

Allergic bronchopulmonary aspergillosis presenting as nephrotic syndrome due to secondary amyloidosis: Case report and systematic review of the literature

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is a complex inflammatory lung disorder complicating bronchial asthma and cystic fibrosis. Although the condition responds to treatment with glucocorticoids and antifungal drugs, lack of timely recognition, and inadequate treatment of ABPA can lead to progressive lung damage. Uncommonly, long standing inflammation and bronchiectasis can also lead to the development of secondary amyloidosis. Herein, we report a case of ABPA, which presented as nephrotic syndrome and progressed rapidly to end-stage renal disease.

KEY WORDS: Allergic bronchopulmonary aspergillosis, allergic bronchopulmonary mycosis, amyloidosis, *Aspergillus*, bronchiectasis, nephrotic syndrome

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INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder encountered in patients with asthma or cystic fibrosis.^[1] The disorder clinically manifests with poor asthma control, fleeting pulmonary infiltrates, and bronchiectasis.^[2] The prevalence of ABPA in asthma in patients attending special asthma/chest clinics is about 13%,^[3] with a global burden of about 5 million cases.^[4] There are an estimated 1.4 million cases in India alone.^[5] The natural history of ABPA is characterized by recurrent exacerbations. If the disorder is not properly recognized or adequately treated, the underlying inflammatory process can progress inexorably and can cause extensive bronchiectasis with pulmonary fibrosis.

Amyloidosis is a complex condition that involves deposition of abnormally folded proteinaceous materials

in several organs including the kidney, spleen, liver, heart, and others.^[6] The kidney is one of the major organs involved in systemic amyloidosis. Herein, we report a case of secondary amyloidosis and nephrotic syndrome, as the presenting manifestation of ABPA.

CASE REPORT

A 54-year-old female presented with complaints of early morning periorbital puffiness and pedal edema. There was no history of hematuria or decrease in urine output. She denied any skin lesions, Raynaud's phenomenon, joint pains, or oral ulcers. There was no history of diabetes mellitus or pulmonary tuberculosis. The patient was a known asthmatic for the past 30 years. Despite inhaled corticosteroids and bronchodilators, her bronchial asthma was poorly controlled for the last two decades, and she experienced recurrent exacerbations

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requiring oral glucocorticoids. On examination, the patient had moon-like facies, pitting pedal edema, proximal muscle weakness, and bilateral wheeze on auscultation of the chest. Rest of the physical examination was unremarkable. Urine examination revealed nephrotic range proteinuria (4.4 g/24-h urine) without any red blood cells or casts. Other investigations revealed hypoalbuminemia (serum albumin, 1.9 g/dL) without azotemia (serum creatinine, 1.0 mg/dL). Rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies were negative. Serology for hepatitis B, hepatitis C, and human immunodeficiency virus was negative. Urine and serum protein electrophoresis did not reveal M band. Serum free light chain assay was negative. Echocardiography was normal. The patient underwent a kidney biopsy for the evaluation of nephrotic syndrome. Renal biopsy was consistent with features of amyloidosis; immunohistochemistry was positive for serum amyloid A (SAA), confirming the diagnosis of secondary amyloidosis [Figure 1]. In view of uncontrolled asthma, she was evaluated for ABPA. *Aspergillus fumigatus*-specific immunoglobulin E (IgE) and total IgE were elevated (2.4 kUA/L and 702 IU/mL, respectively), total eosinophil count was 536 cells/ μ L, and serum precipitating antibodies and skin prick test (Type I) for *A. fumigatus* were both positive. High-resolution computed tomography (CT) of thorax revealed bronchiectasis [Figure 2]. A diagnosis of ABPA was made and the patient was started on oral prednisolone (30 mg/day for 1 month followed by 15 mg/day for 1 month, then 10 mg/day for 1 month and 5 mg/day for 1 month) along with inhaled steroids, long-acting beta-2 agonists, and montelukast 10 mg daily. There was improvement in dyspnea, however, proteinuria persisted.

Four months following the initial presentation, the patient developed oliguria, worsening breathlessness, and progressively increasing serum creatinine. She received multiple sessions of hemodialysis. Subsequently, she

developed odynophagia and dysphagia, for which an esophagogastroscope was performed. Multiple esophageal and antral ulcers were seen. Biopsy from the ulcer showed evidence of secondary amyloidosis without any evidence of cytomegalovirus or herpes simplex virus infection, or candidiasis. Her oliguria worsened, serum creatinine continued to rise (8.9 mg/dL), and she became progressively drowsy. CT of head was normal; blood and urine cultures were sterile. Due to worsening sensorium, the patient required endotracheal intubation. Hemodialysis was continued along with supportive care; however, the patient developed cardiac arrest during hemodialysis and succumbed to her illness.

DISCUSSION

The current case highlights an unusual complication of ABPA, namely, secondary amyloidosis. To the best of our knowledge, nephrotic syndrome due to secondary amyloidosis as a presenting manifestation of ABPA has not been previously reported.

Amyloidosis can be hereditary or acquired, localized, or systemic.^[7] Acquired amyloidosis can either be primary or secondary. Primary amyloidosis involves the deposition of abnormal immunoglobulin amyloid light-chains in patients with plasma cell dyscrasias. On the other hand, secondary amyloidosis occurs in chronic inflammatory disorders such as rheumatoid arthritis and bronchiectasis. Persistent inflammation leads to the release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor- α , which stimulate the synthesis of SAA protein in the liver with subsequent deposition in various organs. Renal involvement is common in secondary amyloidosis. It clinically manifests as nephrotic syndrome progressing to end-stage renal disease.^[8] In ABPA, there is profound Th2 inflammation against *Aspergillus* proteins that are released during fungal growth; this inflammatory cascade goes unabated in untreated patients. This is probably responsible for the occurrence of amyloidosis in the index case.

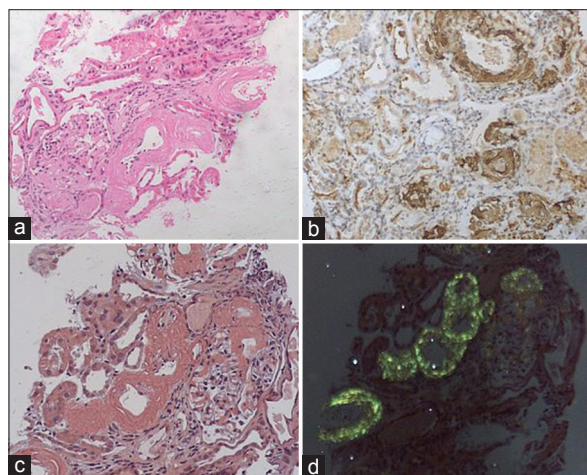


Figure 1: Renal biopsy showing: (a) Eosinophilic acellular material in the walls of blood vessels and mesangium of glomerulus, (b) immunostain showing positivity for serum amyloid A protein, (c) congo red stain highlighting the amyloid deposits around the blood vessels and glomerulus, (d) apple green birefringence of amyloid deposits seen under polarizing microscope

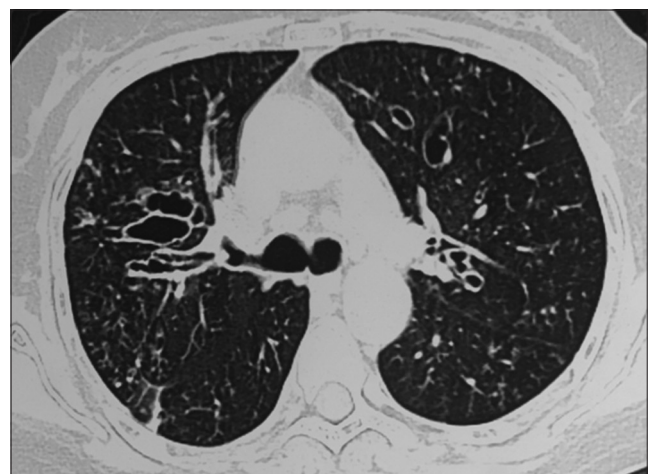


Figure 2: High resolution computed tomography showing central bronchiectasis, nodules, and bronchial wall thickening bilaterally

A systematic search of the PubMed database (from inception till May 1, 2017) with the following search terms was undertaken: ("allergic bronchopulmonary aspergillosis" OR "ABPA" OR "allergic bronchopulmonary mycosis" OR "fungal sensitization" OR "fungal allergy" OR bronchiectasis) AND amyloid*. The search yielded ninety citations, of which idiopathic bronchiectasis, cystic fibrosis, bronchiectasis in immunodeficiencies and Kartagener's syndrome were identified as etiologies of secondary amyloidosis.^[9-11] ABPA as a cause of secondary amyloidosis has been reported only once in the literature [Table 1].^[12] A common feature among the previous reported patients includes the presence of asthma and ABPA for at least two decades before the diagnosis of secondary amyloidosis. One of these patients also had rheumatoid arthritis, which could have contributed to the development of secondary amyloidosis. All these patients died because of their renal failure, within 1 year from the diagnosis of amyloidosis (unrelated to their respiratory ailments) similar to the index case.

The index case offers few important learning points. Following the initial report three decades ago, no further cases have been reported. Undoubtedly, ABPA leading

to amyloidosis is uncommon; however, it also possible that this complication is underrecognized as there are no typical clinical manifestations. For example, in the current case, nephrotic syndrome was diagnosed on the presence of periorbital puffiness and proteinuria, however, ABPA was not suspected. The pulmonary disorder was identified during routine screening for ABPA performed in view of the patient's diagnosis of asthma. In other patients with ABPA, the occurrence of facial puffiness and pedal edema may be ascribed to cor pulmonale and right heart failure.^[13] As there is no specific treatment for secondary amyloidosis, the ideal management is the adequate treatment of chronic inflammation thereby preventing the development of secondary amyloidosis. The index case provides a strong argument for routinely screening asthmatic patients for ABPA, thus making a diagnosis of ABPA before the development of bronchiectasis, thereby avoiding this irreversible consequence of long standing inflammation.

CONCLUSION

ABPA presenting as nephrotic syndrome, due to secondary amyloidosis is uncommon. Early identification and

Table 1: Details of patients with secondary amyloidosis due to allergic bronchopulmonary aspergillosis

Reference	Age/sex	Duration of asthma	ABPA	Other illness	Amyloidosis	Course of the patient	Time to death (after diagnosing amyloidosis)
12	50/male	Since childhood	Diagnosed at 25 years of age Proximal bronchiectasis, skin test for <i>A. fumigatus</i> 6 mm (positive), precipitins for <i>Aspergillus</i> positive, elevated total and <i>Aspergillus</i> -specific IgE, blood eosinophilia, sputum grew <i>A. fumigatus</i>	None	Diagnosed at 49 years of age based on kidney biopsy Serum albumin 2 g/dL, 24 h urine protein 5.75 g, serum creatinine 11.59 mg/dL	Acute on chronic renal failure at 49 years of age. Death at 50 years	1 year
12	54/female	Since childhood	Diagnosed at 32 years Radiograph showed generalized bronchiectasis, skin test 8 mm for multiple antigens, precipitins negative, total and <i>Aspergillus</i> -specific IgE elevated	At 39 years treated for sputum positive tuberculosis. At 49 years, rheumatoid arthritis was diagnosed	Proteinuria was evaluated. At 53 years, amyloidosis noted in rectal biopsy, kidney and splenic biopsies	Acute on chronic renal failure lead to the demise of the patient at 54 years of age	1 year
12	52/female	-	Developed chronic bronchitis, sputum and wheeze, 10-20 years after multiple episodes of tuberculosis. Blood eosinophilia, <i>Aspergillus</i> specific IgE was high, positive <i>Aspergillus</i> precipitins	Culture positive for <i>M. tuberculosis</i> , with severe bilateral lung involvement (at least twice, in second and third decades of life). She required several admissions, artificial pneumothoraces, streptomycin, PAS, isoniazid, and ethionamide	Proteinuria and moderate renal failure noted. Renal biopsy showed amyloidosis	Died due to renal failure	Less than a year
Index case	54/female	30 years	<i>Aspergillus</i> specific IgE elevated precipitins and skin test for <i>A. fumigatus</i> positive. Elevated eosinophil count and total IgE, central bronchiectasis in CT thorax	None	Serum albumin 1.85 g/dL, serum creatinine 1 mg/dL, 24 h urine protein 4.4 g	Acute on chronic renal failure (creatinine 8.86 mg/dL). Amyloidosis proven in kidney and esophageal biopsy	5 months

ABPA: Allergic bronchopulmonary aspergillosis, CT: Computed tomography, IgE: Immunoglobulin E, PAS: Para-amino salicylic acid, *A. fumigatus*: *Aspergillus fumigatus*, *M. tuberculosis*: *Mycobacterium tuberculosis*

adequate treatment of ABPA is essential to prevent the development and/or progression of bronchiectasis, and its irreversible complications. This underscores the need for routinely screening asthmatic patients for ABPA.

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Conflicts of interest

There are no conflicts of interest.

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