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The Diagnosis of Pulmonary Tuberculosis in a Patient with AA Amyloidosis of Unknown Etiology

Etiyolojisi Bilinmeyen AA Amiloidozlu Bir Hastada Akciğer Tüberkülozu Tanısı

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Abstract

It is of utmost importance to consider tuberculosis as a differential diagnosis while investigating secondary amyloid A (AA) amyloidosis, especially in developing countries. An early diagnosis of tuberculosis as the primary cause of secondary AA amyloidosis is important for precise treatment and recovery of the patient. In this case report, we aimed to increase awareness of tuberculosis as an underlying cause of secondary amyloidosis by discussing the clinical features with a review of the literature. A 74-year-old female patient presented with dyspnea. A detailed clinical and laboratory examination revealed impairment in renal function tests, leukocytosis, anemia, high procalcitonin values, pleurisy and pneumonic infiltration in the left lung. From her history, it was learned that 2 years ago, liver and inguinal lymph node lymph node biopsy was reported as systemic AA amyloidosis. Due to the increased serum creatinine values and a decrease in urine output, the patient underwent hemodialysis for a short period of time, and a decrease in urea and creatinine levels was observed after dialysis and adequate urine output was achieved. Mycobacterium tuberculosis complex was detected in the Bronchoalveolar lavage sample taken during bronchoscopy. Congo red staining of the pathology material was compatible with amyloid in the vessel wall, and immunohistochemical staining was positive for AA. The patient was transferred to the tuberculosis service for anti-tuberculosis treatment. In this case, chronic inflammation due to tuberculosis is thought to be in the etiology of secondary amyloidosis. The authors emphasize that secondary amyloidosis should be among our differential diagnoses in patients with nephrotic syndrome and previous tuberculosis history.

Keywords: Amyloidosis, tuberculosis, amyloid A



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Öz

Özellikle gelişmekte olan ülkelerde sekonder amiloid A (AA) amiloidozis araştırılırken ayırıcı tanıda tüberkülozun düşünülmesi büyük önem taşımaktadır. Sekonder AA amiloidozun primer nedeni olan tüberkülozun erken teşhisi, hastalığın tedavisi ve iyileşmesi için önemlidir. Bu olgu sunumunda, sekonder amiloidozun altında yatan bir patoloji olarak tüberkülozun bulunabileceğine yönelik farkındalığın sağlanması amaçlanmıştır, ve bu klinik tabloya ait özellikler literatürdeki veriler ile tartışılmıştır. Yetmiş dört yaşında kadın hasta nefes darlığı şikayeti ile başvurdu. Ayrıntılı klinik ve laboratuvar muayenesinde böbrek fonksiyon testlerinde bozulma, lökositoz, anemi, yüksek prokalsitonin değerleri, plörezi ve sol akciğerde pnömoni ile uyumlu infiltrasyonlar saptandı. Öyküsünden 2 yıl önce karaciğer ve inguinal lenf bezi lenf bezi biyopsisinin sistemik AA amiloidozu olarak raporlandığı öğrenildi. Serum kreatinin değerlerinin yükselmesi ve idrar çıkışının azalması nedeniyle hastaya kısa süre hemodiyaliz uygulandı ve diyaliz sonrası üre ve kreatinin düzeylerinde azalma gözlemlendi ve yeterli idrar çıkışı sağlandı. Bronkoskopi sırasında alınan bronkoalveolar lavaj örneğinde *Mycobacterium tuberculosis* kompleksi saptandı. Patoloji materyalinin Kongo kırmızısı boyaması damar duvarında amiloid ile uyumlu, immünohistokimyasal boyama AA pozitif raporlandı. Hasta antitüberküloz tedavisi için tüberküloz servisine sevk edildi. Bu olguda sekonder amiloidoz etiolojisinde tüberküloza bağlı kronik enflamasyonun olduğu düşünülmektedir. Yazarlar nefrotik sendromlu ve geçirilmiş tüberküloz öyküsü olan hastalarda sekonder amiloidozun ayırıcı tanılarımız arasında olması gerektiğini vurgulamaktadırlar.

Anahtar Kelimeler: Amiloidozis, tüberküloz, amiloid A

Introduction

Amyloidosis is a chronic disease that occurs when abnormally folded amyloid proteins accumulate fibrillarly in the extracellular space in various organs and tissues of the body⁽¹⁾. Amyloidosis that develops secondary to the accumulation of amyloid A (AA) protein in the extracellular space due to chronic infection or inflammatory diseases is defined as AA amyloidosis (secondary amyloidosis)⁽²⁾. The common target organ of AA amyloidosis is the kidney, and rheumatoid arthritis is reported to be the most common underlying disease in AA amyloidosis^(3,4). On the other hand, a previous study from Turkey reported familial Mediterranean fever as the most frequent underlying cause of AA amyloidosis⁽⁵⁾. Nevertheless, it is of great importance to be aware that tuberculosis continues to be a part of the differential diagnosis of secondary AA amyloidosis, especially in developing countries, and to take early precautions in this regard. Some previous case reports and series emphasized that tuberculosis may have an important part in the etiology of secondary AA amyloidosis^(6,7). The awareness of the clinical features of amyloidosis in tuberculosis is crucial for early diagnosis and timely evaluation.

In our case, we reported a case of AA amyloidosis secondary to pulmonary tuberculosis and aimed to discuss the clinical features and course with a review of the literature. Informed consent was obtained from the patient.

Case Report

A 74-year-old female patient presented to the Chest Diseases Emergency Department with dyspnea. Physical examination revealed real in the left basal and diffuse rhonchi in both lungs. In the examinations performed,

there was impairment in renal function tests and metabolic acidosis in the blood gas taken. Leukocytosis and anemia were noted in the first laboratory examinations of the patient. Procalcitonin was elevated, and posterior anterior chest X-ray revealed pleurisy and pneumonic infiltration in the left lung. When the patient's history was questioned, it was learned that she had been diagnosed with asthma for 2 years and had been using inhaler therapy. When the documents of the patient were examined in more detail, it was seen that she applied to a university hospital with uterine bleeding 2 years ago, and imaging studies performed during the pre-operative preparations revealed lesions compatible with multiple metastases in the liver. Liver biopsy was consistent with systemic AA amyloidosis. Because of the inguinal lymph node involvement in positron emission tomography/computed tomography, excised lymph node pathology was also reported as systemic AA amyloidosis. The etiology of secondary amyloidosis was investigated at that time, but the primary cause was not found. The patient was admitted to the department of chest diseases to investigate the etiology of pleural effusion. Empiric antibiotic treatment was initiated due to pneumonic infiltration. Hemodialysis was not planned in the first stage because of adequate urine output with fluid therapy. Compared to the thoracic imaging of the patient 2 years ago, there were still nodules in the left lung, but lesions in the left lung had progression and new fluid development. The computerized tomography images of the patient are given in Figure 1. Pleural fluid was compatible with a transudate. Pleural fluid pathology was reported as benign. Fiberoptic bronchoscopy was performed for nodular lesions and infiltration in the left lung. Bronchoalveolar lavage (BAL) was performed and samples were sent to microbiology and pathology laboratories. Forceps biopsy was performed

on the left upper lobe entrance and blunting of the lingula. The patient was transferred to the internal medicine service because of increased serum creatinine levels and decreased urine output. The patient was taken to the hemodialysis program for a short time, and antibiotherapy started by the chest diseases clinic was continued. Regression was observed in urea and creatinine values after dialysis, and adequate urine output was achieved. Mycobacterium tuberculosis complex was detected in the BAL specimens taken during bronchoscopy. Congo red staining of the pathology material was consistent with amyloid in the vessel wall and immunohistochemical staining revealed positive staining with AA (Figure 2). It was reported as pulmonary involvement of amyloidosis when combined with clinical history. The patient was followed up for a while without hemodialysis, and the treatment was arranged by removing

the hemodialysis program in the internal medicine service. The patient was transferred to the tuberculosis service to start anti-tuberculosis treatment. When the patient is hospitalized in the chest diseases clinic and the most recent biochemical are given in Table 1 and the serological values are given in Table 2. In the etiology of secondary amyloidosis, chronic inflammation due to tuberculosis was thought to be present. She was still hospitalized in the tuberculosis service and anti-tuberculosis treatment was continuing.

Discussion

Although classical information is considered to be a cause of secondary amyloidosis, the association of multidrug-resistant tuberculosis with amyloidosis has rarely been reported⁽⁶⁾. Multidrug resistance was not detected in this study. Balwani et al.⁽⁷⁾ reported a case of coexistent variable

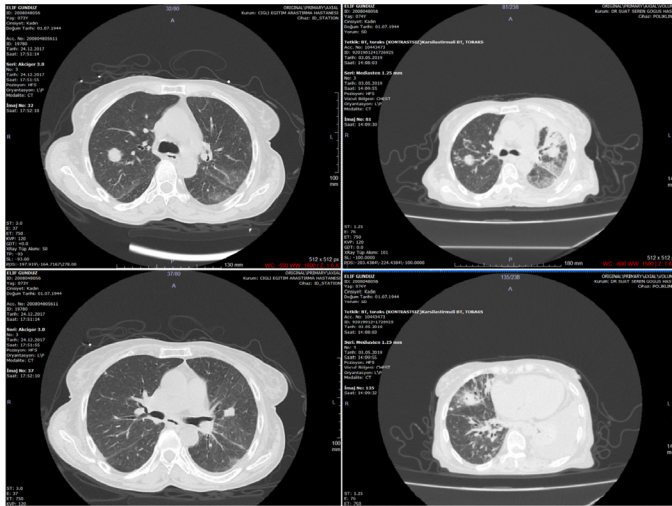


Figure 1. Thoracic computed tomography images of the patient

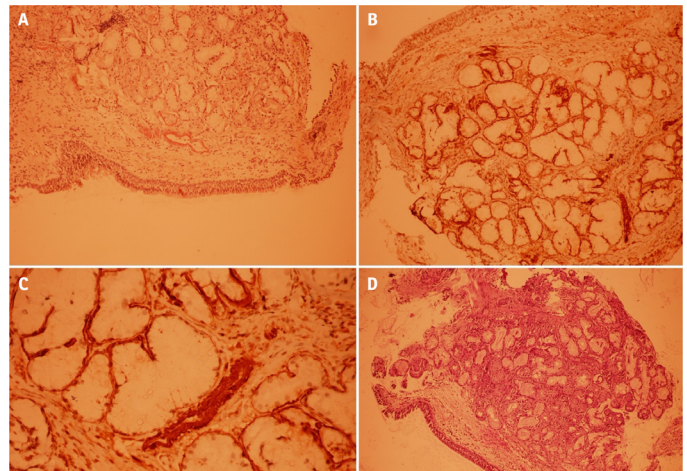


Figure 2. Histopathological images of the forceps biopsy sample. (A-C) Congo red staining, (D) hematoxylin and eosin stain

Table 1. Biochemical and complete blood count values of the case

	The first biochemical values	The most recent biochemical values	The reference range
Urea (mg/dL)	109.3	125.6	16-49
Creatinine (mg/dL)	2.22	1.57	0.5-1.1
Albumin (g/dL)	2.3	2.4	3.5-5.2
Globulin (g/dL)	3.97	3.37	2.3-4.0
CRP (mg/dL)	21.59	2.36	<0.5
Leukocyte (10 ³ /uL)	48.7	7.2	3.6-10
Hemoglobin (gr/dL)	8.5	9	12-18
Platelets (10 ³ /uL)	660	313	150-450
Erythrocyte sedimentation rate	134	48	<20

CRP: C-reactive protein

Table 2. Serological values of the case

	Results	The reference range
Ig A (g/dL)	4.62	0.7-4
Ig M (g/dL)	1.68	0.4-2.3
Total Ig-E (IU/mL)	310	0-100
Ig G (g/dL)	9.69	7-16
C4 (g/dL)	0.5	0.1-0.4
C3 (g/dL)	0.99	0.9-1.8
Procalcitonin (mcg/L)	14.06	0.04-0.1
Ig: Immunoglobulin		

immunodeficiency (CVID) and pulmonary tuberculosis. They reported a case of AA amyloidosis in CVID probably secondary to tuberculosis and repeated respiratory infections. Pulmonary tuberculosis in patients with CVID has rarely been reported⁽⁷⁾. Since T-cell dysfunction can be seen in about half of CVID cases, it is not clear whether concomitant tuberculosis is caused by a defect in T-cell function. Recurrent infections are common in the CVID course, but secondary renal amyloidosis accompanying CVID is extremely rare. CVID usually manifests as recurrent bacterial infections and hypoglobulinemia. It is thought that renal amyloidosis secondary to pulmonary tuberculosis is relatively more common⁽⁷⁾. However, long-term persistent inflammation and chronic fibrotic changes with bronchiectasis can be predisposing factors for secondary kidney amyloidosis. In other words, chronic inflammation due to recurrent respiratory infections with a history of tuberculosis may be responsible for AA amyloidosis. On the other hand, since asymptomatic proteinuria can be observed in patients with CVID disease, the connection between proteinuria and amyloidosis may be missed. In this case, secondary amyloidosis is most likely due to the overlapping effects of tuberculosis and recurrent bacterial infections during the CVID course, and it has been suggested that IVIG treatment may reduce the development of recurrent infectious attacks and thus systemic amyloidosis. Old treated tuberculosis and chronic inflammation due to recurrent respiratory tract infections might be responsible for AA amyloidosis. Thus, pulmonary tuberculosis should be considered in the differential diagnosis of secondary causes of AA renal amyloidosis of unknown origin, especially in endemic settings. Pulmonary tuberculosis (20.33%) was reported in 12 cases in the series of Paydas⁽⁹⁾ containing 59 patients with secondary amyloidosis. Secondary amyloidosis has been expressed as one of the long-term structural and functional sequelae in patients with treated tuberculosis⁽¹⁰⁾.

Patients with treated pulmonary tuberculosis may suffer from permanent sequelae of the disease such as parenchymal disorders (including cavities, fibrosis with destruction and scar carcinoma);⁽⁷⁾ airway disorders (including subglottic stenosis, chronic obstructive airflow obstruction, bronchiectasis, tracheobronchial stenosis, anthracofibrosis, and broncholithiasis); vascular lesions; pleural lesions (ranging from pleural thickening to severe fibrothorax); general complications (including cor pulmonale, secondary amyloidosis, and chronic respiratory failure)⁽¹⁰⁾. It has been shown that chronic infection or inflammatory diseases may cause secondary amyloidosis even without obvious infection or inflammation⁽¹¹⁾. Tank et al.⁽¹²⁾ reported a case of secondary amyloidosis in a 12-year-old patient following disseminated tuberculosis. They stated that secondary amyloidosis may occur 2-7 years after the onset of a chronic inflammatory disease. Childhood kidney amyloidosis is thought to be a rare condition and is always secondary, unlike in adults⁽¹²⁾. Tuberculosis continues to be an important contributing factor in developing countries even today. Lowenstein and Gallo⁽¹³⁾ reported remission in nephrotic syndrome with antibiotic treatment of purulent bronchiectasis in an amyloid case associated with chronic pulmonary tuberculosis and suppurative bronchiectasis. It seems more probable that the very high serum amyloid protein levels seen in patients with severe pulmonary destruction could lead to amyloidosis. The major acute phase response in these patients is probably caused by a combination of extensive tuberculosis and secondary bacterial infection⁽¹⁴⁾. Permanent inflammation supported by chronic diseases leads to an ever-increasing release of pro-inflammatory cytokines that cause an increase in serum AA (SAA) synthesis⁽¹⁵⁾. Before developing reactive systemic amyloidosis, SAA levels are thought to be maintained at high levels for a long time along with the chronic inflammatory process in susceptible individuals, so that the SAA protein needs to be enzymatically cleaved to form secondary amyloidosis fibrils. The major acute phase response is probably thought to be caused by a combination of extensive *M. tuberculosis* and secondary bacterial infection⁽¹⁴⁾. In case of extensive pulmonary destruction and serum AA level is high after sputum becomes negative for *M. tuberculosis*, broad spectrum antibiotics and active physiotherapy are thought to reduce these levels.

Proteinuria is caused by defects in the slit membrane resulting from the accumulation of continuous amyloid and the production of vascular endothelial growth factor caused

by excessive IL-6 expression, although it affects glomerular permeability⁽¹⁵⁾. It has been reported that anti-tuberculosis treatment may not cause any regression in some cases of secondary renal amyloidosis associated with tuberculosis, including latent tuberculosis infection, and this complication may also develop after adequate treatment⁽¹⁶⁻¹⁹⁾. Magro-Checa et al.⁽¹⁵⁾ suggested that in patients with AA amyloidosis who did not respond to conventional anti-tuberculostatics after the correct treatment of tuberculosis, anti-IL6 therapy may be a second-line treatment, and prospective, controlled studies are needed in this regard. When the case records of 40 patients known to have renal amyloid disease in Glasgow Royal Infirmary between 1963 and 73 were analyzed, it was reported that tuberculosis⁽¹⁴⁾ pulmonary, three bones, one renal and one abdominal) constituted 54% of patients with secondary amyloidosis⁽¹⁶⁾. The incidence of renal amyloidosis was investigated in patients with various stages of pulmonary tuberculosis by Nik-Akhtar et al.⁽¹⁷⁾, and it was concluded that 9-11 percent of patients with pulmonary tuberculosis will develop proteinuria due to kidney amyloidosis after a certain period of time. In their study to investigate the rate of tuberculosis causing renal amyloidosis, 81 (35.6%) of 237 patients with renal amyloidosis have been previously reported to have a history of tuberculosis⁽¹⁹⁾. Patients with tuberculosis have been found to have high levels of SAA compared to healthy controls⁽²⁰⁾. SAA was found to be significantly increased in patients with tuberculosis exhibiting cavitory lung lesions compared to those with non-cavitory lung lesions, and similarly, SAA levels were significantly increased in patients with double lesions rather than single lung lesions⁽²⁰⁾.

Conclusion

Secondary amyloidosis should be among our differential diagnoses in patients with nephrotic syndrome and previous tuberculosis history. It is of paramount importance to suspect renal amyloidosis in patients with a known history of tuberculosis presenting with one or more of the features such as bilateral lower extremity edema, hypoalbuminemia, significant proteinuria, and renal insufficiency. Treatment of secondary amyloidosis is directed at controlling the underlying inflammatory process.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: Z.Ö., G.V.Ş., H.A., Z.A., F.G., Concept: Z.Ö., G.V.Ş., H.A., Desing: Z.Ö., G.V.Ş., Data Collection or Processing: Z.Ö., Z.A., F.G., Analysis or Interpretation: Z.Ö., G.V.Ş., H.A., Z.A., Literature Search: G.V.Ş., F.G., Writing: Z.Ö., G.V.Ş.

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