Case report

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IMMUNOGLOBULIN G4 (IGG4) RELATED DISEASE AND GRANULOMATOSIS WITH POLYANGIITIS (GPA) IN CHILDHOOD: A CASE REPORT OF NEW OVERLAP SYNDROME

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Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG) is one of major variants of anti-neutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV) and one of the most common vasculitis in children affecting small- to medium-sized blood vessels. Immunoglobulin G4 (IgG4)-related disease is characterised by inflammatory pseudotumours with elevated serum IgG4 concentrations. Orbital pseudotumour in children can be initial clinical presentation of both IgG4 related disease and GPA. Herein, we describe a young girl with a new overlap syndrome, initially presented with orbital pseudotumour. Furthermore, diagnostic challenges and applied therapy are described. *Acta Medica Medianae 2023;62(3):103-108.*

***Key words**: granulomatosis with polyangiitis (GPA), immunoglobulin G4 (IgG4)-related disease, orbital pseudotumour*

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Introduction

Granulomatosis with polyangiitis (GPA), is one of major variants of anti-neutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV). It is a heterogeneous group of multisystem disorders characterised by pauci-immune necrotising vasculitis, that affects small- to medium-sized blood vessels, together with neutrophil or eosinophil-enriched granulomatous inflammation. AAV is related with the presence of circulating ANCA. GPA, formerly known as Wegener's granulomatosis (WG), is typically associated with granulomatous inflammation of the respiratory tract, necrotising glomerulonephritis and the presence of ANCA, usually directed against myeloperoxidase (MPO) (1, 2). Renal involvement plays a central role in the diagnosis, classification, prognosis and treatment of patients with this disease. Ocular manifestations are seen in up to 60% of adult GPA patients and can occur either in the generalised or in the limited form of the disease. Although rare, GPA is the most common AAV in children, with a strong female predominance (61 to 80%) (3, 4). As opposed to adults with this disease, paediatric patients have ocular manifestations more commonly-up to 43% children with multisystem GPA, as noted in the largest paediatric study to date, conducted on 183 Canadian paediatric patients with GPA (5).

Immunoglobulin G4 (IgG4)-related disease is characterised by elevated serum IgG4 concetrationa together with multiorgan involvement and inflammatory pseudotumours with dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells (6, 7). It has not been recognized as a systemic condition since 20 years ago, when Kiyosawa et al. published several reports of the systemic background of this process (8, 9, 10). Many medical conditions that may include single organ systems can be part of the spectrum of IgG4-related diseases (8). IgG4-related disease with orbital pseudotumour, has been reported only in adult systemic conditions until recently. In the last few years, it is considered to be more common in paediatric population than anticipated previously. According to a recent systematic literature review, ocular manifestations are reaching 44% among children with this disease (11). Herein, we describe a young girl with orbital pseudotumour as an initial

clinical presentation of IgG4 related disease and GPA.

Case report

This previously healthy girl started to have recurrent fever episodes at the age of 3. Five years later a tonsillectomy was performed due to recurrent rhinitis and sore throat. Few days after that, she showed up with ptosis of the right eyelid, together with swelling and redness (Figure 1 A and B). Magnetic resonance imaging (MRI) was performed and it confirmed an orbital pseudotumour. Thus, steroid therapy was initiated (20 mg/day prednisolone course with slow tapering), showing steroid dependent clinical response. However, in the next month she had deterioration presented with fever episodes for two months and septic appearance, nasal obstruction with mucopurulent secretion and recurrent nosebleeds. Triple antibiotics (ceftriaxone, vancomycin, ciprofloxacin) and antimycotics were administrated due to persistently elevated ESR and CRP levels. Meanwhile serology tests for infection were negative and infectious diseases were ruled out. Due to worsening of ocular symptoms, orbital mass extirpation was performed and biopsy has shown a granulomatous lesion and vasculitic infiltration of the blood vessels, with the lack of eosinophilia in both blood and biopsy samples. In addition, a fibrosing chronic inflammatory process rich in plasma cells was observed, that appeared to have considerable IgG4 immuno-staining. Laboratory examination revealed markedly elevated serum IgG4 concentration (1400 mg/dl, cut off 135 mg/dl). This led to the diagnosis of IgG4 related disease, according to ACR/EULAR classification criteria for IgG4-related disease (12). After the pseudotumour extirpation, she was treated with vitamin supplements only and did well for one year. Unfortunately, the girl met a recurrence of the orbital mass in the same eye, along with left ankle arthritis and some granulomatous skin lesions with central induration and spider nevus (Figure 1 C and D). Thus she was referred to paediatric rheumatology clinic for the first time. Chest X-ray showed bilateral hilar adenopathy, without increase of angiotensin-converting enzyme (ACE) levels, to rule out sarcoidosis. MRI showed a relapse of pseudotumour in the right orbit and pan sinusitis. Laboratory findings revealed elevated perinuclear ANCA specific for MPO (p-ANCA=7.8 U/ml, norm <5), while antinuclear and anti-double stranded DNA were both negative, whereas lupus anticoagulant was moderately positive (LAC 1.41) and ESR and CRP highly elevated. Glomerulonephritis (urinalysis revealed proteinuria 1.5 g/24 hours, microalbuminuria and microscopic haematuria) without impairment of renal function (serum BUN 14mg/dl, serum creatinine 58 umol/l, GFR 1.23 ml/1.73 m2/24h) and elevated serum levels of β2-microglobuline (2.15 mg/L), led to the renal biopsy, which confirmed necrotising pauci immune glomerulonephritis. GPA was diagnosed according to EULAR/PRINTO/PRES criteria (13) based on recurrent ocular inflammatory pseudotumour, chronic sinusitis, vasculitic rash, necrotising glomerulonephritis and ANCA positivity. Consequently, high doses of methylprednisolone and cyclophosphamide were commenced monthly for six months with good clinical response (fully resolved nephrological symptoms), followed by slow tapering of corticosteroids for 2 years. At this time, stable remission was maintained with mycophenolate mofetil (MMF, 2 g daily) and hydroxychloroquine (HCQ, 200 mg daily), along with antihypertensives and other symptomatic therapy and vitamin supplements. This was announced previously by our group on European Alliance of Associations for Rheumatology (EULAR) meeting in 2012, however monitoring contiued in the next ten years (14). In the following years, exacerbation of chronic sinusitis was seen on MRI and renal involvement with microproteinuria. At that time rituximab was considered, but due to persistent hypogammaglobulinemia, biologic treatment was withdrawn. Thus, methotrexate (MTX, 15 mg weekly per os) was induced. Nevertheless, the girl was in stable remission of her disease under immunosuppressives and fully vaccinated with the Pfizer COVID-19 vaccine (BNT162b2, without any adverse events), she was tested PCR positive for SARS-CoV2 twice. Firstly, in spring 2021, infection has successfully resolved, without any complications but with deterioration of chronic sinusitis, not requiring therapy change. Secondly, in May of the current year, with similar symptoms. Currently, stabile remission (Birmingham Vasculitis Activity Score, BVAS=0) is maintained along with MTX 10 mg weekly, MMF 1 g and HCQ 200 mg daily, together with antihypertensives and alphacalcidol.

Discussion

GPA is one of the most severe and necrotising vasculitis affecting mainly small vessels, characterised by relapses. Paediatric patients have a similar clinical presentation compared to adults with this disease, but have a different frequency of organ involvement. It appers that ocular manifestations are more common in children than in adults. The largest up-to-date paediatric cohort reported ophthalmic complications (including nonspecific red eye, retro-orbital mass lesion, proptosis, episcleritis, conjuctivits, retinal exudates, haemorrhage and vascular thrombosis or aneurysm) in up to 43% of children with multi system disease (5). In other studies, 35% of paediatric patients had ocular involvement and more than 50% had necrotising glomerulonephritis. Secondly, gender disproportion was found (females predominate in children with GPA) (15). The ocular manifestation may be the only symptom in limited disease or it may be the first feature of GPA before progression

to multi system involvement (16). Long term follow up is therefore necessary to differentiate generalized from limited forms of GPA. There are no definitive diagnostic criteria for the localized disease, as opposed to systemic forms, and there are only a few reports presenting limited orbital GPA in children (17, 18, 19, 20).

On the other hand, IgG4 related disease is extremely rare in children and occurs mainly with orbital manifestations (21, 22). Due to its multifaceted presentation, it is considered substantial mimicker of many inflammatory, neoplastic and infectious diseases. Increased IgG4 levels in serum are often used to confirm IgG4-RD; but, they are neither sensitive nor specific to diagnose. Reliable biomarkers are lacking, so histopathology remains the key to diagnosis (23, 12). However, even orbital biopsy with considerable nimber of IgG4-positive plasma cells alone is are not enough to differentiate between limited form of GPA and IgG4-RD in the orbit (24).

Rcently, a new overlap syndrome between IgG4 related disease and AAV has been proposed in adults (25, 26), pointing to IgG4 subclass of ANCA being implicated as a pathogenic factor in this associated condition (27, 28). This may have been translated to the paediatric population, where notable IgG4 production in IgG4-related disease may promote AAV development in genetically susceptible individuals (29). This hypothesis may be supported with the presence of pauci-immune necrotizing vasculitis seen in the renal biopsy, together with IgG4 positive plasma cells on ocular biopsy of this girl. As noted in European multicenter survey commisoned by the French Vasculitis Study Group, there is a considerable association between AAV, particulary GPA, and IgG4 related disease in adults. This suggests pathophysiological similarities between these two entities, possibly including follicular T helper cells, which are increased in both conditions and are polarised towards the Th-2 subtype, reinforcing the polarisation of IgG4-plasma cells. Furthermore, this study found similar pathogenesis and good sensitivity to rituximab treatment, especially in GPA patients (30).

Some authors noted that since ANCA were predominantly of the IgG isotype, possible pathogenic mechanism of IgG4 subclass of MPO-ANCA in the development of GPA can be explained (27, 30). Most ANCA detected in GPA are directed against proteinase 3, making c-ANCA far more specific than p-ANCA. To the best of our knowledge, there is only one published case of paediatric orbital IgG4 related disease associated with GPA and elevated serum p-ANCA antibodies (31), as seen in our patient.

However, Erden et al. in their recent literature review questioned whether these two entities overlap or mimic each other (32). Similarly, in a case report (33) of a 12-years old boy with GPA that mimicked IgG4 related disease due to unusual orbital manifestation and borderline ANCA. Indeed, orbital GPA lesions can have clinical, radiological and even histopathological features that mimic IgG4 related disease, what can be a major diagnostic pitfall, leading to delayed diagnosis and treatment. (28). However, our patient had clinical and histopathological manifestations, therefore all criteria for both diseases were met, suggesting this new overlap syndrome.

Conclusion

We have described the case of a girl with laboratory and biopsy-proven IgG4 related disease, in whom initial manifestation of GPA was orbital involvement and later developed necrotizing pauci-immune glomerulonephritis and cutaneous manifestations. Furthermore, the apperance of other symptoms confirmed the overlap of GPA and IgG4-related disease, and with immunosuppressive therapy stable remission occurred.

This entity, which is associated with orbital involvement, could be of importance and help to establish early recognition of atypical disease forms, but also to make an earlier diagnosis and initiate treatment in order to prevent potentially fatal consequences of this rheumatic disease.

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BOLEST DEPONOVANJA IMUNOGLOBULINA G4 (IgG4) I GRANULOMATOZA SA POLIANGTISOM KOD DECE: PRIKAZ BOLESNIKA SA NOVIM SINDROMOM PREKLAPANJA

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Granulomatoza sa poliangitisom, prethodno nazivana Wegenerova granulomatoza, jedan je od glavnih oblika vaskulitisa udruženih sa antitelima protiv citoplazme neutrofila (engl. *anti-neutrophil cytoplasm antibody* – ANCA) i najčešći vaskulitis malih i srednjih krvnih sudova kod dece. Bolest deponovanja imunoglobulina G4 (IgG4) karakteriše se inflamatornim pseudotumorima uz povišene vrednosti IgG4 u serumu. Pseudotumor orbite kod dece može biti inicijalna klinička prezentacija obaju pomenutih entiteta. U radu je prikazana devojčica sa neuobičajenom pojavom novog sindroma preklapanja ovih dvaju entiteta, koja se inicijalno prezentovala pseudotumorom orbite. Takođe, predstavljeni su izazovi dijagnostičkog postupka i primenjena terapija. *Acta Medica Medianae 2023; 62(3):103-108.*

***Ključne reči**: granulomatoza sa poliangitisom, bolest deponovanja imunoglobulina G4 (IgG4), pseudotumor orbite*