

## Case Report

## Anti-neutrophil cytoplasmic antibodies negative eosinophilic granulomatous polyangiitis glomerulonephritis in children - A diagnostic dilemma

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## ABSTRACT

Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) refers to small-to-medium vessel vasculitis with multisystemic involvement and is characterized by the presence of ANCA to specifically either proteinase-3 (PR3) or myeloperoxidase (MPO). Eosinophilic granulomatous polyangiitis earlier called as Churg-Strauss vasculitis is a clinicopathological variant of AAV or AAV with granulomatous necrotizing small vessel vasculitis primarily affecting individuals with severe asthma or allergies and rarely reported in the pediatric population. We report a 9-year-old child with pauci-immune crescentic eosinophilic granulomatous glomerulonephritis with heavy eosinophilic infiltration of skin and subcutaneous tissue and negative ANCA. Although he had a recurrent history of cough, there was no history of use of oral or inhalational bronchodilator therapy indicating asthma and no history suggestive history of allergy. He showed significant and rapid clinical as well as biochemical improvement on aggressive immunosuppressive therapy along with plasma exchanges and is under regular follow-up. Diagnosing Eosinophilic granulomatous Polyangiitis glomerulonephritis in children is difficult due to a varied clinical presentation at onset which may evolve over a period of time and due to lack of specific diagnostic tests. High index of suspicion is the key to early diagnosis and successful management.

**Key words:** ANCA, Vasculitis, Glomerulonephritis

**A**nti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) refers to small-to-medium vessel vasculitis with multisystemic involvement and is characterized by the presence of ANCA to specifically either proteinase-3 (PR3) or myeloperoxidase (MPO). Absence or paucity of immune complex deposits in vessel walls is very characteristic; hence, the name “Pauci-immune vasculitis.” Kidneys are one of the primary target organs typically presenting with pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis. Diagnosis is based on a set of clinical, laboratory, and histological criteria. Eosinophilic granulomatous polyangiitis (EGPA) earlier called Churg-Strauss vasculitis (CSS) is a granulomatous necrotizing vasculitis of small and medium-sized vessels that primarily affects individuals with severe asthma or allergies. It has been reported extremely rarely in pediatric population its exact incidence not known. It is one of the clinicopathological variants of AAV, others being microscopic polyangiitis, granulomatosis with polyangiitis (Wegener’s), and single-organ AAV (e.g., renal-limited AAV). All these are characterized by the presence of ANCA in varying proportions.

Kidney involvement in EGPA is typically in the form of necrotizing eosinophilic glomerulonephritis. Due to the rarity of the condition in children pediatric-specific criteria for EGPA have

not been formulated so far [1]. Rarer still is the ANCA negative vasculitis which has the similar clinical and histopathological features but undetectable ANCA autoantibodies [2]. We report a 9-year-old boy who presented with rapidly proliferative glomerulonephritis with eosinophilia with pauci-immune crescentic picture on kidney biopsy.

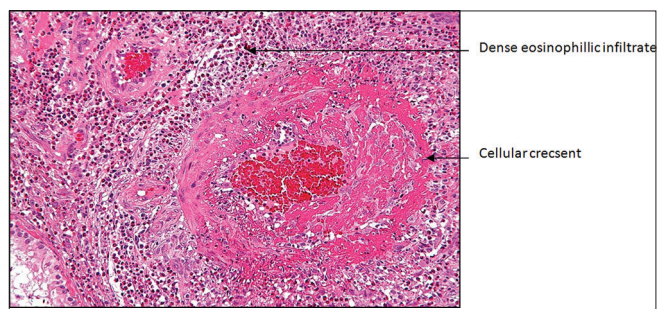
## CASE REPORT

A 9-year-old boy presented with complaints of passing tea colored urine and facial puffiness for 5–6 days. Child also had a history of non-productive cough since past 10–15 days. There was no significant history of fever, decreased urine output, rash, joint pains, or intake of any medication. Parents gave a history of recurrent cough in the past but no history of nebulization or any regular bronchodilator inhalation therapy. On admission; child was hypertensive (blood pressure [BP] 143/100 mm-Hg) with mild periorbital puffiness and pedal edema. He had no pallor, icterus, and petechial rash; clubbing or lymphadenopathy. Respiratory system examination revealed rhonchi all over the chest. Rest of the systemic examination was essentially normal. Provisional diagnosis of glomerulonephritis with acute exacerbation of bronchial asthma was made, and the patient was evaluated further.

Urine microscopic examination showed numerous red blood cells (RBCs), and RBC casts with 3+ proteins on the dipstick and 24 h total urine protein was 7645 mg. He had mild anemia (hemoglobin 9.6g%) and normal platelet count ( $290,000/\text{mm}^3$ ) but repeatedly high leukocyte counts (maximum of  $58,200\text{ cells}/\text{mm}^3$ ) with increased eosinophils (maximum absolute eosinophil count [AEC] of  $40,158\text{ cells}/\text{mm}^3$ ). Peripheral smear revealed abundant eosinophils. The serum urea was 214 mg/dl and creatinine 7.8 mg/dl. Serum C3 was normal (94 mg/dl). ANA was negative. ANCA reports done with ELISA and IF were negative. IgE levels (1515 IU/ml) were found to be elevated. CRP (9.5 mg/dl) and ESR (102 mm in the 1<sup>st</sup> hour) were also elevated. X-ray chest was essentially normal except for mild hyperinflation.

In view of worsening kidney function child was started on intermittent hemodialysis with supportive treatment including antihypertensive agents. After 48 h, renal biopsy was done (Fig. 1). Light microscopy showed cellular crescents in 8 out of 16 glomeruli with marked endocapillary proliferation; neutrophilic infiltrates and tuft necrosis. A non-necrotizing granuloma was also seen in the interstitium with dense inflammatory infiltration of eosinophiles. Immunofluorescence showed minimal capillary wall deposits of Immunoglobulin M (IgM) and C3 with otherwise no staining of immune complexes suggestive of pauci-immune crescentic glomerulonephritis. Biopsy of the overlying skin and subcutaneous tissue showed dense eosinophilic infiltration. The patient was given 3 intravenous pulses of methylprednisolone. 7 sessions of double volume plasma exchange were also done in view of dialysis dependence and severe azotemia. Following this, the total leukocyte count dropped significantly to the range of  $9000\text{--}12,000\text{ cells}/\text{mm}^3$  with AEC of  $<200\text{ cell}/\text{mm}^3$  tested on multiple occasions. Kidney functions improved gradually over next 10 days to serum creatinine of 0.5 mg/dl and good urine output.

Final diagnosis of ANCA negative EGPA with pauci-immune necrotizing crescentic GN was made. The child was also given 6 intravenous pulses of cyclophosphamide at a dose of  $500\text{ mg}/\text{m}^2$  every 3 weeks as part of induction therapy after ruling out any active infection and under strict monitoring for fall in total leukocyte count followed by  $750\text{ mg}/\text{m}^2$  of oral mycophenolate mofetil. He is under regular follow-up and has good urine output with normal blood pressure, AEC, and renal functions. However, he continues to have subnephrotic proteinuria ( $400\text{--}500\text{ mg}/\text{m}^2$ ) for which  $0.3\text{ mg}/\text{kg}/\text{day}$  of oral enalapril has been added with 2 week monitoring of serum creatinine and potassium levels.



**Figure 1: Photomicrograph of the renal biopsy showing eosinophilic vasculitis with crescent formation**

## DISCUSSION

EGPA earlier known as CSS is a multisystem small vessel vasculitis seen in association with ANCA specific for MPO- ANCA or PR3-ANCA or maybe ANCA negative. This condition is rare in childhood population. Chapel Hill Consensus Conference-2012 defines EGPA as necrotizing vasculitis involving small-to-medium vessels with no or minimal immune deposits [3]. EGPA is eosinophil-rich necrotizing granulomatous inflammation of small-to-medium vessels often associated asthma and respiratory symptoms. ANCA is more frequently detected when renal involvement (glomerulonephritis) is present. The prominence of eosinophils in blood and tissues is an essential feature of EGPA and hence the name. Although it is observed that in adults about 25% of patients with EGPA without renal disease are ANCA positive, whereas with any renal disease and in those with documented necrotizing glomerulonephritis ANCA positivity is seen in 75% and 100% cases, respectively [4].

Etiopathogenesis of EGPA remains unclear, evidence suggests genetic predisposition, which may include inherited a tendency of deregulation of cellular immune system. Recent studies have demonstrated primary genetic causes for hypereosinophilia [5,6]. ANCA negative AAV is also a well-recognized entity, where inpatient otherwise fulfills the definition for an AAV but has negative results on serologic testing for ANCA. Patients with ANCA-negative AAV may have ANCA that cannot be detected with current methods or may have ANCA of undiscovered specificity, or pathogenic mechanisms that involve the antibodies like human lysosome-associated membrane protein-2 (hLAMP- 2) that bind to the glomerular, but not the neutrophil hLAMP-2 antigen and found in patients with active vasculitis who are negative for PR3 or MPO. Kain *et al.* proposed evidence of molecular mimicry between LAMP2 and Fim-H bacterial protein which indicates the role of bacterial infection [7].

Diagnosing EGPA in pediatrics is difficult since all the defined criteria may not be present at the time of presentation in children. Moreover, ANCA positivity in pediatric population is found to be very low (25%) [8]. Razonberg *et al.* reported CSS in a 12-year-old boy with asthma and peripheral as well as pulmonary eosinophilia and was ANCA negative [9]. The American College of Rheumatology proposed 6 criteria for the Churge-Strauss syndrome: Asthma, peripheral blood eosinophilia (more than 10% on differential white blood cell count), mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophilia [10]. The presence of 4 or more of these has sensitivity of 85% and specificity of 99.7%. Histologically, there is a typical triad of necrotizing vasculitis, granulomas, and extravascular eosinophilia [8].

Another unusual feature in our case was the absence of long insidious onset and absence of predominant respiratory symptoms including asthma. In pediatric case series by Zwerina *et al.* the most common features reported were asthma (91%), pulmonary infiltrates (85%), sinusitis (77%), skin involvement (66%), cardiac disease (55%), gastrointestinal symptoms (40%), peripheral neuropathy (39%), and kidney disease (16%) [8]. ANCA was

found to be positive in 23% cases. In our child, ANCA was negative despite severe involvement of kidney, but histologically, all the three components of triad were present. Other conditions are leading to peripheral and tissue eosinophilia such as HES, infection-induced, allergy or atopy, drug-induced, and neoplastic conditions were also considered and ruled out by history and relevant investigations. Presence of crescentic necrotizing glomerulonephritis with eosinophilic infiltration and granulomas in renal biopsy is highly specific for EGPA and virtually rules out conditions like interstitial nephritis.

There are no definitive guidelines for immune-suppressive treatment in EGPA. Gayraud *et al.* from French Vasculitis study group presented data on the long-term follow-up of 278 patients with PAN and CSS enrolled in 4 prospective trials between 1980 and 1993 and reported improved renal survival with combined use of corticosteroid and cyclophosphamide in patients with severe vasculitis renal involvement [11]. In our patient, we did induction therapy with IV methyl prednisolone and IV cyclophosphamide. In view of severe renal involvement, we also did plasma exchanges (7 in number) and same is endorsed by various studies. Although mechanism for improvement of renal functions is thought to be removal of pathogenic ANCA, additional mechanism by removal of cytokines and coagulation factors have also been hypothesized [12- 14]. Jayne *et al.* in Randomized controlled trial on using pulse methyl prednisolone or plasma exchanges in addition to oral steroids and cyclophosphamide (MEPEX) showed increased efficacy with plasma exchange in acute stage [15]. Our patient had severe renal involvement with very high creatinine values, oligoanuria as well as severe histological changes (100% crescents) but showed benefit from aggressive initial therapy (high dose IV MP and IV cyclophosphamide with Plasma exchanges).

## CONCLUSION

EGPA diagnosis in children is difficult with varied presentation and lack of diagnostic tests. Kidney involvement is one of the severest manifestations and has a poor outcome if not detected and treated early. High index of suspicion is the key to diagnosis in the presence of compatible clinical picture.

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