Case Report

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Anti-Glomerular Basement Membrane Disease in a Six-year-old Child: A Rare Presentation

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ABSTRACT

Anti–glomerular basement membrane (anti-GBM) disease is rare small vessel vasculitis caused by auto-antibodies targeting auto-antigen expressed in basement membranes of capillary beds in lungs and kidneys. A six-year-old-male presented with fever, cough and generalized weakness for three days with respiratory distress for one day. The child had three prior admissions with similar complaints and was treated as a case of lower respiratory tract infection with severe iron deficiency anemia in past. Multiple packed red cell transfusions were required in these past admissions. In this current admission, he had tachycardia, tachypnea, severe pallor, right sided lung crepitations & bronchial breath sounds. Hemogram showed severe anemia and leukocytosis. Urine examination showed mild proteinuria and microscopic hematuria. Chest X-ray (current admission) showed right middle and lower zone consolidation. HRCT of chest revealed interstitial pattern. Lung biopsy showed pulmonary hemorrhage and positive Prussian blue staining. Raised anti-GBM titers confirmed diagnosis of anti-GBM disease. Renal biopsy revealed normal glomerular morphology on histopathology; with immune fluorescence showing linear positivity for IgG (3+), Kappa (3+), and Lambda (3+). Electron microscopy reported mild effacement of visceral epithelial foot processes and subepithelial/intramembranous electron dense deposits. He was treated with intravenous methylprednisone for 5 days followed by oral prednisolone for one month, which was thereafter tapered to a lower maintenance dose for 18 months. The child received six cycles of intravenous cyclophosphamide along with a daily low dose of steroids. Currently child is asymptomatic after one year of follow-up with seroconversion (anti–GBM titers decreased) and normalization of chest radiograph.

Keywords: Basement Membrane; Glomerular; Hematuria; Hemorrhage; Hemoptysis; Lung; Nephritis; Pulmonary; Renal.

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INTRODUCTION

Anti–glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis caused by the development of auto-antibodies targeting the auto-antigen expressed in basement membranes of capillary beds in lungs & kidneys. The incidence rate is 0.5–1.0 per million population per year with bimodal presentation (3rd & 6th decade); however, pediatric cases are extremely rare with a paucity of incidence data in children.[1] Clinical

presentation ranges from pulmonary hemorrhage to rapidly progressive glomerulonephritis.

CASE REPORT

A six-year-old male child presented with fever, cough and generalized weakness for three days with respiratory distress for one day. He had three prior admissions with similar complaints and was treated as a case of lower respiratory tract infection with severe iron deficiency anemia. Multiple packed red cell transfusions were required in the past admissions (along with oral iron therapy). On examination, the child had tachycardia, tachypnea, and severe pallor. Pulse oximetry saturation was 78% on room air & 98% on face mask (6 L/min oxygen). The child had suprasternal & intercostal retractions. On auscultation, crepitations & bronchial breath sounds were heard on the right side of the chest (infra-mammary & infra-axillary areas). The other systemic examination was normal.

The hemogram showed severe anemia and leukocytosis. Urine examination showed mild proteinuria & microscopic hematuria, which pointed towards possible pulmonary renal syndromes. Chest X-ray (in the current admission) showed right middle and lower zone consolidation

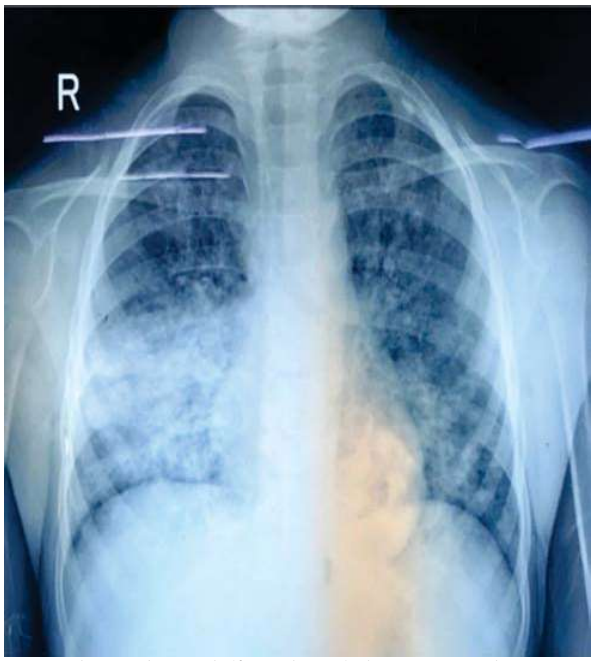

Fig. 1: Chest radiograph (frontal view) showing a patchy opacity in the right mid zone and lower zone.

(Fig. 1). The high-resolution CT scan (HRCT) of chest revealed an interstitial pattern (diffuse ground glass opacities) (Fig. 2). The lung biopsy showed pulmonary hemorrhage and positive

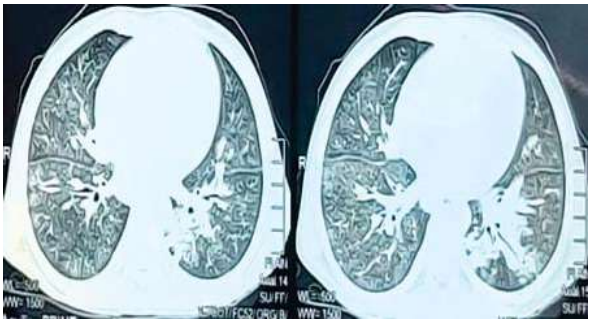

Fig. 2: HRCT chest showing diffuse ground glass opacity with interlobular septal thickening seen throughout all lobes with perihilar predominance and subpleural sparing.

Prussian blue staining (revealing the stained iron in the erythrocytes ingested by alveolar macrophages) (Fig. 3a and 3b). Raised anti-GBM titers (30 U/ml; normal levels 7-10 U/ml) confirmed the diagnosis of anti-GBM disease. The renal biopsy revealed a normal glomerular morphology on histopathology, with immunofluorescence showing linear positivity for IgG (3+), Kappa (3+), and Lambda (3+). Electron microscopy reported mild effacement of visceral epithelial foot processes (15-20%) and subepithelial/intramembranous electron dense deposits (Fig. 4). The acute stage was treated with intravenous methylprednisone (30 mg/kg/day) for 5 days followed by oral prednisolone (2 mg/kg/day) for one month, which was there after tapered to a lower maintenance dose (0.3 mg/kg/day) for 18 months, with serial monitoring of anti-GBM titers. The child received six cycles of intravenous cyclophosphamide (500 mg/m^2 once a month) along with a daily low dose of steroids. Currently child is asymptomatic after one year of follow-up

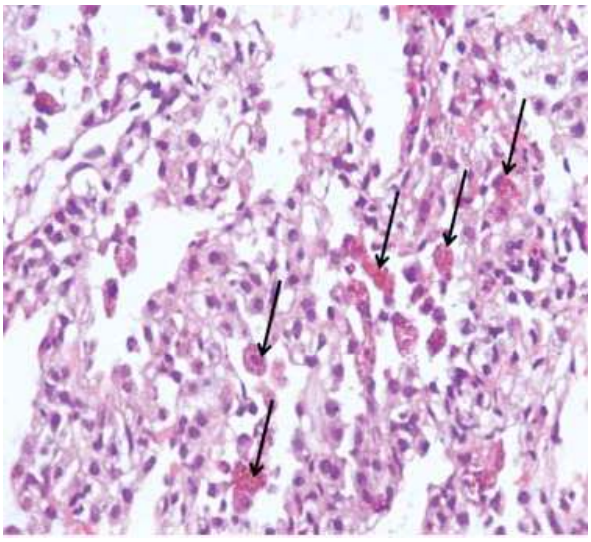

Fig. 3a: Lung biopsy-High power field image (H&E;40x) showing brown coloured hemosiderin laden macrophages (Black arrows).

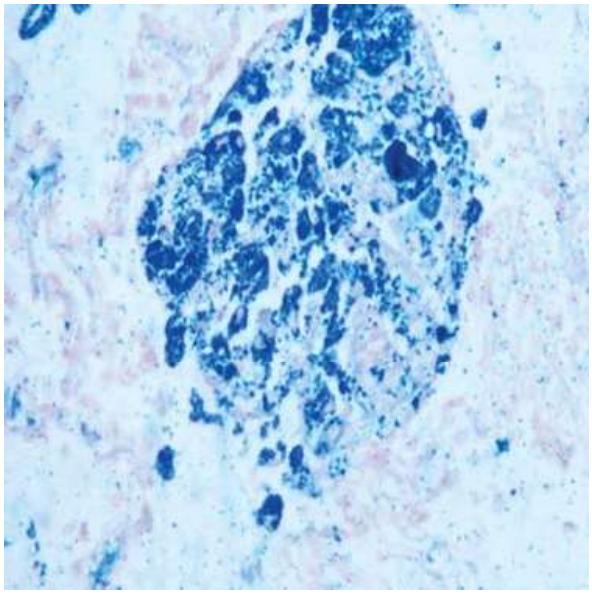

Fig. 3b: Lung biopsy (40x – Prussian Blue) shows the presence of blue colored hemosiderin in high power field.

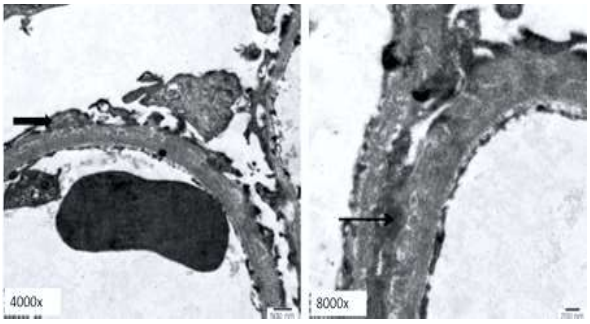

Fig. 4: Electron Microscopy - Mild effacement of visceral epithelial foot processes (Thick arrow) with subepithelial electron-dense deposits (Thin arrow).

with seroconversion (anti–GBM titers decreased to 3.6 U/ml) and normalization of chest radiograph.

DISCUSSION

Basement membranes constitute an anatomic barrier that is made up of connective tissue. Laminin, proteoglycans, and type IV collagen make up their structure. Anti-basement membrane antibodies bind to the non-collagen location of the alpha-3 chain of type IV collagen (that is present both in the alveoli and the glomeruli). Antibodies against the glomerular basement membrane (GBM), alveolar basement membrane, and tubular basement membrane have long been linked to a number of renal disorders, pulmonary diseases, and other organ disorders. Anti-glomerular basement membrane (anti-GBM) disease is a small vessel vasculitis that affects the capillary bed basement membrane of the kidneys and lungs. Although anti-GBM disease is exceedingly rare in children, it accounts for about 20% of all rapidly progressing glomerulonephritis (RPGN) cases.[1] 0.5–1.0 cases per million population is the incidence reported in adults.[2] The data from the USA has shown that 0.4% of all pediatric chronic kidney disease (CKD) stage five cases were due to anti-GBM disease.[3] The new evidence of spatial and temporal clustering of cases raises the possibility that environmental triggers, such as infection, may trigger the disease in those with a genetic predisposition.[4]

The disease often manifests as rapidly progressive glomerulonephritis (RPGN) in 80–90% of cases, necessitating urgent renal replacement therapy. Both adults and children with the disease present in a similar way. A minority of cases may manifest with just pulmonary involvement and up to 60% of them will also develop pulmonary hemorrhage.[5] There are several different types of pulmonary involvement, ranging from asymptomatic radiography or bronchoscopy findings to life-threatening hemoptysis. Chest pain, cough, and shortness of breath are other common pulmonary symptoms. Symptoms of kidney involvement include hypertension and fluid overload, which are typical of acute glomerulonephritis. Both microscopic and macroscopic hematuria can be seen. It has been documented that primary cerebral small vessel angiitis in this disease can cause cerebral involvement, and it typically manifests as seizures.[6]

Anti-GBM antibody detection, either histologically or in serum, aids in the diagnosis.[3] Circulating antibodies could not be found in 10% of patients with anti-GBM disease. Consequently, in situations where there is still a strong clinical suspicion of disease, histological proof of disease through kidney or lung tissue is crucial.[7] Anti-GBM disease can be distinguished from other glomerulonephritis (GN) such as post-infectious, immune complex, and isolated antinuclear cytoplasmic antibody (ANCA) associated GN by the evidence of antibody deposition. Under light microscopy, widespread crescent formation involving more than 80% of the glomeruli is identified, and immunofluorescence (IF) indicates linear IgG deposition along the GBM. Human Leucocyte Antigens (HLA) DRB1*1051 and DRB1*1502 have been linked to this disease in genetic studies, however, HLA-DR7 and DR1 seem to be protective.[3]

The current KDIGO glomerular disease guidelines (2021) provide a detailed description of how to manage anti-GBM disease in children

using a strategy developed from the management of adult disease.[8] Acute apheresis and first line immunosuppressive agents like cyclophosphamide, are used to remove the pathogenic circulating antibody and any potential immune mediators. To stop the production of antibodies, and reduce inflammation, corticosteroids and/or adjunctive immune modifying drugs like mycophenolate mofetil (MMF) are used.[9] If cyclophosphamide is contraindicated, then B-cell depleting drug rituximab is recommended, and in more severe disease, it may be used as a disease adjunct. However, these studies on rituximab did not show improvements in renal outcomes. A small case series in adults showed meaningful improvement in respiratory disease using rituximab as an induction agent, but there is a paucity of pediatric data.[10] When necessary, supportive care may involve the use of antihypertensive medications as well as kidney replacement therapy.

Anti-GBM disease does not frequently have a relapsing, remitting pattern, in comparison to many other autoimmune diseases. The majority of children (91%) survive if treatment is started, although renal disease frequently progresses to an advanced stage and may require dialysis and/or renal transplant.[5] The prognosis is guarded in children with rapid progression of the renal disease and pulmonary hemorrhage.

CONCLUSION

Many a times the diagnosis of anti-GBM disease is delayed and made after the onset of the chronic kidney disease. Children with anemia and repeated respiratory manifestations should be investigated for immunological causes, since early diagnosis and treatment can be life saving (in an otherwise rapidly fatal anti-GBM disease).

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Author Contributions:

DJB & MST were equally involved in conceptualization collecting data, clinical treatment, literature search & drafting the manuscript (First Authors). NK & MA helped in collecting data, clinical treatment, literature search & drafting the manuscript.

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