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# Primary pulmonary amyloidosis associated with multiple myeloma

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## ÖZET

### *Primer pulmoner amiloidozis ile multipl miyelom ilişkisi*

*Amiloidoz çözümlülüğü olmayan protein yapısında bir maddenin bir veya birden çok organın ekstraselüler matriksinde de-polanması ile karakterize bir sendromdur. Amiloidin solunum yollarını tutması nadir olup, farklı klinik tablolara neden olabilmektedir. Primer idiyopatik amiloidozis düşük insidansı ve değişken klinik bulguları nedeni ile tanı güçlüğü yaratan bir hastalıktır. Bu olgu sunumunda difüz interstisyel infiltrasyon bulguları ile ortaya çıkan ve transbronşiyal biyopsi ile AL tipi amiloidozis tanısı alan bir multipl miyelom olgusunu bildiriyoruz.*

**Anahtar Kelimeler:** Pulmoner amiloidozis, multipl miyelom.

## SUMMARY

### *Primary pulmonary amyloidosis associated with multiple myeloma*

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*Amyloidosis is a syndrome characterized by the deposition of an insoluble proteinaceous material in the extracellular matrix of one or several organs. Respiratory tract involvement with amyloid is rare and deposition of lower respiratory tract has been recognized in a variety of situations with different presentations. Primary idiopathic amyloidosis may be a diagnostic problem because of its low incidence and its variable manifestations. We report herein a case with multiple myeloma presenting diffuse interstitial infiltration, in which pulmonary AL type amyloidosis was diagnosed through transbronchial lung biopsy.*

**Key Words:** Pulmonary amyloidosis, multiple myeloma.

Amyloidosis is a syndrome characterized by the deposition of an insoluble proteinaceous material, in the extracellular matrix of one or several organs. Amyloid is a pathologic proteinaceous substance, deposited between cells in various tissues and organs of the body in a wide variety of clinical settings (1-3). Amyloid deposition may occur in association with inflammatory, hereditary, or neoplastic conditions; it may develop as part of a disorder of immunoglobulins; or it may involve a single organ. Amyloid protein takes up Congo red stain and exhibits apple-green birefringence under polarized microscopy. There are multiple clinically and biochemically distinct forms of amyloid sharing a unique morphology. Among the 14 biochemically distinct forms of amyloid proteins that have been identified, AL (amyloid light chain), AA (amyloid associated) and A $\beta$  are the three most common ones (3).

Amyloidosis may be systemic (generalized), involving several organ systems, or it may be localized, when deposits are limited to a single organ. Systemic pattern is subclassified into primary amyloidosis and secondary amyloidosis (3,4). The most common form of systemic amyloidosis is AL amyloidosis, resulting from fibril formation by monoclonal antibody light chains and it is generally associated with primary idiopathic amyloidosis and rarely multiple myeloma. Less than 20% of cases with AL amyloidosis have myeloma. Nevertheless, AA amyloidosis occurs mostly a complication of chronic inflammatory disease and so called secondary, reactive or acquired amyloidosis and effective treatment of underlying conditions reduces the incidence of disease.

Respiratory tract involvement in amyloidosis is rare. Amyloid deposition of lower respiratory tract has been recognized in a variety of situations

with different presentations. Five types of lower respiratory tract involvement are recognized; isolated nodular deposits of the tracheobronchial tree, diffuse tracheobronchial infiltration, isolated nodular pulmonary amyloidosis, diffuse pulmonary parenchymal amyloidosis and mediastinal and hilar adenopathy (1-6).

We, herein, report a case with multiple myeloma and pulmonary amyloidosis (AL type) presenting with diffuse interstitial infiltration. By presenting this case, we aim to underline the fact that, although it is rarely seen, pulmonary amyloidosis should be kept in mind in differential diagnosis of diffuse interstitial infiltration, especially in patients with rapidly progressing dyspnea.

#### CASE REPORT

A 55 year-old male was admitted to our hospital in May 2002 with one month history of severely progressive dyspnea, cough, and hemoptysis. He had habit of smoking 60 pack-years. He had no other medical or surgical history. In physical examination, the patient was dyspneic, had cyanosis. There was no oedema, icter and clubbing. His body temperature was 36.5°C, blood pressure 100/60 mmHg, pulse rate 80 per minute and respiratory rate 24 per minute. On auscultation, there were end inspiratory crackles at the right and left lung bases.

Laboratory tests revealed that his total serum protein was 6.1 mg/dL. Immunoglobulin G was elevated to 604 mg/dL. Immunoelectrophoresis demonstrated a monoclonal increase of lambda type IgG. Other laboratory data were as follows: haemoglobin 15.5 g/dL, white blood cells 12.800/mm<sup>3</sup>, platelet count 270.000/mm<sup>3</sup>, erythrocyte sedimentation rate 16 mm/hour, albumin 4.2 g/dL, lactate dehydrogenase 400

IU/L, alkaline phosphatase 91 IU/L, calcium 9.2 mg/dL, uric acid 7.5 mg/dL. Bence-Jones proteins were not detected in the urine.

Chest X-ray showed bilateral diffuse pulmonary interstitial infiltration (Figure 1). A spiral computed tomography (CT) scan of the chest revealed bilateral diffuse pulmonary interstitial infiltration (Figure 2). Pulmonary function tests demonstrated mild restrictive disease with a reduced DLCO (38% predicted). All lobar and segmental bronchies were open on fiberoptic bronchoscopy. In bronchoalveolar lavage,  $10 \times 10^6$  cells was counted, and in differential cytology; 96% of cells was macrophages, 3% of cells was lymphocytes and 1% of cells was polymorphonuclear leucocytes and CD4/CD8 ratio was 0.56 and non-diagnostic. The transbronchial lung biopsy specimens revealed marked inflammatory mononuclear cell infiltration

and nodular amyloid deposits in the bronchiolar walls (Figure 3). A rectal tissue biopsy was positive for amyloid deposits (Figure 4). Iliac crest biopsy showed monoclonal lambda positive plasma cell infiltration (Figure 5).

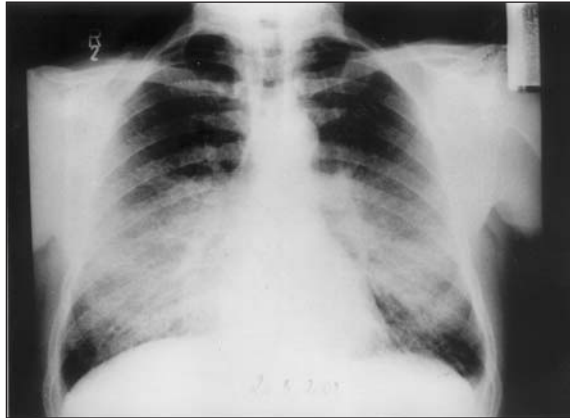


Figure 1. Chest X-ray, showing bilateral diffuse pulmonary interstitial infiltration.



Figure 2. Spiral CT scan of thorax, showing bilateral diffuse pulmonary interstitial infiltration.

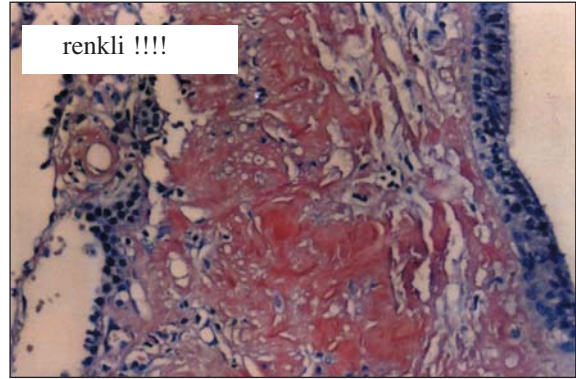


Figure 3. Transbronchial lung biopsy, showing a marked inflammatory mononuclear cell infiltration and nodular amyloid deposits in the bronchiolar walls.

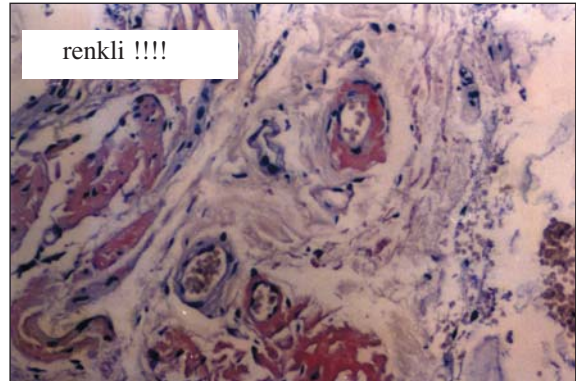


Figure 4. Rectal tissue biopsy, showing positive for amyloid deposits.

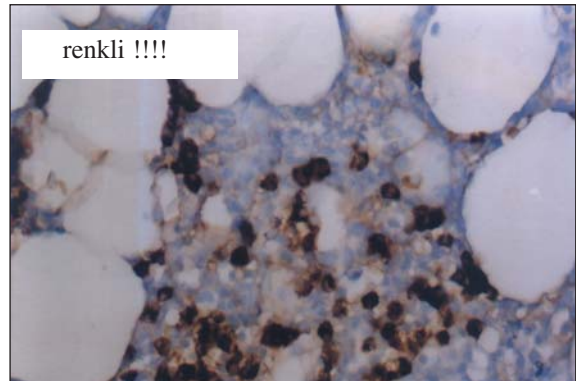


Figure 5. Iliac crest biopsy, showing monoclonal lambda positive plasma cell infiltration.

## DISCUSSION

Although it has long been known that primary systemic amyloidosis has a propensity to involve the lung, cases have been infrequently reported in the literature (7,8). Primary idiopathic amyloidosis may be a diagnostic problem because of its low incidence and its variable manifestations. Less than 100 cases of tracheobronchial amyloidosis have been described (9). However; Celli et al. reported that 11 of 12 patients, in whom primary systemic amyloidosis had been diagnosed before death, had prominent intra-alveolar amyloid deposits at the time of autopsy (10). Smith et al. found that 23 of 26 patients with primary systemic amyloidosis had pulmonary involvement (11). In autopsy series it has been shown that pulmonary involvement with primary systemic amyloidosis was usually present (8,10,11).

Primary pulmonary amyloidosis is generally seen in 5<sup>th</sup> decade. Cordier et al. reported, 21 patients with primary systemic amyloidosis had a mean age of 59.8 years, whereas Capizzi et al. reported that the mean age of their 17 patients was 56.6 years (12,13).

The clinical manifestation of primary systemic amyloidosis are protean, but certain symptom complexes suggest its presence; such as idiopathic sensorimotor, peripheral neuropathy, autonomic neuropathy, restrictive cardiomyopathy, nontrombocytopenic purpura, rheumatoid like arthritis, macroglossia, haemorrhagic diathesis, idiopathic nephrotic syndrome, idiopathic carpal tunnel syndrome. The varied pattern of involvement of the lower respiratory tract by amyloidosis gives rise to several different clinical and radiologic presentation (1). Patients presenting with primary pulmonary amyloidosis have symptoms similar to those caused by various airway disorders. The symptoms depend on the magnitude of the deposits. The most common symptoms at presentation were dyspnea, cough, hemoptysis and hoarseness (3,13). Amyloidosis may involve the lung in five patterns, and these patterns may occur alone or in

combination with each other (6). Diffuse pulmonary interstitial infiltration with amyloid had usually been reported in association with systemic amyloidosis (8,12). Our patient was a 55 year-old man presenting with dyspnea, cough and hemoptysis, and with bilateral linear interstitial shadowing on chest X-ray film.

Pulmonary amyloidosis sometimes include hilar or mediastinal adenopathy or mediastinal masses secondary to amyloidosis. Hilar adenopathy may be unilateral or bilateral, and it may be calcified (14,15). Our case had no hilar or mediastinal adenopathy. Cardiac amyloidosis is associated with increased left ventricular wall thickness, normal or decreased left ventricular cavity size, and congestive heart failure with normal or mildly reduced left ventricular ejection fraction. Chest X-ray films usually show nonspecific cardiomegaly, often accompanied by pulmonary congestion or pulmonary deposition of amyloid (16,17). Electrocardiography and echocardiography disclosed no further abnormalities in our case.

The diagnosis of amyloidosis established by demonstration of the characteristic apple-green birefringence of Congo red stained tissue specimens under polarization microscopy (1). A biopsy should be taken from an organ suspected of being infiltrated with amyloid material. If this can not be done for any reason, rectal biopsy or abdominal fat aspiration is the preferred technique (1). Patients with amyloidosis generally have an increased risk for bleeding, but cases have been reported with the diagnosis of pulmonary amyloid nodules by fine-needle aspiration or CT-guided transbronchial biopsy without any bleeding complication (18-20). Bronchoscopic lung biopsy (transbronchial biopsy) were done without major complications in our patient, and was diagnostic since transbronchial lung biopsy specimens revealed marked inflammatory mononuclear cell infiltration and nodular amyloid deposits in the bronchiolar walls. Also rectal tissue biopsy confirmed the diagnosis.

A substantial number of patients with pulmonary amyloidosis associated with systemic amyloidosis also have multiple myeloma, Waldenström's macroglobulinemia or other plasma cells dyscrasia. Fewer than 20% of patients with AL have myeloma, and about 15 to 20% of patients with myeloma have amyloidosis (4). Five of the 35 patients (14%) in Mayo Clinic series who had systemic amyloidosis had associated multiple myeloma, and in John Hopkins series, 8 of 31 (25.8%) patients with systemic amyloidosis had multiple myeloma (8,11). Also in our case, pathologic examination of bone marrow biopsy revealed multiple myeloma.

The prognosis for patients with generalize amyloidosis is poor. Renal failure, cardiac disease and respiratory failure are the most frequent causes of death. The median survival time after the diagnosis of amyloidosis was 2.8 years. In multiple myeloma associated amyloidosis, survival may be even shorter, with a recent estimate of four months from diagnosis. Pulmonary hypertension was found at a median of 73 days before death (4,21).

If a patients with AL amyloidosis is treated with autologous transplantation, frequently achieves durable complete remissions of the plasma cell disease and marked improvement in amyloid related organ dysfunction (22,23). AL patients who are elderly or ineligible for autologous transplantation may be treated with oral melphalan and prednisone. But response rate of this treatment is only about 20-25% after one year (23-25).

Primary pulmonary amyloidosis may be a diagnostic problem, because of its low incidence and its variable manifestations. But it should be kept in mind in differential diagnosis of a patient with severely progressive dsypnea and diffuse bilateral pulmonary infiltration, especially if this clinical presentation is occurring in a myeloma patient.

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