A 70-Year-Old Man With Large Cervical and Mediastinal Lymphadenopathies

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We present a case of a 70-year-old man with enlarged mediastinal and cervical lymph nodes that provided interesting radiologic and pathologic observations. The 70-year-old black man was found to have enlarged mediastinal lymph nodes. He had symptoms of atypical chest pain and generalized weakness for 2 weeks prior to the diagnosis. He denied shortness of breath, fever, chills, or night sweats. He was treated for hypertension and onychomycosis. Basic laboratory findings were within normal limits. Pulmonary function tests at the time of presentation showed FEV₁, FVC, and FEV₁/FVC ratio of 123% predicted, 133% predicted, and 0.7, respectively. Meanwhile, total lung capacity and carbon monoxide diffusing capacity were 103% and 107% predicted, respectively. Two weeks before he presented to our institution, the patient underwent bronchoscopy with transbronchial biopsies of the right lower lobe and endobronchial ultrasound-guided transbronchial needle aspiration of the right hilar lymph nodes.

CHEST 2015; 148(1):e8-e13

The patient's clinical examination was unremarkable except for a palpable right cervical lymph node of 3 cm in diameter with rubbery consistency. His lung examination was within normal limits.

Chest radiography showed a soft tissue prominence in the right suprahilar and subcarinal regions. CT scan of the chest revealed multiple enlarged homogeneous lymph nodes with fine stippled calcifications in the paratracheal, subcarinal, and right hilar regions, the largest being 3.5 cm in diameter (Fig 1). Tracheal dimensions and the appearance of the wall were normal (Fig 1F).

Interferon- γ release assay was positive; meanwhile, HIV enzyme-linked immunosorbent assay, histoplasma antigen, coccidioides antibody, syphilis IgG, and

cryptococcal antigen were negative. Our initial differential diagnosis included sarcoidosis; TB or nontuberculous mycobacterial infection; lung, head, neck, or germinal cell cancer; lymphoma; histoplasmosis; and coccidioidomycosis.

Tissue slides from both bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), performed at an outside institution, were reviewed carefully. A biopsy specimen consisted of five fragments of alveolated lung parenchyma, which were unremarkable, and three fragments of bronchial wall, which showed patchy, mild, nonspecific chronic inflammation. A lymph node specimen did not show malignant cells. Gram and acid-fast bacillus stains and bacterial and mycobacterial cultures of the BAL specimen were negative.

Manuscript received December 12, 2014; revision accepted March 17, 2015.

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FUNDING/SUPPORT: Dr Tonelli is supported by CTSA KL2 [Grant RR024990] from the National Center for Research Resources (NCRR),

a component of the National Institutes of Health (NIH), and by the NIH Roadmap for Medical Research.

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DOI: 10.1378/chest.14-3124

Figure 1 – A, Chest radiograph showing normal lung parenchyma and opacity at the level of the right paratracheal and hilar regions (arrows). B-E, Contrast CT scan of the chest with arrows pointing at the right cervical lymph node that underwent excisional biopsy (B), right paratracheal adenopathy (C, D), and hilar adenopathy (E). F, Coronal section at the level of the trachea in a noncontrast CT scan of the chest, done a few days before the contrast study. *Tracheal lumen.

Figure 2 – Pathology examination of the right cervical lymph node (magnification $\times 100$). A, Amyloid with Congo-red positivity. B, Apple-green birefringence with Congo-red staining.

During his first clinic visit, we performed a percutaneous biopsy of a right supraclavicular lymph node that showed inflammation and was negative for malignant cells. Flow cytometric analysis showed no immunophenotypic evidence of a lymphoproliferative disorder. Therefore, surgical lymph node excisional biopsy of the right supraclavicular lymph node was carried out. Interestingly, this biopsy specimen showed amorphous eosinophilic material that was Congo-red positive with apple-green birefringence under polarized light (Fig 2). Laser microdissection and tandem mass spectrometry of the tissue revealed λ -immunoglobulin light chains.

Further workup included a bone marrow biopsy, which showed unremarkable trilineage hematopoiesis. There was no demonstrable population of clonal plasma cells. CD138-positive plasma cells were increased slightly, but remained below 5% and had polytypic κ and λ expression. Cytogenetic karyotyping showed normal male karyotype.

What is the diagnosis?

Diagnosis: Primary amyloidosis localized to pulmonary lymph nodes without systemic involvement

Serum and urine protein electrophoresis, free light-chain assay, cardiac biomarkers, echocardiogram, skeletal survey, and bone marrow biopsy showed no evidence of systemic amyloidosis.

Discussion

Amyloidosis is the term used to denote a heterogeneous group of disorders characterized by deposition of fibrillar proteins in the extracellular matrix of one or more organs. There are several forms of amyloidosis. The two major types are primary (AL) and secondary (AA) amyloidosis. AL amyloidosis, the most common form of systemic amyloidosis, is an acquired plasma cell dyscrasia characterized by deposition of monoclonal immunoglobulin light chain fragments in various organs of the body.¹ AL amyloidosis is the type that most commonly affects the lungs.²⁻⁴ AA amyloidosis results from chronic inflammatory conditions that increase the acute-phase reactant serum amyloid A that then deposits as amyloid fibrils.⁵ This form most commonly affects the kidneys.⁵ Another particular and less common type of amyloidosis is caused by transthyretin (prealbumin) deposition. This condition can be (1) age related,⁶ with deposition of this thyroxine and retinol carrier protein particularly in the heart, or (2) familial, with accumulation of the mutant protein in the peripheral nervous system and heart.⁷ Because the mutant protein is produced in the liver, liver transplant can prevent progression of the disease in the familial group.^{7,8}

Pulmonary amyloidosis can present as part of a widespread process or be localized to the respiratory tract.⁹ It is classified based on the site where amyloid deposits (Table 1): (1) trachea-bronchial, the most common; (2) diffuse interstitial, diffuse parenchymal, or alveolar-septal disease, characterized by amyloid deposition in the pulmonary interstitium; (3) nodular disease, in which amyloid forms nodules (amyloidomas); (4) intra- and extrathoracic adenopathy; (5) pleural disease; (6) laryngeal disease; and, rarely, (7) diaphragmatic disease.^{2,9} Localized lymph node amyloidosis is rare^{4,10-12} because the lung parenchyma is usually affected.¹³

Clinical Discussion

The signs and symptoms of pulmonary amyloidosis are nonspecific. A common presentation includes

shortness of breath, cough, expectoration, hemoptysis, and chest tightness. Dyspnea and cough are the most frequent manifestations of tracheobronchial amyloidosis. In this condition, plaques in the tracheobronchial tree may cause tracheal stenosis or distal airway obstruction, resulting in recurrent pneumonia or postobstructive atelectasis.¹⁴ Nodular amyloidosis is usually asymptomatic but may be associated with recurrent pneumonia, atelectasis, and respiratory failure.^{9,14}

Respiratory failure is more likely to occur in the diffuse alveolar-septal form, which portends a worse prognosis. Rare manifestations include recurrent pleural effusions,¹⁵ pulmonary hypertension,¹⁶ and pulmonary infarction with hemoptysis caused by amyloid deposition in the pulmonary blood vessels.¹⁷ Laryngeal amyloidosis is also uncommon and is characterized by hoarseness, stridor, and dysphagia.¹⁸ Pulmonary function testing varies according to presentation, from normal to obstructive (tracheobronchial amyloidosis) or restrictive patterns (diffuse alveoloseptal disease or pleural effusions).⁹ Proximal airways disease can present as fixed airway obstruction on flow-volume loops.

Radiologic Discussion

The imaging characteristics of amyloidosis are nonspecific. Chest radiographs are normal in most cases. CT scan findings include nodular and reticular opacities, diffuse and irregular airway wall thickening with calcifications and luminal narrowing, and pleural plaques.¹⁹ Tracheobronchial amyloidosis may cause tracheal stenosis or postobstructive atelectasis.²⁰ Nodular amyloidosis is associated with peripheral subpleural nodular densities of variable size (0.5 mm to 5 cm) with sharp, lobulated margins and calcifications.^{21,22} These nodules are generally localized to the lower lobes. The alveolar-septal form of amyloidosis is characterized by interlobular septal thickening, diffuse interstitial or alveolar infiltrates, and, rarely, diffuse parenchymal nodules.^{23,24} In lymph node amyloidosis, the mediastinal and hilar lymph nodes are enlarged and may show speckled calcification.^{24,25} Scintigraphy with radioisotope-labeled amyloid P component evaluates the extent and distribution of amyloid deposits in the body²⁶ and has a sensitivity and specificity for diagnosing AL or AA amyloidosis of 90% and 93%, respectively.²⁷ ¹⁸F-fludeoxyglucose PET scanning has been found to be positive in patients with intrathoracic amyloid.²⁸ In patients with biopsy-proven

TABLE 1] Salient Features of Different Pulmonary Forms of Amyloidosis

Types of Pulmonary Amyloidosis	Clinical Characteristics	Prognosis	Treatment
Tracheobronchial	Most common type	Good	Observation
	Diffuse wall thickening with luminal narrowing of the airways		Laser therapy (Nd:YAG)
	Circumferential calcification involving the membranous portion		Cryotherapy
	Dyspnea, cough, recurrent pneumonia, atelectasis, and tracheal stenosis		Low-dose external beam radiation
			Balloon dilatation
Alveolar: septal/diffuse parenchymal/diffuse interstitial			Stenting
	Uncommon	Poor	Systemic chemotherapy
	Diffuse interstitial and/or alveolar opacities		Hematopoietic stem cell transplant
	Highly symptomatic, commonly with respiratory failure		
Nodular	Uncommon	Good	Conservative management in asymptomatic patients
	Single or multiple pulmonary nodules (amyloidomas), usually localized to the lower lobes and subpleural areas		Surgical resection of nodules if concern for malignancy
	Frequently asymptomatic but may be associated with pneumonia, atelectasis, and/or respiratory failure		
Thoracic lymphadenopathy	Uncommon	Good (except in systemic forms)	Observation
	Cough, dyspnea, wheezing		Medical treatment
	Can narrow the airway lumen		Stenting
	Extrathoracic adenopathy is more common		Surgical (infrequently)
Pleural	Recurrent pleural effusions	Poor	Thoracentesis/chest tube placement
	Uni- or bilateral		Pleurodesis
	Exudative or transudative		
Laryngeal	Dyspnea, cough		
	Extremely rare	Good if localized; relapses may occur after excision	Surgical excision by laryngoscopy (important to exclude malignancy by biopsy)
	Hoarseness and dyspnea		
Diaphragmatic	May mimic laryngeal neoplasm		
	Very rare	Not available	Treatment of diaphragmatic dysfunction
	Respiratory failure can occur as a result of diaphragmatic paralysis		
	Patient may become ventilator dependent		

AL pulmonary amyloidosis, PET scan positivity varies from 30% to 70%^{29,30} with standardized uptake values ranging from 1.8 to 6.8.⁹ ^{99m}Tc-DPD

(3,3-diphosphono-1,2-propanodicarboxylic acid) scintigraphy specifically detects transthyretin-related cardiac amyloidosis.³¹

Pathologic Discussion

Amyloidosis is the pathologic accumulation of extracellular proteins in a β -pleated configuration. Biopsies of the airways, lung parenchyma, and/or mediastinal lymph nodes are required for the diagnosis of pulmonary amyloidosis. The yield of EBUS-TBNA and percutaneous or transbronchial fine-needle aspiration for the diagnosis of thoracic amyloidosis is unknown because the data are limited. There are few case reports of mediastinal amyloidosis diagnosed by EBUS-TBNA^{32,33} or amyloid pulmonary nodules diagnosed by fine-needle aspiration.^{4,34-36}

Amyloid appears as an amorphous eosinophilic waxy material on hematoxylin and eosin staining. It typically shows apple-green birefringence under polarized microscopy with Congo-red staining and intense yellow-green fluorescence on thioflavin T stain. Amyloidosis must be distinguished from amyloid-like deposits, which are made of amorphous eosinophilic material but show negative histochemical and immunohistochemical stains for amyloid. Amyloid-like deposits are frequently, but not always, associated with nonamyloid immunoglobulin light-chain deposition disease.³⁷ Amyloidomas consist of well-circumscribed dense amorphous eosinophilic amyloid protein, surrounded by an inflammatory cell infiltrate that consists of plasma cells and lymphocytes with an occasional granulomatous reaction.³⁸

The type of amyloidosis is determined by immunohistochemical staining of the biopsy specimen. κ or Λ chains on immunofluorescence microscopy are seen in AL amyloidosis. AA amyloidosis shows positive staining of the serum amyloid A component. Laser microdissection of the amyloid-containing tissue with subsequent tandem mass spectrometry is the most accurate method for identifying the subtype of amyloid deposition. Using laser microdissection, cells of interest are isolated from Congo-red-stained paraffin sections placed on glass microscopic slides. The amyloid type is identified with mass spectrometry-based proteomic analysis, a technique that has a very high sensitivity and specificity (both $\geq 98\%$).³⁹ Chromosomal abnormalities, such as monosomy of chromosome 18 (most common) and trisomy of chromosomes 7, 9, 11, 18, and X, are seen frequently in patients with AL amyloidosis.⁴⁰

Treatment varies widely from conservative to aggressive interventions. The nodular form of pulmonary amyloidosis is generally asymptomatic and can be managed conservatively by observation. In these patients, an indolent B-cell lymphoproliferative disorder must be excluded.⁴¹ The diffuse alveolar-septal form of

pulmonary amyloidosis has a poor prognosis and often requires systemic chemotherapy or hematopoietic stem cell transplant. If the patient is not a candidate for stem cell transplant, a combination of melphalan and high-dose dexamethasone is known to improve survival.⁴² Local bronchoscopic treatment with balloon dilation, stent placement, laser surgery, or radiation therapy is indicated for tracheobronchial amyloidosis. Localized lymph node amyloidosis is usually managed conservatively in asymptomatic patients; however, in symptomatic patients, surgical debulking, laser, or radiation therapy can be used.⁴³ Pleural amyloidosis with effusions is managed by repeated thoracentesis, chest tube placement, and pleurodesis.

Conclusions

The diagnosis of respiratory amyloidosis is challenging because of its nonspecific clinical and radiologic presentation; therefore, surgical biopsy is necessary. Because the patient had symptoms (chest pain/dysphagia), he received oral dexamethasone, with good symptomatic response. The patient's latent TB was treated simultaneously with isoniazid for 9 months.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: NIH only provided salary support for Adriano R. Tonelli.

Other contributions: CHEST worked with the authors to ensure that the Journal policies on patient consent to report information were met.

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