dL). She was also in acute renal failure with large hematuria, 3+ proteinuria, and elevated creatinine (2.0 mg/dL).

Patient 2

A healthy 11-year-old female presented to our emergency room with right eyelid swelling and redness. She was treated for preseptal cellulitis with oral prednisone and amoxicillin-clavulanate, but did not seek follow-up care until there was another episode of right eye swelling 9 months later. She also had cough, chest tightness, and wheezing that was attributed to new-onset reactive airway disease. Laboratory studies revealed leukocytosis (13 200/μL), thrombocytosis (432 000/μL), and an elevated sedimentation rate (32 mm/h). MRI revealed a unilateral intraorbital mass, concerning for inflammatory pseudotumor. This was excised and pathology revealed scattered histiocytes, multinucleated giant cells, chronic inflammation, and fibrosis. The orbital mass recurred within 1 year along with 2 new subcutaneous nodules on her flank. Biopsy of these nodules revealed granuloma formation, vasculitis, and extravasated eosinophils (Figure 1B).

Hospital Course

Patient 1

Chest computed tomography (CT) was notable for 2 to 3 tiny perihilar nodules with some patchy ground glass areas. Renal biopsy revealed pauci-immune crescentic glomerulonephritis with necrotizing changes. Laboratory workup was positive for perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA; 1:160 titer) and MPO (myeloperoxidase) antibodies (>100 U/mL with reference range <6 U/mL), which, in conjunction with the biopsy findings, led to the diagnosis of microscopic polyangiitis (MPA). The patient was subsequently treated with pulse doses of intravenous steroids, oral cyclophosphamide (2 mg/kg/day), and 4 weekly rituximab infusions (375 mg/m^2/dose). Despite aggressive therapy she required dialysis for renal failure and ultimately received a living related donor kidney transplant.

Patient 2

The ensuing workup was significant for thrombocytosis (559 000/μL), anemia (nadir of 7.3 g/dL), and elevated markers of inflammation (erythrocyte sedimentation rate 87 mm/h, C-reactive protein 2.92 mg/dL). In addition, she had positive p-ANCA (1:80 titer) with MPO antibodies (>100 U/mL with reference range <6 U/mL). Serum IgE was elevated at 441 kU/L (reference range <114

[1]Nemours/A.I. duPont Hospital for Children, Wilmington, DE, USA

Corresponding Author:
Amanda R. Schlefman, Department of Pediatric Rheumatology, A.I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA.
Email: aschlefm@nemours.org

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

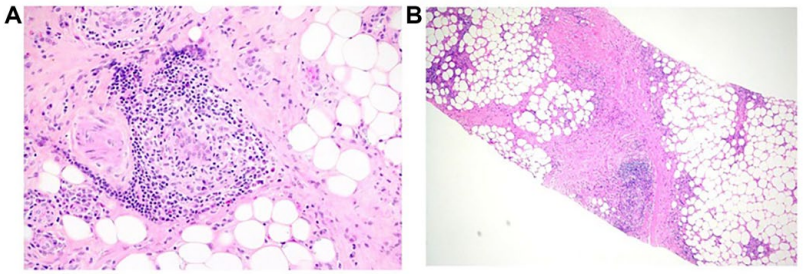

Figure 1. (A) Orbital biopsy from Patient 1 reveals dense vasocentric neutrophilic inflammatory infiltrate with multinucleated histiocytes and punctate necrosis. (B) Flank mass biopsy from Patient 2 shows septal and lobular panniculitis with focal vasculitis, granulomatous inflammation, and increased eosinophilic infiltration.

Table 1. Characteristics of Patients Diagnosed in Our Pediatric Rheumatology Division.

Patient	Age (Years), Gender	Serology	Diagnosis	Diagnostic Modality	Disease Course	Treatment	Outcome
1	6, female	+p-ANCA	Microscopic polyangiitis	Renal biopsy	• Glomerulonephritis	Steroids	Remission on maintenance mycophenolate, tacrolimus, prednisone
		+MPO antibody			• Dialysis complicated by peritonitis	Cyclophosphamide	
					• Kidney transplant	Rituximab	
2	11, female	+p-ANCA	Churg-Strauss syndrome	Subcutaneous nodule biopsy	• Erythema induratum-like flank lesions	Steroids	Remission on maintenance azathioprine
		+MPO antibody			• Glomerulonephritis	Cyclophosphamide	
					• Hashimoto's thyroiditis, then Graves' disease		

kU/L). Chest CT revealed ground glass densities in the upper lobes and focal opacities in the lung bases. Based on the histologic features of the biopsy with prominent eosinophils, p-ANCA/MPO, elevated serum IgE, and lung findings including asthma, she was diagnosed with Churg-Strauss syndrome (CSS). She later developed microscopic hematuria and proteinuria with pauci-immune crescentic glomerulonephritis and necrosis on renal biopsy. She received pulse doses of intravenous steroids and 9 doses of monthly cyclophosphamide infusions (750 mg/m^2/dose). She is currently maintained on azathioprine (200 mg daily). She has also been followed by Endocrinology initially for Hashimoto's thyroiditis and now for the development of Graves' disease.

Final Diagnosis

ANCA-associated vasculitis. Patient 1: microscopic polyangiitis; Patient 2: Churg-Strauss syndrome.

Discussion

We report herein the cases of 2 young females who presented with periorbital swelling, identified as orbital pseudotumor, and ultimately were diagnosed with ANCA-associated vasculitis, specifically MPA and CSS (Table 1). Orbital pseudotumor as the presenting symptom of these subtypes of ANCA-associated vasculitis has not been reported in the literature.

Granulomatosis with polyangiitis (GPA), MPA, and CSS collectively make up the primary ANCA-associated vasculitides (AAV). They are characterized by inflammation of small- to medium-sized blood vessels in which circulating immunoglobulins cause direct injury to the vessel walls.[1]

The differentiation of ANCA-associated vasculitis subtypes is based on clinical and laboratory data. Both patients presented solely with orbital complaints. Although Patient 1 was otherwise asymptomatic, laboratory studies showed overwhelming evidence of chronic systemic inflammation and renal failure. Imaging revealed pulmonary nodules and interstitial lung disease. Orbital biopsy was histologically consistent with a necrotizing vasculitis without documented granulomas, and renal biopsy confirmed scant deposits on immunofluorescence. All of the AAV have a classic pauci-immune pattern on immunofluorescence microscopy. MPA is histologically distinct from the other AAV due to the absence

Table 2. Identified Publications for Pediatric Patients With ANCA-Associated Vasculitis Presenting as Orbital Pseudotumor.

Study	Year of Publication	Cases Described	Diagnosis
Parelhoff et al[10]	1985	N = 5	GPA, 5; CSS, 0; MPA, 0
Chipczynska et al[11]	2009	N = 4	GPA, 4; CSS, 0; MPA, 0
Boulter et al[12]	2012	N = 5	GPA, 5; CSS, 0; MPA, 0
Gajic-Veljic et al[13]	2013	N = 1	GPA, 1; CSS, 0; MPA, 0

Abbreviations: GPA, granulomatosis with polyangiitis; CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis.

of granulomatous inflammation. Further testing on Patient 1 indicated the presence of p-ANCA and MPO antibodies. The p-ANCA pattern with antibodies against MPO is strongly associated with MPA and CSS, while c-ANCA pattern and anti-PR3 antibodies are highly sensitive and specific for GPA. Although p-ANCA can be seen in 10% to 26% of GPA patients,[2] we felt that this patient's serology and lack of granulomas were more indicative of MPA.

Patient 2 did not report extra-orbital symptoms until her second presentation when she was diagnosed with new-onset asthma. Orbital biopsy findings were nonspecific; however, biopsy of the subcutaneous nodules displayed vasculitis, granulomas, and prominent extravasated eosinophils. As in the first case, Patient 2 had serologic findings of p-ANCA positivity, anti-MPO antibodies, and an abnormal chest CT. Later in the course, renal biopsy revealed a paucity of immune deposits and necrotizing inflammation. This patient's serology, as previously discussed, is more suggestive of MPA or CSS. Granulomatous inflammation raises suspicion for GPA or CSS. The presence of eosinophils on histology is highly characteristic of CSS, although not specific as this can be seen in smaller quantities in GPA patients. Asthma is the hallmark of patients with CSS and infiltrates on lung imaging can be seen. Peripheral eosinophilia >10% is a common finding in CSS[3] but may not be seen in all cases. This patient's constellation of symptoms and objective data led to a diagnosis of CSS.

The exact incidence and prevalence of MPA and CSS in children are unknown but are thought to be low. It is estimated that primary vasculitis is diagnosed in only 3% of children who are referred to Rheumatology clinic.[4] To our knowledge, there have been less than 50 total cases of pediatric CSS reported. Studies comparing adults and children with CSS reveal that children have more lung, gastrointestinal, and cardiac involvement but less musculoskeletal, nervous system, and renal involvement.[5] MPA occurs more frequently in childhood than CSS. Children with MPA tend to have less hypertension than adults but a higher incidence of renal failure and chronic kidney disease.[6] There may also be skin, lung, and gastrointestinal involvement in pediatric MPA.

Ocular disease in AAV has been increasingly recognized in the absence of or along with systemic disease. The incidence of eye involvement is highest in GPA, followed by CSS with rare reports in MPA.[7] Studies have estimated that ocular manifestations occur in 50% to 60% of adults with AAV, and may be the presenting symptom in up to 16%.[8] Data from the largest cohort to date of childhood vasculitis reports ocular involvement in 31% to 43% of pediatric patients with GPA and MPA.[9] Orbital pseudotumor specifically has not been reported in childhood CSS or MPA, thought it has been published as the presenting symptom of childhood GPA (Table 2).

Parelhoff et al's study[10] from 1985 described a young female who presented with orbital pseudotumor and was ultimately diagnosed with GPA. At that time there were 4 other cases of pediatric GPA in the literature that presented with inflammatory orbital pseudotumor. A case series from a children's hospital in Poland[11] presented 4 children who were diagnosed with GPA in the Department of Ophthalmology from 1995 to 2008. They all presented with unilateral eyelid swelling and imaging confirmed orbital pseudotumor. A retrospective case series from a single pediatric center in Oxford[12] looked at 10 children who presented to the Rheumatology Department from 1999 to 2010 with inflammatory eye lesions. Initial symptoms were orbital or periorbital swelling, some one-sided and others bilateral. Five of these patients were diagnosed with GPA. The remaining diagnoses included idiopathic orbital pseudotumor, atypical mycobacterial infection, and sarcoidosis. Gajic-Veljic et al's case series from a university hospital system in Serbia[13] reported 3 pediatric patients who were diagnosed with GPA from 1992 to 2011. Two patients never developed ocular symptoms while the third presented with unilateral eyelid swelling, ptosis, and episcleritis, and MRI revealed orbital pseudotumor. In all these case series the diagnosis of GPA was made based on clinical and laboratory data, as well as histopathology.

Conclusion

The literature reports that 16% to 19% of childhood GPA presents with orbital inflammatory pseudotumor.[11-13]

With the absence of clinical reports of this presentation in MPA or CSS, these vasculitides might not be given much thought in the differential diagnosis. Our case reports emphasize that MPA and CSS should be considered in patients who present with orbital pseudotumor. Prompt identification is ideal, as these diseases can have long-term morbidity. Regular follow-up may be needed for the patient to evolve and fulfill the diagnostic criteria.

Acknowledgments

We would like to thank Jing Jin, MD, PhD, Jonathan Salvin, MD, and Mihir Thacker, MD, for exceptional clinical care of our patients.

Author Contributions

ARS: Contributed to conception or design; contributed to acquisition, analysis, or interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
ACB: Contributed to conception or design; contributed to acquisition, analysis, or interpretation; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MGL: Contributed to conception or design; contributed to acquisition, analysis, or interpretation; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
CDR: Contributed to conception or design; contributed to acquisition, analysis, or interpretation; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Siomou E, Tramma D, Bowen C, Milford DV. ANCA-associated glomerulonephritis/systemic vasculitis in childhood: clinical features-outcome. *Pediatr Nephrol*. 2012;27:1911-1920.
2. Bohm M, Gonzalez Fernandez MI, Ozen S, et al. Clinical features of childhood granulomatosis with polyangiitis (Wegener's granulomatosis). *Pediatr Rheumatol*. 2014;12:18. doi:10.1186/1546-0096-12-18.
3. Cabral D, Benseler S. Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In: Cassidy JT, ed. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2005:521-543.
4. Iudici M, Puéchal X, Pagnoux C, et al; French Vasculitis Study Group. Childhood-onset systemic necrotizing vasculitides: long-term data from the French Vasculitis Study Group Registry. *Arthritis Rheumatol*. 2015;67:1959-1965. doi:10.1002/art.39122.
5. Gendelman S, Zeft A, Spalding S. Childhood-onset eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome): a contemporary single-center cohort. *J Rheumatol*. 2013;40:929-935.
6. Sun L, Wang H, Jiang X, et al. Clinical and pathological features of microscopic polyangiitis in 20 children. *J Rheumatol*. 2014;41:1712-1719.
7. Schmidt J, Pulido JS, Matteson EL. Ocular manifestations of systemic disease: antineutrophil cytoplasmic antibody-associated vasculitis. *Curr Opin Ophthalmol*. 2011;22:489-495.
8. Watkins AS, Kempen JH, Choi D, et al. Ocular disease in patients with ANCA-positive vasculitis. *J Ocul Biol Dis Infor*. 2010;3:12-19.
9. Cabral DA, Canter DL, Muscal E, et al; ARChiVe Investigators Network within the PedVas Initiative. Comparing presenting clinical features of 48 children with microscopic polyangiitis (MPA) against 183 having granulomatosis with polyangiitis (GPA). An ARChiVe study. *Arthritis Rheumatol*. 2016;68:2514-2526.
10. Parelhoff ES, Chavis RM, Friendly DS. Wegener's granulomatosis presenting as orbital pseudotumor in children. *J Pediatr Ophthalmol Strabismus*. 1985;22:100-104.
11. Chipczynska B, Gralek M, Hautz W, et al. Orbital tumor as an initial manifestation of Wegener's granulomatosis in children: a series of four cases. *Med Sci Monit*. 2009;15:CS135-CS138.
12. Boulter EL, Eleftheriou D, Sebire NJ, Edelsten C, Brogan PA. Inflammatory lesions of the orbit: a single paediatric rheumatology centre experience. *Rheumatology (Oxford)*. 2012;51:1070-1075.
13. Gajic-Veljic M, Nikolic M, Peco-Antic A, Bogdanovic R, Andrejevic S, Bonaci-Nikolic B. Granulomatosis with polyangiitis (Wegener's granulomatosis) in children: report of three cases with cutaneous manifestations and literature review. *Pediatr Dermatol*. 2013;30:e37-e42.