Granulomatosis with polyangiitis with isolated orbital involvement in children: a case report successfully treated with rituximab and review of literature

Riancho-Zarrabeitia L[1], Peiró Callizo E[2], Drake-Pérez M[3], García Montesinos B[4], Terán N[5], Martínez-Taboada VM[6]

ACTA REUMATOL PORT. 2019;44:258-263

ABSTRACT

We report the case of a 15-year old girl who presented with a non-tender right upper eyelid swelling. Magnetic resonance confirmed the presence of an enlargement of the orbicular muscle with moderate contrast enhancement. Biopsy revealed the presence of necrotizing granulomatous vasculitis. Further studies ruled out systemic involvement. Thus, she was diagnosed with isolated granulomatosis with polyangiitis (GPA). Treatment with steroids and methotrexate was started. Due to the persistence of the lesion, rituximab (RTX) was added with excellent clinical and radiological response. This is, to the best of our knowledge, the first case of isolated orbital GPA treated with RTX in a pediatric patient.

Keywords: Pediatric; ANCA-associated vasculitis; Orbital inflammatory disease.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a small and medium-sized vessel vasculitis associated with the presence of anti-neutrophil cytoplasmic antibody (ANCA). The incidence of GPA in European pediatric population is less than 0.5 cases per million[1]. It may affect any organ system with potential life-threatening morbidities, thus an early diagnosis and prompt treatment are needed. Cases with isolated organ affection are extremely rare [2], and literature about the optimal treatment is scarce. We present the first case of pediatric GPA with limited orbital involvement successfully treated with rituximab (RTX).

1. Rheumatology Department. Hospital Sierrallana
2. Rheumatology Department. Hospital Universitario Marqués de Valdecilla
3. Radiology Department. Hospital Universitario Marqués de Valdecilla
4. Maxillofacial Surgery Department. Hospital Universitario Marqués de Valdecilla
5. Pathology Department. Hospital Universitario Marqués de Valdecilla
6. Rheumatology Department. Hospital Universitario Marqués de Valdecilla. IDIVAL. University of Cantabria

CLINICAL CASE

A 15-year-old girl with unremarkable personal and family history, presented with a one-month history of non-tender right upper eyelid swelling. Visual acuity and ocular movements were impaired. Her blood tests including full blood count and complete chemistry were normal, and acute phase reactants were between normal limits. Orbital ultrasonography and magnetic resonance imaging (MRI) confirmed the diffuse mass within the orbicular musculature in the outer edge of the right orbit, slightly hyperintense with moderate contrast enhancement (Figure 1). A biopsy of the mass was performed showing lymphocytic infiltration around and within the wall of medium and small vessels, and necrotizing granulomas (Figure 2). A systemic evaluation ruled out any other organ affection. ANCA test was repeatedly negative. With the suspicion of GPA with isolated orbital involvement, treatment with prednisone (40 mg per day for 3 weeks followed by 5 mg dose reduction every 10 days until dose of 20 mg per day, then 2.5 mg dose reduction every week) and methotrexate (20 mg weekly) was started. After initial improvement, when tappering prednisone to 15 mg per day, the upper eyelid swelling recurred. The clinical worsening was confirmed with a new MRI. Then, treatment with RTX 375 mg/m^2/week for 4 weeks was started and followed by maintenance therapy consisting of 500 mg every 6 months. The patient presented a good clinical response, with complete resolution of the lesion in the radiological control one year after starting RTX.

DISCUSSION

GPA is a very infrequent vasculitis in childhood, with a female predominance and a mean age at diagnosis between 11 to 14 years[2]. Most commonly affected organs include ear nose and throat, kidney and lungs[3,4]. Subglottic stenosis or nasal deformities such as saddle nose deformity are more commonly observed in children than in adults. More than 90% of patients are positive for ANCA[5], being c-ANCA the most common pattern. However, up to 40% of cases with single organ GPA are ANCA negative. The frequency of ocular involvement, according to a recent meta-analysis, is 24% of cases[3]; nevertheless, orbital involvement is infrequent as initial manifestation and exceptional as a single-organ affection[4,5]. In Table I we summarize previously reported cases of paediatric GPA with orbital affection. Due to the absence of controlled trials in paediatric GPA, adult therapeutic approaches are recommended. Thus, high dose steroids and preferably cy-

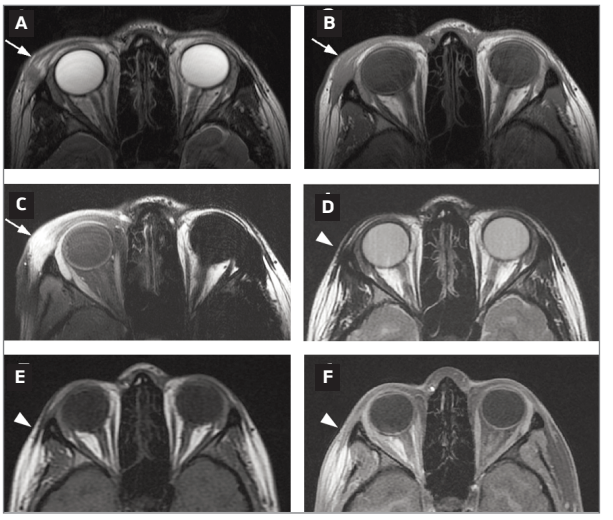

FIGURE 1. Diagnostic MRI with axial T2WI (A), axial T1WI (B), and axial contrast enhanced T1WI (C) shows a poorly defined mass in the external periorbital region, with heterogeneous T2 signal intensity and avid enhancement (arrows). Follow up MRI 1 year after treatment onset with axial T2WI (D), axial T1WI (E), and axial contrast enhanced T1WI (F) shows complete resolution of the mass (arrow heads).

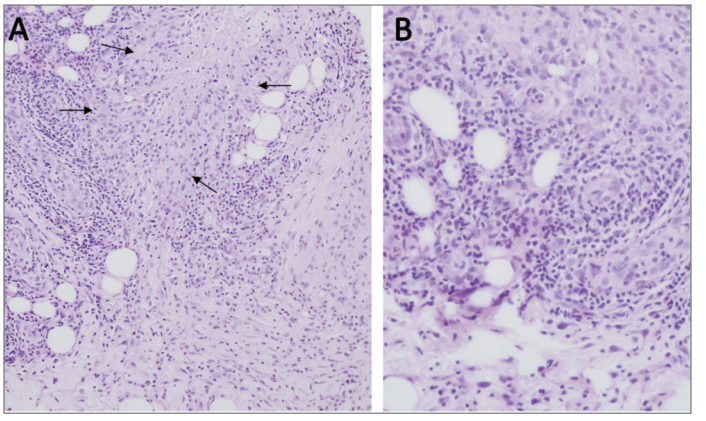

FIGURE 2. Histological examination revealed a granulomatous inflammatory process with lymphohistiocytic infiltrate, necrotizing granulomas and small and medium-sized vessels vasculitis. (A) Panoramic view of the diffuse inflammatory infiltrate with a necrotizing granuloma (between the arrows) (PAS). (B) Detail of small-sized vessels with lymphohistiocytic infiltrate and activated endothelium (PAS).

TABLE I. GPA WITH ORBITAL AFFECTION IN PAEDIATRIC POPULATION

Author, year	Age	Sex	Ocular symptoms	Systemic organ involvement	ANCA	Imaging test	Biopsy	Treatment
Moorthy AV, 1977[10]	10	F	Bilateral proptosis	6 months later: Hematuria and proteinuria, renal insufficiency, sinusitis, nasal ulcers	ND	ND	Orbit: granulomatous vasculitis Kidney: proliferative GN	GC+CFM at kidney affection
Parelhoff ES 1985[11]	9	F	Unilateral proptosis, periorbitary swelling	Maxillary sinusitis 22 months later: hematuria, proteinuria, renal insufficiency, lung nodules, seizures	ND	CT: intraorbital swelling	Orbit: lymphoplasmocitic infiltrate, focal nodular inflammation and macrophagues with foamy citoplasm Kidney: proliferative GN	GC + CFM at kidney affection Kidney transplant
Perry SR, 1997[12]	5	F	Eyelid swelling	No	ND	ND	Órbit: necrotizing vasculitis	GC+CFM
Wardyn KA, 2003[13]	7	F	Ptosis Proptosis	Hematuria, proteinuria	Negative c-ANCA 1:80	CT: intraorbital masses	Órbit: fibrinoid necrosis and neutrophils and mononuclear infiltration Kidney: Proliferative GN	Retrobulbar GC GC + CFM
Ziakas NG, 2004[14]	5	F	Eyelid swelling, ocular motility, mass on the lacrimal gland site	No	c-ANCA 1:160 PR3	MRI: diffuse swelling at the lacrimal gland region	Mixed granulomatous and active inflammation. Inflammatory infiltration around and within the walls of small vessels	GC
Levi M, 2007[15]	12	M	Dacryoadenitis Conjunctivitis Iritis	Otitis media Bronchitis	Not done	ND	Kidney	GC+MTX
	10	M	Upper eyelid edema, erythema Iritis	Hematuria Proteinuria	Positive	ND	Kidney	GC,CFM,MTX,IFX

continues on the next page

TABLE I. CONTINUATION

Author, year	Age	Sex	Ocular symptoms	Systemic organ involvement	ANCA	Imaging test	Biopsy	Treatment
	9	M	Eyelid edema, erythema Limited motility Proptosis	No	Not done	ND	Orbit	GC
	12	F	Eyelid edema Proptosis Limited motility	Abdominal pain,vomiting	Negative	ND	Orbit and kidney	GC
Martínez-Gutierrez JD, 2008[16]	7	F	Displacement of the globe Eyelid swelling	3 years after ocular symptoms: subglotic stenosis, lung and kidney affection	Negative	CT and MRI: infiltration and enlargement of lacrimal glands and sinusitis	Orbit: non-specific histiocytic infiltrate with plasmacytoid, lymphocytes and eosinophilic cells Lacrimal gland: perivascular and periductal cell infiltrate with granulomatous aspect	GC at diagnosis GC+CFM+IFX posteriorly
Chipczynska B, 2009[17]	7	F	Eyelid swelling, unilateral exophthalmia (all patients)	Sinusitis GN	Negative	CT/MRI: Tumor masses in the orbit (all patients)	Orbit: Inflammatory pseudotumor Renal biopsy: necrotizing GN	GC+ MTX/CFM (all patients)
	11	F		Hearing impairment	cANCA +		Orbit: Necrotizing vasculitis with leukocytoclasia and necrotizing granulomas surrounded by histiocytes and giant cells	
	8	M		Otitis media Hearing impairment	cANCA+		Orbit Necrotizing vasculitis with leukocytoclasia and necrotizing granulomas surrounded by histiocytes and giant cells	

continues on the next page

TABLE I. CONTINUATION

Author, year	Age	Sex	Ocular symptoms	Systemic organ involvement	ANCA	Imaging test	Biopsy	Treatment
	9	F	Eyelid swelling, unilateral exophthalmia	Fevers Rheumatic pains	Atypical ANCA	CT/MRI: Tumor masses in the orbit	Orbit: Necrotizing vasculitis with leukocytoclasia	GC+ MTX/CFM
Dey M, 2011[18]	9	F	Eyelid swelling	Saddle-nose deformity, otitis	cANCA 1:20 pANCA 1:40	CT: soft tissue swelling in lacrimal gland	Órbit: chronic inflammation with perivascular infiltrates	GC
Ure E, 2016[19]	9	F	Eyes redness, eyelids edema, ptosis and exophtalmus	GN	cANCA	MRI: bilateral intraorbital--extraconal soft tissue lesions	Orbit: thickening of the vessel wall, microthrombus and perivascular lymphocytic infiltration in the vessels lumen and fibrosis in the lacrimal gland Kidney: crescentic glomerulonephritis	CFM, RTX Topical GC
Drobysheva A, 2018[20]	12	M	Unilateral eyelid swelling + ptosis	No	cANCA 1:20	MRI: infiltrative lesion of the orbit	Orbit: fibrovascular tissue with dense collagenous fibrosis and mixed inflammatory infiltrate with plasma cells	GC+ MTX

F: female; M: male; ND: no data; ANCA: anti-neutrophil cytoplasmic antibody; c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; IR: insuficiencia renal; GN: glomerulonephritis; CT: computed tomography; MRI: magnetic resonance imaging; GC: glucocorticoids; MTX: methotrexate; CFM: cyclophosphamide; IFX: infliximab; RTX: rituximab

clophosphamide (CYP) are used as induction therapy, although there is an increase in the use of RTX[3-6]. In our case, due to the absence of systemic symptoms and the potential gonadal toxicity of CYP, methotrexate and corticosteroids were prescribed initially. RTX was then started because of refractoriness as a second line therapy. Some cases of GPA with orbital affection successfully treated with RTX have been published in adulthood[7-9], but no cases with limited orbital involvement have been previously reported in children.

In our case, the patient presented with a limited affection of the orbicular musculature, reasonably ruling out any systemic involvement. Treatment with steroids and methotrexate was started. RTX was associated due to refractoriness, with excellent response and disappearance of the lesion.

CONCLUSIONS

GPA can exceptionally present as a single-organ disease in childhood. RTX might be considered as a potential treatment in cases refractory to conventional immunosuppressive therapy.

CORRESPONDENCE TO
Víctor Martínez Taboada
Rheumatology Department
Hospital Universitario Marqués de Valdecilla
Av. Valdecilla, 25
39008 Santander, Cantabria, Espanha
E-mail: vmartinezt64@gmail.com

REFERENCES

1. Sacri AS, Chambaraud T, Ranchin B, Florkin B, See H, Decramer S et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. Nephrol Dial Transplant 2015; 30 Suppl 1:i104-i112.
2. Calatroni M, Oliva E, Gianfreda D, Gregorini G, Allinovi M, Ramirez GA et al. ANCA-associated vasculitis in childhood: recent advances. Ital J Pediatr 2017; 43:46.
3. Iuidici M, Quartier P, Terrier B, Mouthon L, Guillevin L, Puechal X. Childhood-onset granulomatosis with polyangiitis and microscopic polyangiitis: systematic review and meta-analysis. Orphanet J Rare Dis 2016; 11:141.
4. Jariwala MP, Laxer RM. Primary vasculitis in childhood: GPA and MPA in childhood. Front Pediatr 2018; 16: 6:226.
5. Cabral DA, Canter DL, Muscal E, Nanda K, Wahezi DM, Spalding SJ et al. Comparing Presenting Clinical Features in 48 Children With Microscopic Polyangiitis to 183 Children Who Have Granulomatosis With Polyangiitis (Wegener's): An ARChiVe Cohort Study. Arthritis Rheumatol 2016; 68:2514-26.
6. Morishita KA, Moorthy LN, Lubieniecka JM, Twilt M, Yeung RSM, Toth MB et al. Early Outcomes in Children With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2017; 69:1470-9.
7. Baslund B, Wiencke AK, Rasmussen N, Faurschou M, Toft PB. Treatment of orbital inflammation with rituximab in Wegener's granulomatosis. Clin Exp Rheumatol 2012; 30(1 Suppl 70):S7--10.
8. Bitik B, Kilic L, Kucuksahin O, Sahin K, Tufan A, Karadag O et al. Retro-orbital granuloma associated with granulomatosis with polyangiitis: a series of nine cases. Rheumatol Int 2015; 35:1083-1092.
9. Joshi L, Tanna A, McAdoo SP, Medjeral-Thomas N, Taylor SR, Sandhu G et al. Long term outcomes of rituximab therapy in ocular granulomatosis with polyangiitis: impact on localized an nonlocalized disease. Ophtalmology 2015; 122:1262-1268.
10. Moorthy AV, Chesney RW, Segar WE, Groshong T. Wegener granulomatosis in childhood: prolonged survival following cytotoxic therapy. J Pediatr 1977; 91:616-618.
11. Parelhoff ES, Chavis RM, Friendly DS. Wegener's granulomatosis presenting as orbital pseudotumor in children. J Pediatr Ophthalmol Strabismus 1985; 22:100-4.
12. Perry SR, Rootman J, White VA. The clinical and pathologic constellation of Wegener granulomatosis of the orbit. Ophthalmology 1997; 104:683-94.
13. Wardyn KA, Ycinska K, matuszkiewicz-rowinska J, Chipczynska M. Pseudotumour orbitae as the initial manifestation in Wegener's granulomatosis in a 7-year-old girl. Clin Rheumatol 2003; 22:472-474.
14. Ziakas NG, Boboridis K, Gratsonidis A, Hatzistilianou M, Katriou D, Georgiadis NS. Wegener's granulomatosis of the orbit in a 5-year-old child. Eye (Lond) 2004; 18: 658-660.
15. Levi M, Kodi SR, Rubin SE, Lyons C, Golden R, Olitsky SE et al. Ocular involvement as the initial manifestation of Wegener's granulomatosis in children. J AAPOS 2008; 12:94-96.
16. Martínez-Gutierrez JD, Mencia-Gutierrez E, Gutierrez-Díaz E, Rodriguez-Peralto JL. Bilateral idiopathic orbital inflammation 3 years before systemic Wegener's granulomatosis in a 7-year-old girl. Clin Ophthalmol 2008; 2:941-944.
17. Chipczynska B, Gralek M, Hautz W, Zegadlo-Mylik M, Kocyla-Karczmarewicz B, Kanigowska K 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.
18. Dey M, Lawyi L, Wilson RS. Orbital Wegener's granulomatosis as the initial presentation in a 9-year-old child. J R Soc Med 2011; 104:332-334.
19. Ure E, Kayadibi Y, Sanli DT, Hasiloglu ZI. Orbital involvement as the initial presentation of Wegener granulomatosis in a 9-year-old girl: MRimaging findings. Diagn Interv Imaging 2016; 97: 1181-1182
20. Drobysheva A, Fuller J, Pfeifer CM, Rakheja D. Orbital granulomatosis with polyangiitis mimicking IgG4-related disease in a 12-year-old male. Int J Surg Pathol 2018; 26: 453-458