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Amyloidosis as a Renal Complication of Chronic Granulomatous Disease

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Chronic granulomatous disease is a rare primary immunodeficiency disorder, which leads to increased susceptibility to recurrent infections and severe inflammatory manifestations. There have been reports regarding different aspects of genitourinary involvement in chronic granulomatous disease, some of which are hydronephrosis, granulomatous cystitis, and glomerulonephritis, but among these complications, amyloidosis is rather rare. We report a patient with chronic granulomatous disease that developed amyloidosis later in the course of the disease.

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Case Report

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency of innate immunity with an increased susceptibility to recurrent infections and severe inflammatory manifestations.[1] The disease results from defects of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, culminating in an inability of the phagocytes in generating superoxide, leading to the defective killing of pathogenic organisms. In fact, the majority of infections in CGD are as a result of *Staphylococcus aureus*, *Pseudomonas* species, *Nocardia* species, and fungi (such as *Aspergillus* species and *Candida albicans*).[2]

Obviously, CGD is a genetically heterogenous group of defects, and it is caused by one of the several mutations that structurally alters the enzyme NADPH oxidase. The mode of inheritance can be either X-linked (XLCGD with a deficiency in $gp91^{phox}$ in approximately 70% of the patients) or autosomal recessive (ARCGD with deficiencies in $p47^{phox}$, in 25% of the patients, or even rarer, in $p22^{phox}$, $p67^{phox}$, or $p40^{phox}$).[1] However, with an incidence of 4 to 5 per million, CGD still causes significant morbidity,[1,3] particular infections, and autoimmune and inflammatory complications.[4] The onset of disease is earlier for those patients with XLCGD compared to whom with ARCGD.[5] Also, patients with XLCGD have a double risk of developing inflammatory responses than the patients with ARCGD do.[1]

Because of the progress in diagnosis and management of the associated infections, the patients' life expectancy has considerably increased; therefore, the inflammatory manifestations have become an increasingly relevant issue in CGD. Nevertheless, most patients present with infectious illness, which includes sinopulmonary disease, abscesses, or lymphadenitis. A crucial aspect of CGD is the link between infection and inflammation. It is still unclear whether the inflammation is linked to the infection, or it is even antigen-driven.[1]

Chronic granulomatous disease is the most common inherited phagocyte disorder of clinical significance. In approximately 2-thirds of patients, the first symptoms of CGD appear during the 1 year of life.[6] As a result of chronic infectious and inflammatory stimulation, these patients can have a variety of complications. There have been reports regarding different aspects of genitourinary involvement in CGD, and some of the most common manifestations include hydronephrosis,

granulomatous cystitis, glomerulonephritis, and urinary tract infections,[7] which typically occur in those with gp91^{phox} and p22^{phox} deficiencies.[8] Eosinophilic cystitis has also been described in CGD.[8] Among these complications, amyloidosis is rather rare. Bloomberg and coworkers described a patient with CGD who had urinary symptoms and renal involvement. In 1976, there was a report of a patient with ulcerative cystitis; thereafter, there were reports of 3 patients with chronic granulomatous disease who had granulomatous cystitis, too.[7] Freifeit and colleagues described chronic glomerulonephritis in a 12-year-old boy with CGD.[9] Furthermore, a report of renal aspergillosis resulting in renal abscess formation has been published.[10]

Xantogranulomatous pyelonephritis as a granulomatous manifestation in a CGD patient, and also renal amyloidosis in another patient with kidney transplant and recurrent urinary tract infections,[11,12] have been described separately. In 2008, Kaltenis and coworkers reported a boy (previously diagnosed with CGD at the age of 6.5) who developed infection which was accompanied by high fever and pulmonary, mediastinal, and paravertebral infiltrations.[13] *Aspergillus niger* was cultured on bronchial secretions, obtained by bronchoscopy. Shortly after that, proteinuria manifested and progressed to the nephrotic level. A skin biopsy indicated a diagnosis of amyloidosis. In 1971, Benditt and coworkers isolated a different protein from amyloid fibrils derived from a monkey suffering from amyloidosis associated with CGD.[14] We present a patient with CGD that developed amyloidosis later in the course of the disease.

CASE REPORT

A 22-year-old man was referred to our clinic with a medical history of recurrent pulmonary infections and fever. He was born to a consanguineous family with a background of a sibling's death due to an unknown cause at the age of 4. In addition, he had several admissions in the hospital due to respiratory tract infections and distress.

Chest computed tomography scan (Figure 1) at the age of 22 years demonstrated multiple fibrotic bands and scars associated with cicatricial emphysematous change. Owing to the history of multiple episodes of pulmonary infection, an immunodeficiency workup was completed, (Table). Meanwhile, an open lung biopsy was performed, and its pathologic evaluation revealed chronic granulomatous disease of the lung. Nitro blue tetrazolium test showed impaired neutrophil oxidative burst consistent with the diagnosis of

Laboratory Data

Parameter	Value
CBC	
Leukocyte, × 10^9/L	5.3
Polymorphonuclear cells%	69.7
Lymphocytes, %	22.7
Hemoglobin, g/dL	10.3
Hematocrit, %	32.5
Mean corpuscular volume, μm^3	73.2
Mean corpuscular hemoglobin, pg/cell	23.2
mean corpuscular hemoglobin concentration, g/dL	22.1
Platelet, × 10^9/L	117
Urinalysis	
Appearance and color	Clear and yellow
Specific gravity	1016
pH	6
Glucose	Negative
Protein	+++
Blood	Negative
Leukocyte	Oct-15
Erythrocyte	03-Apr
Cast	Fine granular
24-hour urine collection	
Urine volume, mL	1000
Creatinine, mg/h	0.8
Calcium, mg/h	54
Protein, mg/h	3000
Immunologic workup	
IgG, mg/dL	15
IgM, mg/dL	1.6
IgA, mg/dL	3.9
IgE, mg/dL	346
Nitro blue tetrazolium	0
Complement C3	1.3
Complement C4	0.36
Biochemistry	
Cholesterol, mg/dL	122
Triglyceride, mg/dL	138
Aspartate aminotransferase, U/mL	26
Alanine aminotransferase, U/mL	11
Total protein, mg/dL	4.5
Albumin, mg/dL	2.3
Others	
Antineutrophil antibodies	Negative
Anti-double-standed DNA	0.1
Perinuclear antineutrophil cytoplasmic antibodies	1.4
Cytoplasmic antineutrophil cytoplasmic antibodies	1.4

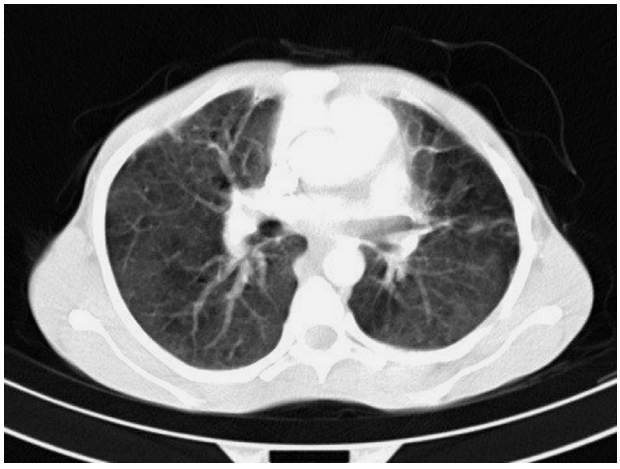

Figure 1. Fibrotic bands and scars associated with cicatricial emphysematous change

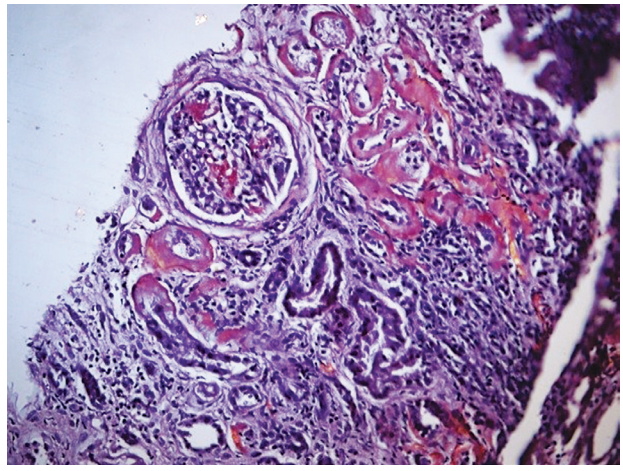

Figure 3. The kidney tissue stained with Congo-red indicative of amyloid deposits in he tissue.

CGD. The Western blot assay showed a decreased expression of the $p22^{phox}$ protein consistent with ARCGD.

Because of the nephrotic range proteinuria which persisted after the improvement of the patient's fever, a kidney biopsy was performed. A light microscopy revealed glomerular deposition of eosinophilic material in the mesangium. These depositions were Congo-Red positive. The immunohistochemical evaluation was negative for lambda and kappa light chains and positive for amyloid A. These findings were in favor of the secondary amyloidosis (Figures 2 and 3).

DISCUSSION

Five genes with two different inheritance patterns are involved in CGD pathogenesis: *CYBB* ($gp91^{phox}$, XLCGD) , *CYBA* ($p22^{phox}$, ARCGD) , *NCF1* ($p47^{phox}$, ARCGD), *NCF2* ($p67^{phox}$, ARCGD), and *NCF4* ($p40^{phox}$, ARCGD). The most common genotype, XLCGD, involves mutations in the β-chain of the cytochrome b558, *CYBB*, $gp91^{phox}$, ARCGD, caused by mutations of $p22^{phox}$, *CYBA*, the α chain of the cytochrome accounts for less than 5% of cases and is located on 16q24. Failure to produce either member of the cytochrome heterodimer ($gp91^{phox}$ or $p22^{phox}$) prevents a significant expression of the other; both subunits are required to stabilize each other within the membrane.

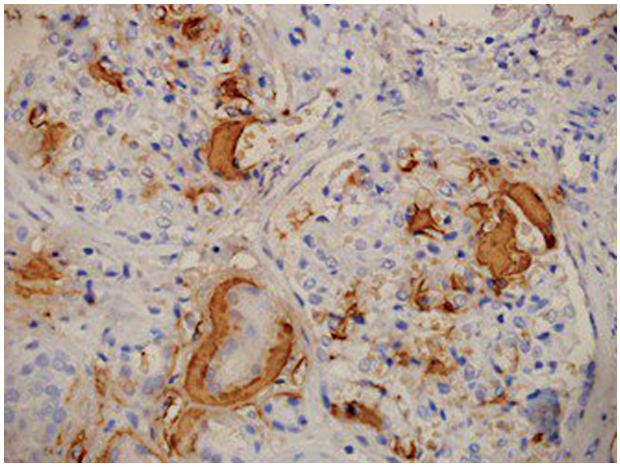

Figure 2. Immunohistochemistry reveals that amyloid deposits are positive in tissue samples, indicative of secondary amyloidosis.

Clinically, CGD is quite variable. The gastrointestinal and genitourinary tracts are frequently involved in CGD, sometimes as the site of the presenting complaint, sometimes asymptomatically. Granulomatous involvement and infectious complications result in major genitourinary conditions in patients with CGD.[2] The urogenital tract is the 2nd most commonly affected organ according to the inflammatory complications. Walther and coworkers found that 38% of CGD patients had some kind of urologic event. In a series of 60 patients with CGD, 40% of them had urologic manifestations including urethral and ureteral strictures , urinary tract infections and altered renal function.[15] In this population, the frequency of end-stage renal disease is approximately 3%.[16] All patients with urologic strictures had defects of the membrane component of NADPH oxidase ($gp91^{phox}$ or $p22^{phox}$(.[15] However, the fact that kidney disease occurs more commonly in p47-deficient CGD suggests specific roles for $p47^{phox}$ in renal physiology, more than the production of reactive

oxygen species alone.[17]

Considering these renal inflammatory complications, there are only a few case reports regarding CGD and the development of amyloidosis. One of these has occurred after kidney transplantation and recurrent urinary tract infections.[12] The other case reported by Kaltenis and coworkers described a boy with CGD who developed amyloidosis after recurrent pulmonary infections. In this specific case, *Aspergillus niger* was cultured on bronchial secretions which were collected by bronchoalveolar lavage.[13] Kidneys are the organs, which are commonly affected by amyloidosis; however, the amyloidosis development is quite rare in CGD, and there are only a few cases of CGD associated with renal amyloidosis, mentioned in the literature (some of the genitourinary complications found in CGD are summarized in Figure 4). To our knowledge, the exact time of pathologic changes occurrence consistent with amyloidosis in the context of CGD is unknown. However, it seems that amyloidosis can occur as a result of the recurrent infections and inflammation in CGD.

Amyloidosis can occur in association with almost any chronic inflammatory state or chronic infections.[18] The factors that determine the risk for amyloidosis as a complication of inflammation are not clear because many individuals do not demonstrate tissue amyloid deposition despite longstanding inflammatory disease. It seems that secondary systemic amyloidosis, occurring in CGD, is a consequence of uncontrolled sustained inflammation, which is usually the result of recurrent infections.[2] The secondary systemic amyloidosis which is synthesized in the liver is an acute phase reactant. The chronic inflammation results in elevation of secondary systemic amyloidosis, which is the precursor to the fibril formation of amyloidosis A. The sustained overproduction of secondary systemic amyloidosis in auto-inflammatory and chronic inflammatory

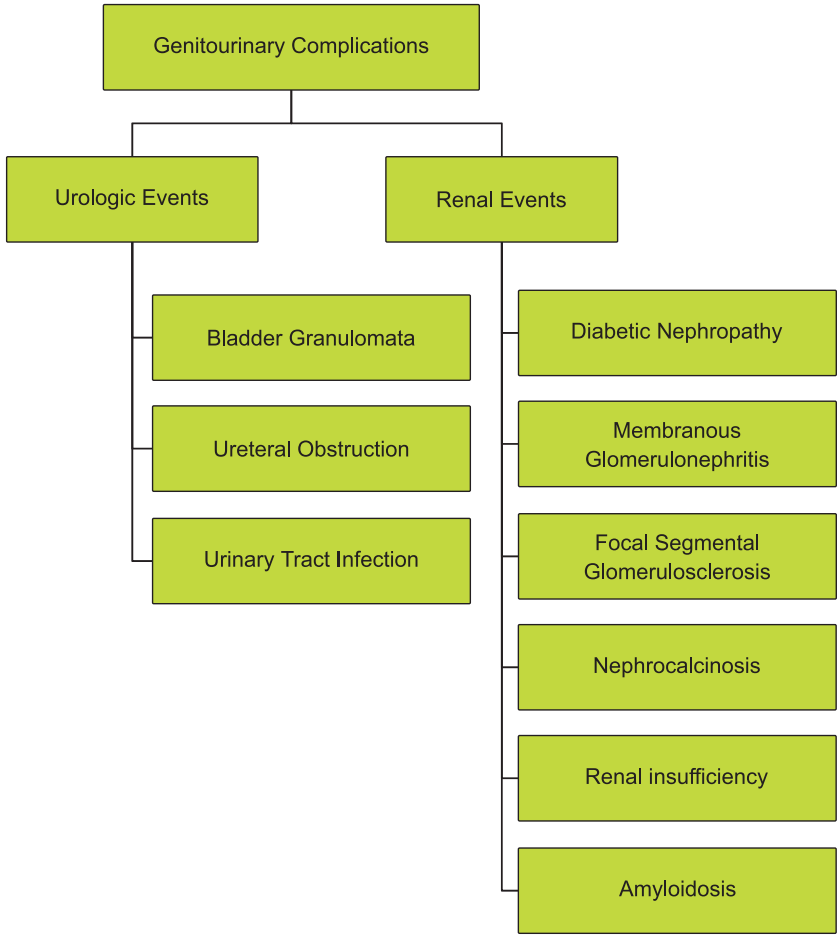

Figure 4. Genitourinary complications of chronic granulomatous disease

diseases is the major factor in the development of amyloidosis.[19] Other factors such as the environment may also play a role. Regardless of the amyloidosis cause, clinical symptoms will usually begin 10 years after the onset of inflammatory disorders as in the case presented. Amyloidosis should be considered as an inflammatory complication of disease in CGD patients with proteinuria. It is still unclear why amyloidosis occurs only in a few of the patients afflicted with CGD. The role of specific mutations (as in this case $P22^{phox}$) should also be evaluated as the cause of amyloidosis in different CGD mutations. As the previous reports were not indicative of the specific mutation causing amyloidosis, we suggest that amyloidosis occurring in the certain mutations which are causing CGD, could be an issue for the further studies.

CONFLICT OF INTEREST

None declared.

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