CASE REPORT

Immunoglobulin A Nephropathy, Celiac Disease, and Immune Complex Pneumonitis: A Rare Case Report of an Immunoglobulin A-Associated Pathologic Trifecta

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ABSTRACT

Introduction: The systemic manifestations of immunoglobulin A (IgA) nephropathy with lung involvement include diffuse alveolar hemorrhage due to monoclonal IgA disorders, IgA-variant Good pasture's syndrome, and Henoch-Schoenlein purpura. However, pneumonitis due to IgA immune complex has rarely been reported as the pulmonary manifestations of IgA nephropathy.

Case Presentation: A 35-year-old woman presented with 2 years of progressive shortness of breath, dry cough, low-grade fever along with progressive loss of appetite, and loss of weight. She underwent renal, duodenal, and lung biopsies. She was diagnosed with a rare combination of IgA-mediated nephropathy, IgA-associated celiac disease, and IgA-mediated immune complex cavitary lung disease.

Discussion: Secretory IgA may be acting as an immune complex or proinflammatory agent to provoke the signs and symptoms in this case. Thus, the respiratory process may incite renal disease or vice-versa. Further research is needed to analyze the possibility of such associations.

INTRODUCTION

Immunoglobulin A (IgA) nephropathy may be a primary disease process or secondary to other disease processes. It may also be the only manifestation of systemic diseases. There is a strong association of IgA nephropathy with liver disease, particularly alcoholic cirrhosis. There is also an association found with hepatitis B- and C-associated liver disease. It is also found that diseases with an impaired gut mucosal barrier are associated with IgA nephropathy. Wide association is found with celiac disease, though inflammatory bowel disease, egg protein allergy, and lactose intolerance are also studied. Systemic diseases like HIV, monoclonal gammopathy, and malignancy are also considered to have associations with IgA nephropathy.[1]

Association of IgA nephropathy with celiac disease can rarely have pulmonary manifestations including obstructive airway disease, interstitial lung disease, or pulmonary hemosiderosis (Lane-Hamilton syndrome).[2]

CASE PRESENTATION

A 35-year-old female patient presented with a history of progressive shortness of breath and dry cough for 2 years. There was no history suggestive of underlying autoimmune disease, clinically significant environmental allergies, serious systemic recurrent bacterial infections, illicit drug exposure, or recent tuberculosis exposure. Treatment of her coughing with bronchodilators over the past 2 years had been ineffective. She presented to us with an increase in symptoms over the previous 4 months including low-grade fever, progressive loss of appetite, and loss of weight. The patient was referred to our hospital with the initial computed tomography showing nodular changes in parenchyma and repeat computed tomography showed cavitation (Figure 1A and 1B). No prior radiographs were available. The pre-admission hemogram reported leucocytosis with neutrophilic predominance, which later changed to lymphocytic predominance. Urine examination was not done prior to admission. Sputum analysis done before admission showed negative results for Acid fast bacilli smear, cartridge based nucleic acid amplification test, and Mycobacteria Growth Indicator Tube culture for mycobacterium. The patient was given repeated doses of antibiotics and nebulization, but steroids were not prescribed.

On admission, the patient was afebrile, with tachycardia (116 beats per minute), tachypnea (36 beats per minute), and pulse oxygen saturation of 82% on ambient air. Respiratory system examination demonstrated bilateral rales. The arterial blood gas analysis documented hypoxemic respiratory failure (pH 7.45, pCo2 35 mmHg, pO2 43 mmHg, HCo3 22.1 mmol/L). There was neutrophilic leucocytosis, with high levels of acute-phase reactants (C-reactive protein = 5 mg/L; erythrocyte sedimentation rate = 80 mm/h). Initial contrast-enhanced computed tomography of the chest demonstrated nodules which progressed to cavitation over 6 weeks (Figure 1A and 1B). Bronchoalveolar lavage revealed neutrophilic predominance with negative pyogenic, fungal, and tubercular cultures. The urine examination showed microscopic hematuria and proteinuria of 1.6 g/d. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti- glomerular basement

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membrane antibodies were all negative. The complement factor levels were normal.

After informed consent was obtained, the patient underwent renal biopsy; revealing mesangial proliferation with coarse granular deposition of IgA in immunofluorescence (Figure 2A and 2B). The diagnosis of celiac disease was confirmed by a positive serum IgA-tissue transglutaminase and a duodenal biopsy that showed villous atrophy with lymphocytic infiltration into the submucosa. Among immunoglobulin classes, elevated circulating IgA subclass levels were observed (894 mg/dL). She also underwent transbronchial lung biopsy demonstrating proliferation of type 2 pneumocytes and a large area of hemorrhage. Immunofluorescence showed coarse granular deposits of IgA in fibrinogen in alveoli and blood vessel (Figure 3A and 3B).

The unique cooccurrence of IgA nephropathy, celiac disease, and IgA-mediated immune complex pneumonitis with cavitation was established. A gluten-free diet was initiated; however, no response was observed at end of 6 weeks, and, hence, systemic oral corticosteroids (1 mg/kg) were added. The patient showed marked improvement in symptoms and resolution of proteinuria and hypoxemic respiratory failure over a period of 1 month. Table 1 provides a timeline of the case.

DISCUSSION

The association of IgA nephropathy with celiac disease is hypothesized to be secondary to dysfunctional IgA in circulation produced due to abnormal gut response to gluten antigen.[3] The abnormal circulating immunoglobulin triggers kidney dysfunction due to immune complex deposition. Correspondingly, a similar trigger dysfunction in the lungs manifests as diffuse alveolar hemorrhage and bronchiolitis. In this case, the patient did not have evidence of progressive renal failure or diffuse alveolar hemorrhage.

It is considered that the disease is predisposed by mucosal barrier disruption, causing B lymphocytes to be triggered to produce peculiar IgA. This IgA forms an immune complex that gets deposited in the kidneys to cause the disease. Genetic and familial predispositions are being speculated. It is considered that the increase in the circulation of the galactose-deficient form of IgA1 triggers the disease. The degree of circulation of the galactose-deficient form is directly proportional to the probability of disease occurrence. The exposed hinge region in such IgA triggers the antibodies to form complexes that get deposited with complement activation, leading to renal disease. In the current case, there are also high levels of circulating IgA levels. Though the subtyping is not done, it may be hypothesized that deposition of such complexes might have triggered lung injury apart from IgA nephropathy.[4]

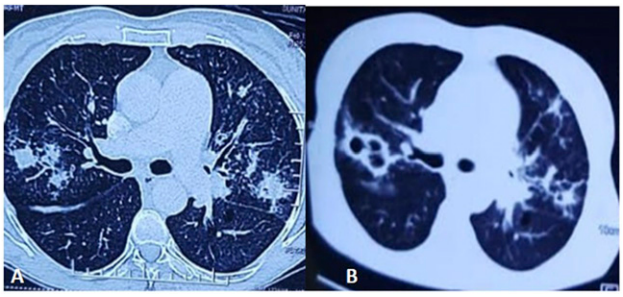

Figure 1. **(A)** Computed tomography thorax shows bilateral nodular opacities in upper lobe. **(B)** The bilateral opacities progressed to cavitation in 6 weeks.

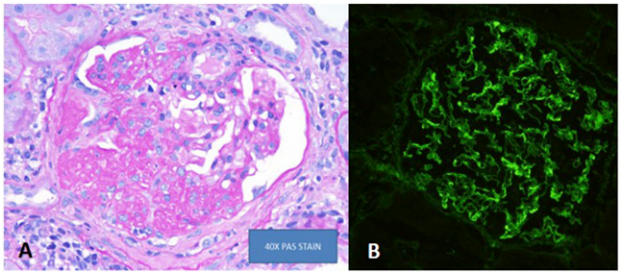

Figure 2. **(A)** Light microscopy: PAS-stained kidney biopsy demonstrated mesangial proliferation. **(B)** Immunoflorescence: IgA granular deposition.

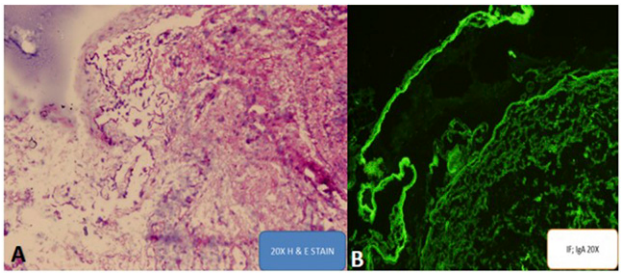

Figure 3. **(A)** Light microscopy: Hematoxylin and eosin-stained lung biopsy demonstrated inflammatory infiltrate. **(B)** Immunoflorescence: IgA granular deposition (2+) in alveolar basement membrane.

The pathologic evaluation now adds crucial prognostic information exceeding the clinical variables alone. MEST or Oxford scores include pathologic features consistently and independently associated with the renal outcome. The score incorporates mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy and interstitial fibrosis (T). An essential goal of deriving a histologic scoring system is shortening the time frame of observation required to accurately predict which patients are at risk of adverse outcomes.[3]

In the literature, pneumonitis due to IgA immune complex, as the pulmonary manifestation of IgA nephropathy, has only been previously reported once.[5] Cavitary lung disease has not been documented previously.[6] The plausible

Table 1. Timeline table

Date	Visit information	Diagnostic testing	Interventions
February 10, 2019	A 35-year-old female patient presented with progressive dyspnea over the past 4 months, low-grade fever, progressive loss of appetite, and loss of weight. She had received antibiotics but there was no relief.	Initial contrast-enhanced computed tomography of her chest demonstrated nodules, which progressed to cavitation over 6 weeks. Bronchoalveolar lavage revealed neutrophilic predominance with negative pyogenic, fungal, and tubercular cultures. The urine examination showed microscopic hematuria and proteinuria of 1.6 g/d.	Workup for cause of proteinuria initiated.
March 1, 2019	Patient underwent serological investigations. Contraindication for renal biopsy ruled out.	In the workup for proteinuria, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane, antibodies were all negative. The complement factor levels were normal. Renal biopsy revealing mesangial proliferation with coarse granular deposition of IgA in immunofluorescence.	Workup for cause of IgA nephropathy.
March 10, 2019	After receiving the renal biopsy report, the patient underwent serological investigations and duodenal biopsy for evaluation of IgA nephropathy.	In workup for evaluating the cause of IgA nephropathy, her IgA-TTG was positive, and subsequent duodenal biopsy showed villous atrophy with lymphocytic infiltrate in the submucosa. Among immunoglobulin classes, elevated circulating IgA subclass levels were observed. She underwent transbronchial lung biopsy, demonstrating IgA deposition in the alveolar basement membrane and sub-endothelium of bronchioles.	With the possibility of celiac-associated lung disease, she was started on a gluten-free diet with no response and required domiciliary oxygen support.
May 1, 2019	After 6 weeks of gluten-free diet, there was no improvement in symptoms. Hence, systemic oral corticosteroids (1 mg/kg) were added.	Patient's respiratory failure improved. Also, proteinuria resolved completely after 1 month of therapy.	Singular diagnosis of IgA nephropathy, celiac disease, and IgA-mediated immune complex pneumonitis established.

explanation may be due, in part, to the lack of lung biopsy performed in patients with IgA nephropathy.

Secretory IgA is known to exist on the mucosal surfaces of the respiratory and gastrointestinal tracts, providing a primary defense against local infections. Secretory IgA remains the most probable source of IgA nephropathy. It is frequently associated with illness in an IgA-secreting organ, such as those of the respiratory or gastrointestinal tracts.[5] Thus, a respiratory process may incite renal disease or vice-versa. Hence, both processes are end-organ consequences of a single systemic disease mediated by IgA. Further research is needed to analyze the possibility of such associations. ❖

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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