



MOC-CME Review

A 10-year-old girl with persistent ocular swelling

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Identify the differential diagnosis of ocular swelling in a child
- Discriminate between orbital GPA and allergic disease
- Identify the manifestations of GPA in pediatric population

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Target Audience

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Clinical Vignette

A 10-year-old previously healthy girl presented with unilateral painless right eyelid swelling. On July 4, 2015, her family visited a waterpark, where she developed a headache, fever to 103°F, and was noted to have a swollen right eye. The fever resolved after 2 days but the eye swelling persisted. She was evaluated by her pediatrician and empirically treated with an oral antibiotic (cefdinir), with perceived minimal improvement in the swelling. An ophthalmic evaluation performed at the end of July showed moderate periorbital edema of the right eye without erythema or warmth. Visual acuity was 20/40 in the right eye and 20/20 in the left eye and conjunctivae and corneas were clear bilaterally. Pupillary examination was normal without an afferent pupillary defect. There was no optic nerve edema. She was given a diagnosis of right eye preseptal cellulitis and treated with a 10-day course of amoxicillin-clavulanic acid without improvement. Subsequent magnetic resonance imaging (MRI) of the orbits was reportedly normal. After MRI, she was given trimethoprim and sulfamethoxazole, with some improvement but no resolution of the right eye swelling.

In October, she developed swelling and redness of the left eye associated with transient low-grade fever and weakness. Evaluation in the emergency department included computed tomography (CT) without contrast that visualized mild right periorbital soft tissue swelling with unremarkable paranasal sinuses. She was discharged home on oral diphenhydramine.

She presented to a pediatric rheumatologist in late October secondary to persistent and more visible bilateral eye symptoms. She also complained occasionally of an abdominal pain but was otherwise asymptomatic. The laboratory evaluation was remarkable for an increased erythrocyte sedimentation rate (ESR; 37 mm/hour) and platelet count (436,000/ μ L). However, owing to the absence of systemic symptoms and a negative family history, a rheumatologic condition was believed to be unlikely.

She underwent allergy evaluation in October for possible inhalant allergy causing simultaneous allergic conjunctivitis and eye swelling. She did not report allergic conjunctivitis symptoms,

such as watery or itchy eyes, but did acknowledge year-round sneezing and rhinorrhea. Her examination was significant for prominent bilateral suborbital swelling (right greater than left) and allergic shiners without conjunctival injection. Allergy skin prick test results were positive for dust mites, dog dander, tree and grass pollen, and she was diagnosed with seasonal and perennial allergic rhinoconjunctivitis. Environmental control measures for dust mites were implemented in her bedroom and she was put on daily oral antihistamine (fexofenadine), intranasal fluticasone, and ketotifen eye drops.

Despite these treatments, the bilateral eye swelling continued to worsen and in December she developed right eye proptosis and ptosis. She was referred to an oculoplastic surgeon who found decreased visual acuity in the right eye and ordered CT of the orbits. CT visualized bilateral retro-orbital masses that were more pronounced on the right (Fig 1). Biopsy examination of the tissue was read as follicle formation and replacement of the orbital fat by a fibrosis process. A mixed population of CD20⁺ B lymphocytes (mostly confined to the follicles) and CD3⁺ T lymphocytes diffusely distributed in the sclerotic stroma was present in addition to many CD138⁺ plasma cells. Many of these cells were positive for immunoglobulin (Ig) G, with rare IgG4-positive stains. In situ hybridization for κ - and λ -light chains showed slight κ predominance. Grocott methenamine silver stain and acid-fast bacilli stain were negative for fungus and mycobacteria organisms. There were areas of necrotizing granulomas with giant cells and focal alteration of collagen and associated granular-type fibrosis. Although no vasculitis was seen, granulomatosis with polyangiitis (GPA) was considered a possible diagnosis. ESR was increased at 47 mm/hour and perinuclear antineutrophil cytoplasmic antibodies (ANCA) were positive at 1:60 with positive antimyeloperoxidase antibodies higher than 1.0. Cytoplasmic ANCA and proteinase-3 antibodies were negative.

Differential Diagnosis

The differential diagnosis of eye swelling is extensive and presented in Table 1. The initial acute onset of unilateral eye swelling, fever, and decreased visual acuity detected at eye examination is

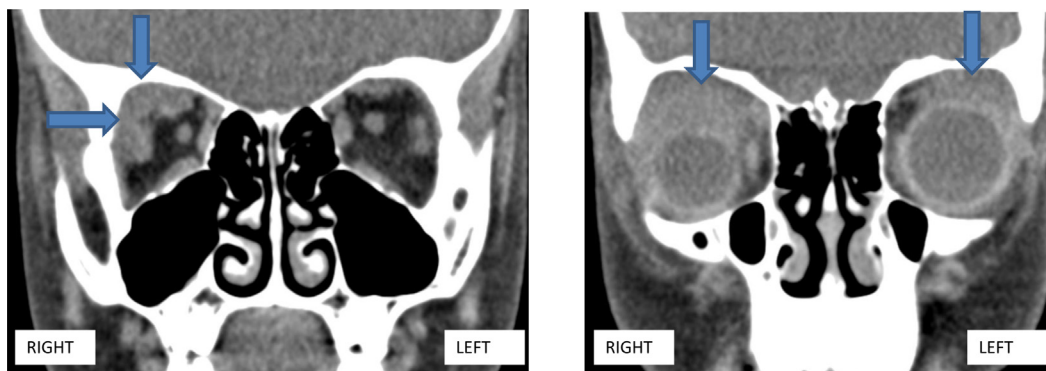


Figure 1. Computer tomograms of orbits without contrast obtained 5 months into the disease before starting treatment. A large infiltrative extraconal soft tissue mass in the superolateral aspect of the right orbit and a smaller soft tissue mass on the left are visible (arrows). The masses are partly inseparable from the adjacent extraocular muscles and lacrimal glands. There is mild deformity of the right globe without gross evidence of intraocular invasion. There is no gross evidence of bony invasion or extra-orbital extension.

highly suspicious for an infectious etiology. The most likely diagnoses considered were preseptal and orbital cellulitis. However, the patient received multiple courses of antibiotics for 2 to 3 months with minimal to no improvement of the persistent swelling. Her fever resolved promptly and over time symptoms progressed to the contralateral eye, making infection less likely. In addition, the initial imaging finding was not consistent with infection.

An allergic etiology also was seriously considered because of the chronicity of symptoms, progression to bilateral eye involvement, and history of symptoms consistent with allergic rhinitis. Her skin prick test reaction identified multiple environmental triggers, allowing contact dermatitis and allergic rhinoconjunctivitis to be added to the differential. However, her symptoms never decreased with antihistamines, intranasal corticosteroids, or allergen-decreasing lifestyle changes. There was no history of product or chemical exposures to the eyelids that were suggestive of irritant contact dermatitis. Chronic angioedema was an alternative diagnosis considered to explain her bilateral eyelid swelling. The recurrence of symptoms without urticaria or known recurrent exposure to allergens was more consistent with hereditary or acquired angioedema. However, complement studies were performed and results were within normal limits, ruling out hereditary or acquired forms of angioedema.

Because the patient developed proptosis and ptosis months into her clinical course, thyroid-related orbital disease can be considered in the differential diagnosis (Table 1). Pediatric thyroid orbital disease typically presents with periorbital edema, proptosis, and/or lid lag, although symptoms are usually mild. However, her thyroid function study results were within normal limits.

Idiopathic orbital inflammatory syndrome or orbital pseudotumor can present with unilateral or bilateral proptosis and eyelid swelling, as in this patient. This disorder is a benign inflammatory mass that invades any part of the orbit. Classic presentations are sudden onset of pain, proptosis, conjunctival injection, ocular motility restriction, and edema of the affected eye in a middle-age woman.¹ Pediatric patients have a relatively low incidence of this disorder.² In addition, pediatric symptoms usually initiate bilaterally and include uveitis, disc edema, and eosinophilia at tissue biopsy examination.^{2,3} The present patient's clinical symptoms were not consistent with the acute symptoms of orbital pseudotumor, making this diagnosis unlikely.

Blepharochalasis is a rare disorder characterized by intermittent flares of painless, nonerythematous, bilateral eyelid edema and typically presents in childhood and early adolescence. However, clinical flares typically last only approximately 1 to 2 days and usually involve only the upper eyelids.

Melkersson-Rosenthal syndrome is another rare syndrome on the differential, characterized by recurrent swelling of the face and lips, facial paralysis, and fissures and cracks of the tongue. Facial swelling typically includes eyelid and/or lips and presents in school-age children.⁴ Although the present patient lacked tongue and neurologic involvement, patients might have only a single symptom of the triad. Noncaseating granulomatous lymphangitis characterizes tissue biopsy findings of Melkersson-Rosenthal syndrome, which is contrary to the present patient with necrotizing granulomas at biopsy examination.⁴

The retro-orbital soft tissue masses noted on the child's CT scan several months into illness were a concern for a possible primary malignancy such as rhabdomyosarcoma, lymphoma, or metastasis. An enlarging orbital malignancy could explain her chronic peri-orbital swelling and late development of proptosis and ptosis. She lacked other systemic symptoms, and her laboratory results were within normal limits. An oncologist reviewed her tissue pathology and had low suspicion for malignancy.

Tissue biopsy examination was ultimately the most useful diagnostic tool, indicating the etiology of her symptoms as GPA. GPA accounts for the necrotizing granulomas noted on the tissue biopsy specimen of the orbit and can account for her previously increased ESR (Table 1).

Wegener granulomatosis (ie, GPA) is a chronic systemic vasculitic disease that targets small and medium-size vessels of any organ in the body. It is characterized by necrotizing granulomatous inflammation of the vessels, most commonly in the upper and lower respiratory tract and the kidneys in children. Limited ocular GPA can manifest in the eye alone, with different symptoms in the orbit, the eye, and even the optic nerve.

Pathophysiology of GPA

Granulomatosis with polyangiitis is strongly associated with the presence of ANCA within neutrophils, which can be cytoplasmic or perinuclear. The role of ANCA in the pathogenesis of GPA is unknown. Cytoplasmic ANCA are often directed against proteinase-3.⁵ The leading hypothesis suggests that ANCA activate neutrophils and monocytes, which target endothelial cells and lead to activation of the complement pathway and to endothelial damage. ANCA also can trigger vasculitis by activating neutrophils to release chromatin fibers and deposit them in the kidney.⁵

Epidemiology

Granulomatosis with polyangiitis is rare, occurring in approximately 3 cases per 100,000 adults. The age of onset is the fourth to

Table 1
Differential Diagnosis of Persistent and/or Progressive Eye Swelling

	Features	Pathomechanism and etiology
Infectious		
Cellulitis: preseptal or orbital	eyelid swelling, tenderness, erythema or induration, discharge, fever, pain with eye movement, leukocytosis	common bacteria: <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Streptococcus pyogenes</i> ; pediatric cases: <i>Haemophilus influenzae</i> ; immunocompromised host: mucormycosis (zygomycosis)
Tuberculosis of eyelid	abscess or mass on surface of eyelid, usually localized swelling or palpable mass	result of hematogenous spread or extension of nearby skin infection with <i>Mycobacterium tuberculosis</i>
Allergic or irritant		
Allergic angioedema	bilateral facial swelling including eyes and lips, urticaria	IgE-mediated type 1 hypersensitivity in which mast cells and basophils are activated and histamine, leukotrienes, etc, are released secondary to allergen exposure
Allergic rhinoconjunctivitis	bilateral conjunctival injection, eyelid edema, chemosis, tearing, rhinorrhea, allergic shiners with history of allergen exposure	inflammation of mucous membranes secondary to allergen exposure-induced IgE-mediated activation of inflammatory mediators (type 1 hypersensitivity)
Irritant contact dermatitis	eyelid swelling and erythema, pruritus, erythema with history of irritant exposure	disruption of integrity of epithelial skin barrier by irritant resulting in permeability and inflammation of skin
Angioedema		
Hereditary or acquired angioedema	bilateral facial swelling including eyes and lips, without urticaria	deficiency in level of C1 inhibitor resulting in increased bradykinin release
Thyroid disease		
Thyroid ophthalmopathy	bilateral eye swelling, proptosis, ptosis, and lid lag	hypothyroidism or hyperthyroidism
Malignancy		
Primary tumor or metastases	unilateral or bilateral eye swelling, proptosis, ptosis, constitutional symptoms, mass on imaging, lymphadenopathy	primary: neuroblastoma, rhabdomyosarcoma, lymphangioma, liposarcoma, and lymphoma; metastases: neuroblastoma, breast cancer
Autoimmune or chronic inflammatory		
Idiopathic orbital inflammatory syndrome orbital pseudotumor	unilateral or bilateral eye swelling, redness, and pain; photophobia, proptosis, periorbital edema, chemosis, conjunctival injection, and occasionally diplopia	mechanism unknown, hypothesized to be autoimmune, mediated by T and B cells; complete remission in response to high-dose systemic corticosteroids
Granulomatosis with polyangiitis (Wegener granulomatosis)	unilateral or bilateral eye swelling, episcleritis, scleritis, uveitis, proptosis, ptosis, conjunctival injection, with systemic involvement (upper and lower respiratory, renal)	etiology unclear, likely related to ANCA activation of immune system
Sarcoidosis	unilateral or bilateral orbit swelling, with ptosis, uveitis, ophthalmoplegia, and systemic involvement (arthralgias, lower respiratory tract, skin rash, etc)	unknown etiology, associated with noncaseating granuloma, T lymphocyte, and phagocyte accumulation in affected tissue
Systemic lupus erythematosus	multiorgan involvement including eye swelling, malar rash and mucocutaneous ulcers, renal failure, fatigue, fever, weight loss, arthralgias	mechanism hypothesized to be mediated by immune complex and antibody formation and deposition and complement activation
Dermatomyositis (juvenile)	bilateral periorbital edema, Gottron papules, heliotrope rash, proximal muscle weakness	mechanism not fully understood, believed to be secondary to environmental trigger that causes dysregulation of innate and adaptive immune systems
Unknown etiology		
Blepharochalasis	intermittent, nonerythematous cyclical upper eyelid swelling lasts 1–2 d, with up to 3–4 attacks per year; eyelids become wrinkled, redundant, discolored, and thinned	unknown etiology; biopsy shows atrophy, fragmentation, markedly decreased amounts of elastic fibers in dermis; there might be perivascular infiltration with lymphocytes, histiocytes, mast cells, plasma cells, and eosinophils; patients could have IgA antibodies directed against elastic fibers
Melkersson-Rosenthal syndrome	eyelid swelling associated with cracked or fissured lips, facial paralysis (uni- or bilateral)	unknown etiology; noncaseating granuloma are seen at tissue biopsy examination
Cutis laxa	loose and pendulous skin; folds around eyes, face, head, neck, and all over body	unknown etiology possibly related to elastin degradation
Floppy eyelid syndrome	elastic upper eyelid, chronic papillary conjunctivitis with eye tearing and burning, easy inversion of eyes, unilateral or bilateral; associated with obstructive sleep apnea	associated with decreased tarsal elastin of unknown mechanism
Lax eyelid (dermatochalasis)	lax and redundant eyelid skin of upper and lower lids bilaterally, loss of superior or peripheral vision fields	normal aging of skin resulting in loss of elasticity and skin thickness

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; Ig, immunoglobulin.

sixth decades of life in adults, with peak incidence in the sixth decade. The 2 sexes are affected equally by most accounts.⁶ In children, GPA usually occurs in the second decade of life and has a female predominance.⁷ The incidence of disease is approximately 0.1 to 0.64 cases per 100,000 in pediatrics.^{5,8,9}

Presentation

Granulomatosis with polyangiitis often presents with nonspecific symptoms affecting any organ system and can include recurrent upper respiratory symptoms refractory to allergic and infectious treatments. A 2014 study by Bohm et al¹⁰ reported that children are most likely to develop involvement in the ear, nose,

and throat (91%), constitutional symptoms (89%), respiratory or pulmonary symptoms (79%), renal symptoms (68%), mucosa and skin symptoms (64%), and musculoskeletal symptoms (59%). Gastrointestinal and central nervous system involvement are uncommon. Overall, children are more likely to have generalized multifocal disease at presentation and have more occurrences of subglottic stenosis and nasal deformity than adults.⁷ Table 2 presents a comparison of clinical features of GPA in children and adults.

The present patient presented with ocular manifestations of GPA, which are seen in 35% to 50% of children (50% to 60% of adults) by most reports and can affect all parts of the eye.⁵ Ocular disease can present with different eye symptoms, including pain, edema or

Table 2Common Manifestations of Granulomatosis with Polyangiitis in Children and Adults¹⁰

System	Children	Adults
Constitutional ENT	fever, weight loss, malaise recurrent sinusitis, discharge, and epistaxis; nasal septum ulcerations or saddle nose; subglottic stenosis; otitis media, otorrhea	fever, malaise recurrent nasal discharge, and epistaxis; recurrent sinusitis; recurrent otalgia, conductive or sensorineural hearing loss
Ocular	conjunctivitis, edema, keratitis, blepharitis	scleritis, episcleritis, periorbital edema or proptosis
Respiratory	tracheal or endobronchial stenosis, obstruction, pulmonary nodules hemoptysis, alveolar hemorrhage	pulmonary nodules, hemoptysis
Renal	glomerulonephritis, hematuria or RBC casts	hematuria, glomerulonephritis
Vascular	venous thromboembolism less common	venous thromboembolism
Musculoskeletal	arthralgias, myalgias	arthralgias, myalgias
Skin and mucosa	petechiae, purpura	purpura, skin ulcers

Abbreviations: ENT, ear, nose, and throat; RBC, red blood cell.

erythema of the eyelids, pain on extraocular eye movements, conjunctival injection, proptosis, scleritis, and episcleritis. Involvement of the optic nerve by compression from local inflammation and granulomas can result in vision loss and lead to proptosis.^{11,12}

Diagnosis

Approximately 85% to 95% of patients, adult and children, with systemic GPA have serum positivity for cytoplasmic ANCA staining patterns. Five percent to 20% have positivity for cytoplasmic ANCA against proteinase-3. Overall, ANCA positivity using immunofluorescence and enzyme-linked immunosorbent assay is the most sensitive and specific laboratory criterion for diagnosis in children and adults.⁶

Laboratory tests can demonstrate increased levels of inflammatory makers (ESR and C-reactive protein), mild anemia, leukocytosis, and hypoalbuminemia. Eosinophilia is not a feature of GPA and can be used to distinguish GPA from Churg-Strauss syndrome.¹³ CT or MRI can help identify masses in the orbit and extent of surrounding involvement. Biopsy examination ultimately confirms the diagnosis but is not necessary for the diagnosis.

In 2010, diagnostic criteria to classify GPA in pediatrics were developed based on common disease presentations in pediatrics and are discussed below.¹⁰

European League Against Rheumatism, Paediatric Rheumatology International Trials Organisation, and Paediatric Rheumatology European Society Classification Criteria for GPA in Children

Any 3 of the following 6 criteria must be met¹⁰:

1. Histopathology (granulomatous inflammation)
2. Upper airway involvement (nasal discharge or epistaxis, crusts, or granulomata; nasal septum perforation or saddle nose deformity; sinus inflammation)
3. Laryngo-tracheo-bronchial involvement
4. Pulmonary involvement by chest x-ray or CT
5. Cytoplasmic ANCA positivity
6. Renal involvement

These criteria exclude eye involvement; thus, limited ocular GPA might not be detectable according to the diagnostic criteria. In addition, ANCA is positive only in 50% to 65% of patients with limited GPA.¹¹ Thus, a high clinical suspicion of ocular disease based on symptoms and laboratory findings are needed or the diagnosis can be missed.

Treatment

The recommended treatment regimen for GPA depends on the extent of disease and location. Ocular GPA treatment has not been well studied but it is effectively treated as systemic GPA, because many patients develop systemic involvement. Cyclophosphamide is one of the most effective agents used with high-dose corticosteroids to treat GPA. Up to 90% of patients have treatment response to cyclophosphamide and nearly 75% of them will have full remission after 1 course (3 to 6 months) of therapy.^{14,15} Thirty percent to 50% of patients with initial therapeutic response can relapse and require an additional course. Cyclophosphamide can cause multiorgan toxicity and thus is not always used in patients with milder, localized disease.

Rituximab also has been recently approved for use with glucocorticoids as therapy. It has been shown to decrease ANCA positivity in patients better than cyclophosphamide and is not inferior to cyclophosphamide in inducing remission.¹⁴ The most common

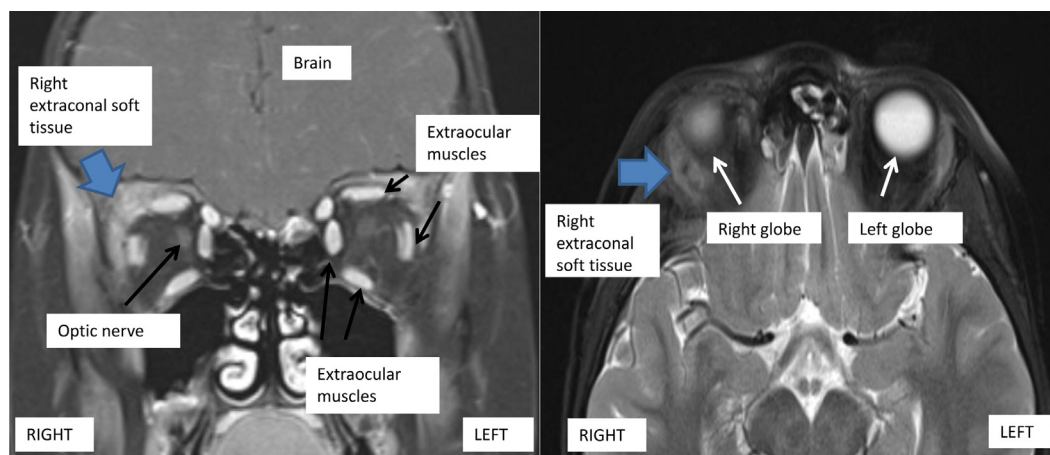


Figure 2. Magnetic resonance images of the face and neck with and without contrast obtained 9 months into the disease after completion of high-dose oral steroid therapy course. There are ill-defined infiltrative areas of enhancing low T1 and T2 signal abnormality involving the post-septal extraconal soft tissues of the superolateral orbits (right greater than left), compatible with the known auto-inflammatory process.

adverse effects of rituximab treatment of GPA include infusion reactions (most common with the first infusion and subside with repeated infusions) and infection occurring at rates of 6% and 36%, respectively.¹⁴ Maintenance therapy options include azathioprine, methotrexate, leflunomide, monoclonal antibodies (ie, rituximab), or lower-dose glucocorticoids continued for at least 18 months.

GPA can have high clinical morbidity, often resulting in hospital admissions and morbidities. Pediatric populations develop higher levels of permanent ear, nose, and throat disease throughout their disease course, such as hearing loss and nasal septal and upper airway deformities requiring tracheostomies.¹⁶ Up to 50% of patients with orbital involvement have significant vision loss.¹¹ When left untreated, there has been up to 90% fatality rate at 1 to 2 years, with respiratory and/or renal failure being the most common cause of death.¹⁶ Ultimately, the overall survival rate is 85% to 100% in patients who respond well to therapy and are induced into remission.

Clinical Course

This child was prescribed rituximab, but within minutes of the first infusion, she developed tachycardia, hypotension, and generalized flushing despite pretreatment with antihistamine and oral steroid. She was subsequently treated with a high dose of oral prednisolone over 5 months with gradual decrease of the ocular swelling and normalization of ESR and C-reactive protein. After 5 months, she was weaned off oral steroid and started maintenance therapy with adalimumab. Follow-up MRI in April after completion of the oral steroid therapy showed persistent masses in the post-septal extraconal soft tissues of the superolateral orbits, which were greater on the right (Fig 2).

Summary and Conclusion

A 10-year-old girl developed a sudden onset of right eye swelling in association with a transient febrile illness. Despite repeated courses of oral antibiotics for presumed preseptal cellulitis, ocular swelling persisted and over 4 months gradually progressed and involved the contralateral eye. Repeated evaluations were remarkable for increased ESR and positive allergy test results for inhalant allergens, which raised the possibility of allergic rhinoconjunctivitis as a cause of her symptoms. Increased ESR was initially dismissed as unremarkable in the absence of systemic symptoms and negative family history of autoimmune or chronic inflammatory diseases. After 5 months, the child developed right eye ptosis and proptosis and CT of the orbits without contrast showed extraconal soft tissue masses in the superior and lateral

orbits, which were greater in the right than in left. Ocular tissue biopsy examination was read as consistent with GPA. GPA is a rare disease in childhood but usually has an onset in the second decade of life and has a female predominance. Ocular manifestations have been reported in 30% to 50% of pediatric patients and GPA should be considered in the differential diagnosis of persistent ocular swelling in children with increased levels of an inflammatory marker (eg, ESR).

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