

Pediatric ANCA-associated vasculitis presented with various clinical findings mimicking IgA Vasculitis and IgG4-related disease: Two cases

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Abstract

Granulomatous polyangiitis (GPA) is the most common anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), characterized by necrotizing inflammation of small and medium-sized vessels. It can affect various organs, particularly the lung, kidneys, upper respiratory tract, ears, and skin. Diagnosis of AAV poses significant challenges due to its diverse clinical features. This report presents two interesting cases of GPA: one with rare ocular involvement, who subsequently developed end-stage kidney disease (ESKD), and the other with palpable purpura mimicking immunoglobulin A vasculitis, who relapsed with mastoiditis while in renal remission. Early and effective treatment can improve patient prognosis, highlighting the importance of increasing disease awareness during initial diagnosis and in pediatric AAV patients experiencing relapses.

Keywords: ANCA, vasculitis, IgG4, IgA, case report

Introduction

Anti-neutrophil cytoplasmic antibody- (ANCA) associated vasculitis (AAV) is a small vessel vasculitis characterized by pauci-immune necrotizing inflammation of small vessels. Constitutional symptoms and multiple organ/system manifestations, including recurrent epistaxis, chronic sinusitis, subglottic stenosis, hemoptysis, pulmonary nodules (involving the upper and lower respiratory tract), hematuria, proteinuria, renal impairment (crescentic glomerulonephritis), skin rash, red eye, arthritis, mastoiditis, and hearing loss, among others, may be observed [1].

Consequently, the diagnosis of AAV poses significant diagnostic challenges, and delays in diagnosis are common. This report presents two interesting cases of GPA: one with ocular involvement and mild renal impairment that progressed to end-stage kidney disease (ESKD), and the other with palpable purpura mimicking immunoglobulin A vasculitis (IgAV), who subsequently relapsed with mastoiditis while in renal remission.

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Informed Consent

The authors stated that the written consent was obtained from the parents of the patients presented with images in the study.

Conflict of Interest

No conflict of interest was declared by the authors.

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Case presentation

Case 1

A 14-year-old female patient was admitted to our hospital two years ago with complaints of swelling and redness on the skin of her left upper eyelid (Figure 1A). Her family history was unremarkable. Physical examination was normal except for left eyelid edema and hypertension (blood pressure: 180/100 mmHg). Laboratory tests revealed a creatinine level of 2.64 mg/dL, 24-hour urine protein excretion of 5415 mg/day, C-reactive protein (CRP) level of 1.32 mg/L (normal range: 0–5), erythrocyte sedimentation rate (ESR) of 67 mm/h, antinuclear antibody (ANA) by IFA of +2, and anti-MPO-ANCA of +1.

It was noted that the patient's creatinine level at her first admission for eye complaints a year ago was 1.1 mg/dL. Additionally, her ESR was 68 mm/h, CRP was 52.31 mg/L, and urinalysis showed +3 protein and +3 blood reaction. Orbital magnetic resonance (MR) imaging revealed an orbital pseudotumor and dacryoadenitis in the left eye.

Kidney biopsy showed moderate tubular atrophy/interstitial fibrosis and cellular crescent formation in 1/8 glomeruli, while the remaining glomeruli had global glomerulosclerosis. The patient was diagnosed with GPA with renal and orbital involvement, and treatment was initiated with pulse methylprednisolone (MPZ) (1 g daily for 3 days) followed by 60 mg/day of prednisolone.

The patient received five sessions of therapeutic plasma exchange (TPE) and six monthly intravenous pulse cyclophosphamide courses. The prednisolone dose was gradually tapered, and azathioprine was prescribed for maintenance therapy. At 6 months of treatment, the creatinine level was 3.31 mg/dL, and proteinuria was 828 mg/day. Hemodialysis was initiated on the 18th month of treatment due to pericardial effusion development when the creatinine level was 4.8 mg/dL.

Kidney transplantation from a living donor was performed 16 months later. Currently, the patient is in remission with a well-functioning allograft, and the parents have given written consent to publish this report and the image.

Case 2

A 12-year-old male patient presented to a local hospital complaining of pain and swelling in his wrists, ankles, and knees, red-purple purpuric rashes on his palms and ankles, and darkening of his urine. Laboratory tests revealed a CRP level of 200 mg/L (normal range: 0–5), ESR of 105 mm/h, a 24-hour urine protein level of 1200 mg, a C3 level of 145 mg/dL, a C4 level of 30 mg/dL, and normal creatinine levels. He was diagnosed with IgA vasculitis (Henoch-Schönlein purpura), and oral corticosteroid therapy was initiated.

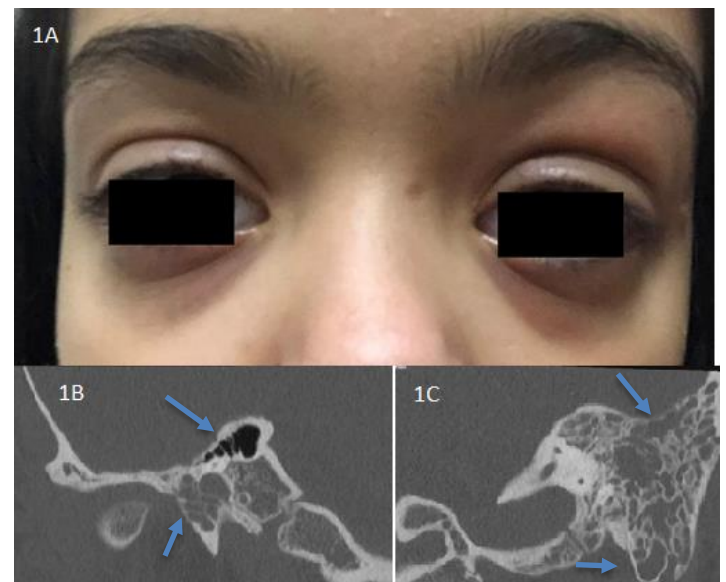
The patient was referred to our hospital for further evaluation when his creatinine level increased. His past medical and family histories were unremarkable. On physical examination, the only finding was purpuric rashes on the lower extremities. Laboratory tests revealed a serum creatinine level of 2.4 mg/dL and a 24-hour urine protein level of 3184 mg. C-ANCA was 2+, p-ANCA was negative, ANA was negative, anti-ds DNA was negative, and the anti-glomerular basement membrane (GBM) antibody was negative.

Kidney biopsy showed pauci-immune diffuse necrotizing crescentic glomerulonephritis with the cellular crescent formation in 20/36 glomeruli. Thorax and paranasal computed tomography (CT) scans were normal. The patient was diagnosed with GPA. Three days of pulse methylprednisolone (MPZ) therapy followed by 60 mg oral prednisolone with gradual tapering, six doses of monthly pulse cyclophosphamide, and seven sessions of therapeutic plasma exchange (TPE) were administered due to severe renal involvement.

The creatinine level decreased to 1.17 mg/dL. On follow-up, four doses of rituximab (375 mg/m²) one week apart were given due to persistent nephrotic-range proteinuria (5610 mg/day). The patient was prescribed mycophenolate mofetil as maintenance therapy, and serum creatinine and urinary protein levels returned to normal. While in remission, the patient presented with hearing loss in the left ear in the 24th month of treatment. Temporal CT showed pneumatized petrous apex on the right, soft tissue densities in the petrous apex, mastoid air cells, epitympanum, and mesotympanum in the middle ear cavity consistent with mastoiditis (Figure 1B and C).

Laboratory tests showed that serum creatinine level had risen to 1.16 mg/dL, CRP was 76.5 mg/L, ESR was 76.5 mm/h, and proteinuria was 1366 mg/day, with c-ANCA being positive. This was accepted as disease exacerbation, and the patient's symptoms improved with the initiation of 60 mg/day prednisolone and the second course of rituximab treatment, resulting in a significant response. The patient's parents have given their written consent to publish this report and the image.

Figure 1: A: Proptosis, upper lid swelling, mild ptosis and hyperemia in the left periorbital area (Case 1). B: The decreasing aeration of the mastoid cells and hypodense soft tissue densities in the mastoid cells in the computer tomography imaging (Right mastoid) (Case 2). C: The absence of middle ear aeration and increased soft tissue densities in the mastoid cells, epitympanum, and mesotympanum mastoid in the computer tomography imaging (Left mastoid).



Discussion

Childhood AAV patients may present with a wide variety of clinical symptoms, and diagnosing AAV can be challenging for clinicians because it can mimic other diseases. Orbital involvement may be the first or only clinical presentation in 30% of GPA patients. Orbital GPA is difficult to diagnose because its clinical manifestations often overlap with other inflammatory disorders, such as IgG4-related disease [2]. The clinical

manifestations of ocular GPA result from inflammation of ocular structures, including orbital fat, orbital nerves, extraocular muscles, lacrimal glands, and optic nerve. Patients may present with ocular pain, erythema and edema of the eyelids, nasolacrimal duct obstruction, epiphora, limited extraocular muscle movements, proptosis, diplopia, and vision loss [3,4]. ANCA titers are positive in only 50-65% of these patients [3].

In our first case, we observed eyelid edema, proptosis, and erythema, and MRI revealed orbital pseudotumor and dacryoadenitis. Accompanying proteinuria and hematuria were also noted at the patient's admission to our clinic, and GPA was confirmed with a kidney biopsy. Periorbital biopsy was not performed, and therefore IgG4 staining was not available. This case of GPA is presented to emphasize that ocular involvement, albeit rare, might be the initial finding and that systemic evaluation is extremely important.

In a large study conducted in Canada of children with GPA, 43% of those with the multisystem disease had ophthalmic complications [5]. In a European study, this rate was half as common, at 21%, and the median time to progression to ESKD was 12.9 years, while the median time to diagnosis was one month. No statistical correlation was found between the time of diagnosis and the risk of ESKD [6]. Therefore, GPA should be considered in the differential diagnosis of protracted eyelid edema and redness.

Palpable purpura in the lower extremities, which is the main finding of IgAV, can also be observed in GPA, as in our Case 2 [7], which underscores the importance of differential diagnosis. Some patients present with recurrent otitis or mastoiditis that does not respond to medical and surgical treatment and are subsequently diagnosed with GPA [8,9]. In previous reports, sensorineural hearing loss was observed in 10% and otitis/mastoiditis in 17% of patients with GPA with multisystem involvement [5,10]. However, mastoid involvement is less common in pediatric patients than in adults with GPA.

After induction therapy, one or more disease recurrences may occur in half of the patients in remission with maintenance therapy [9]. The most common disease recurrences are in the kidney, lung, and upper respiratory tract [5]. In Case 2, the patient relapsed with mastoiditis while following up under remission with low-dose steroids and mycophenolate mofetil. Although pediatric patients with GPA presenting with mastoiditis have been reported [1], to our knowledge, this is the first reported case of a pediatric patient relapsing with mastoiditis. The success of surgical treatment is limited in cases of mastoiditis and otitis due to GPA, and immunosuppressive therapy is the mainstay of treatment in these patients [8,9]. Indeed, mastoid involvement was successfully treated with steroids and rituximab in our case.

Early diagnosis and prompt treatment in patients with GPA are critical for improving prognosis. Combination therapy with corticosteroids plus cyclophosphamide or corticosteroids plus cyclophosphamide and TPE is recommended for induction therapy in pediatric AAV patients [5]. Corticosteroids combined with rituximab can also be used in induction therapy [3]. Both of our cases received combination therapy. However, one had progressed to ESKD and subsequently received a kidney allograft. On the other hand, the other patient relapsed with mastoiditis

while on maintenance therapy and was successfully treated with a combination of steroids and rituximab.

Conclusion

Since AAV mimics various clinical entities, it should be considered in pediatric patients who visit hospitals repeatedly for specific reasons. Taking the patient's history carefully, performing a detailed physical examination, and closely monitoring the patient can lead to a proper diagnosis. We believe that increasing awareness of the disease in the initial diagnosis and in relapses in pediatric AAV patients is critical for achieving early and effective treatment and improving patient prognosis.

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