

# Pulmonary and Tracheobronchial Amyloidosis

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## ABSTRACT

Amyloidosis is a collection of diseases in which different proteins are deposited as insoluble  $\beta$ -pleated sheets, disrupting organ function. Each precursor protein induces a separate spectrum of organ involvement, and different disease manifestations within the lung. Although autopsy data often demonstrate amyloid deposits in various compartments of the lung, few of the pathologic findings are expressed clinically. We review the pulmonary pathology, radiology, clinical presentations, and treatment options for each of the major systemic and localized forms of amyloidosis. This review focuses on amyloid derived from immunoglobulin light-chain protein (AL disease), which most frequently involves the lung in both systemic and localized forms of the disease. Manifestations of AL-related lung disease range from nodules identified on incidental chest films to diffuse alveolar-septal deposition mimicking diffuse alveolar damage. We discuss respiratory failure due to diaphragm invasion, proximal tracheal disease, and diffuse alveolar-septal deposition. Guidelines for evaluation of patients with amyloid are presented.

**KEYWORDS:** Amyloidosis, tracheobronchial amyloidosis, lung diseases

**Objectives:** Upon completion of this article, the reader will understand the importance of amyloid fiber type on the spectrum of pulmonary manifestations and the natural course of disease in patients with systemic amyloidosis.

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Amyloidosis is caused by overexpression of specific proteins culminating in the extracellular deposition of insoluble  $\beta$ -pleated sheets of fibers. These deposits disrupt function of the target organ. Mistakenly identified as carbohydrate by Virchow in 1854,<sup>1</sup> amyloid deposits are composed of linear arrays of subunit proteins complexed with glucosaminoglycans and serum amyloid P (SAP). Amyloid deposits occur in systemic and organ-limited forms. In systemic amyloidosis, the composition of subunit proteins in the  $\beta$ -pleated sheets dictate the

pattern of organ involvement, the rapidity of disease advancement, and disease outcome. Consequently, identifying the type of amyloidosis strongly impacts the diagnostic differential of radiographic abnormalities.

## CLASSIFICATION

Classification of systemic amyloidosis is based on the different subunit proteins (Table 1), which define organ involvement and disease manifestations. The nomen-

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**Table 1 Classification of Major Systemic Amyloidoses**

Type	Protein Subunit	Clinical Syndrome
AL	Monoclonal immunoglobulin ( $\kappa$ or $\lambda$ light chains)	Systemic disease: Primary amyloidosis; multiple myeloma; Waldenstrom's lymphoma Local disease: Skin, urinary tract, lungs, larynx, eyes
AA	Serum amyloid A protein	Chronic inflammatory conditions (arthritides, infections, familial Mediterranean fever)
ATTR	Variant (mutant) transthyretin Wild-type transthyretin	Familial amyloidotic polyneuropathy and cardiomyopathy Senile cardiomyopathy
A $\beta_2$ M	$\beta_2$ -microglobulin	Dialysis or renal failure-related disease affecting joints and spine

AA, secondary amyloidosis; AL, primary systemic amyloidosis; ATTR, hereditary amyloidosis; A $\beta_2$ M, dialysis-associated amyloidosis.

clature includes an "A" for amyloid and a letter indicating the protein involved. There are four major categories of systemic amyloidosis: (1) primary or immunoglobulin light-chain (AL) disease, (2) secondary or amyloid protein A (AA) disease, (3) hereditary or mutant transthyretin (ATTR) disease, and (4) dialysis-associated or  $\beta_2$ -microglobulin ( $\beta_2$ M) disease. Other less prevalent forms of amyloid disease exist, locally affecting the pancreas (islet amyloid polypeptide, AIAPP) and brain ( $\beta$ -amyloid precursor protein, A $\beta$ ), or genetically transmitted systemic disease (apolipoprotein AI, gelsolin, fibrinogen, lysozyme precursor proteins). The discussion here focuses on systemic amyloidoses with associated pulmonary manifestations, including secondary (AA), hereditary (ATTR), and most importantly, primary (AL) disease.

## Secondary (AA) Amyloidosis

### DEMOGRAPHICS

AA or reactive amyloidosis results from excessive production and organ-deposition of an acute-phase reactant, serum amyloid A protein (SAA). In the United States, 1% of patients with chronic inflammatory conditions (rheumatic disease, infections, familial Mediterranean fever, malignancies) will develop AA amyloidosis. In Europe, the incidence rises to 5 to 10% of patients with chronic inflammatory conditions. American patients are infrequently referred to amyloid centers. Over the past 10 years, the Amyloid Treatment and Research Program at Boston University School of Medicine has evaluated only 21 patients with AA disease.

Although AA amyloid affects several organ systems, survival is determined by renal involvement.<sup>2</sup> In a series of 64 patients with AA disease, patients with renal failure had a mean survival of 11 months, whereas those with normal renal function survived 57 months.<sup>2</sup> Cardiopulmonary disease did not impact outcomes. Some patients live more than 10 years with AA disease.

### PATHOGENESIS

During inflammatory states, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  upregulate hepatic synthesis of serum amyloid A protein. Following cleavage, the amino terminus of SAA complexes with glucosaminoglycans (heparan sulfate) and serum amyloid P component, forming  $\beta$ -pleated sheets. Deposition of the processed SAA fibril occurs in target organs such as the kidneys (91%), gastrointestinal tract (22%), liver (5%), nerves (3%), and lymph nodes (2%).<sup>2</sup>

### LUNG INVOLVEMENT IN AA DISEASE

Autopsy data from seven patients with AA disease who had no respiratory complaints antemortem revealed mild amyloid deposition in the airways and pulmonary vessels of three cases, but no alveolar-septal disease.<sup>3</sup> The absence of interstitial disease in AA amyloidosis was corroborated by an autopsy series at Johns Hopkins Hospital, where only 1 of 113 cases with AA disease demonstrated any parenchymal pulmonary amyloid.<sup>4</sup> As predicted by pathological findings, clinical series rarely identify patients with pulmonary manifestations of AA amyloid. In a series of 64 AA patients at the Mayo Clinic, none exhibited clinical signs of heart or lung involvement.<sup>2</sup> In general, radiographic abnormalities in patients with AA disease are attributable to the underlying condition, not pulmonary amyloid. Familial Mediterranean fever (FMF) is an occasional exception to the rule, rarely developing diffuse opacities, hilar adenopathy, and pulmonary hypertension.<sup>5-7</sup>

## Hereditary (ATTR) Amyloidosis

### DEMOGRAPHICS

Two forms of amyloid disease arise from the precursor protein, transthyretin (TTR): (1) hereditary or familial amyloidosis, derived from mutant TTR, and (2) senile systemic amyloidosis, caused by insoluble complexes of normal TTR.<sup>8</sup> Hereditary amyloidoses are rare autosomal dominant diseases, with a prevalence of less than 1

in 100,000 people in the United States.<sup>9</sup> These estimates may underrepresent the extent of disease, however. Recent identification of a variant TTR (isoleucine 122) associated with late-onset cardiac amyloidosis has been found in 4% of the African American population in the United States.<sup>10</sup> Despite developing new therapies for ATTR, the Amyloid Program at Boston University evaluated only 110 ATTR patients over the past 15 years, emphasizing the rarity of the disease. Untreated, survivorship is 7 to 15 years after diagnosis.<sup>9</sup>

### PATHOGENESIS

Deposition of mutant TTR (heredofamilial disease) or wild-type TTR (senile systemic amyloidosis) is the basis of this amyloid disease. Plasma TTR, a 55 kDa tetramer, is a transport protein principally synthesized by the liver. Single amino acid substitutions of TTR alter monomer folding and promote  $\beta$ -pleated sheet formation. The spectrum of organ involvement and clinical presentation is determined by characteristics of each mutant TTR protein; more than 60 variants have been described. Peripheral neuropathy and cardiomyopathy are the most frequent findings. Lung involvement is rare. Autopsies at Johns Hopkins Hospital from 1889 to 1977 identified three patients with familial (ATTR) amyloidosis, two of whom had interstitial lung amyloid deposits.<sup>4</sup> Review of a 14-year experience at the Mayo Clinic included one patient with ATTR; diffuse interstitial infiltrates were present on chest x-ray.<sup>5</sup> Of the 110 ATTR patients evaluated at Boston University School of Medicine, five (4.5%) had abnormal chest x-rays—three (2.7%) with bilateral pleural effusions, and two (2%) with basilar opacities.

The incidence of senile systemic amyloidosis increases with age. Data from 340 autopsies revealed pulmonary vascular or alveolar-septal amyloid deposits in 2% of patients less than 80 years old, 10% among patients aged 80 to 84 years, and 20% in patients older than 85 years.<sup>11</sup> In autopsies of octogenarians with senile cardiac amyloidosis, alveolar-septal and pulmonary vascular deposition rivaled heart involvement, occurring twice as often as kidney and colonic sites.<sup>12</sup> Despite histologic evidence of amyloid, there are few manifestations of lung disease. Among six patients with senile systemic amyloidosis reported in a clinical series from the Mayo Clinic, all were identified at autopsy and had normal or “nonspecific” antemortem chest radiographs.<sup>5</sup>

## Immunoglobulin Light-Chain (AL) Amyloidosis

### DEMOGRAPHICS

Estimates of the age-adjusted incidence of systemic AL amyloidosis are 5.1 to 12.8 million person-years, or approximately 3200 new cases annually in the United States.<sup>13</sup> According to the National Center for Health

Statistics, the incidence is 4.5 per 100,000.<sup>14</sup> The Amyloid Treatment and Research Program at Boston University School of Medicine evaluated over 492 new patients with AL disease between 1996 and 2001. Importantly, all prevalence estimates are likely confounded by misdiagnoses and underreporting.

### PATHOGENESIS

Organ involvement in AL disease, be it systemic or localized, arises from the deposition of monoclonal  $\kappa$  or  $\lambda$  immunoglobulin (Ig) light chains. In systemic disease, clonally expanded plasma cells residing in the bone marrow secrete excessive quantities of monoclonal Ig, which circulates in blood to target organs. Typically AL deposits are composed of the variable region of  $\lambda$ VI or  $\kappa$ I light-chains. Less commonly, part or all of the Ig constant region is represented. Genotyping of these two light-chain subgroups suggests that genetic rearrangements may underlie production of amyloidogenic proteins in AL disease. Amyloid deposition is widespread in AL disease, although only specific organs may be clinically involved.<sup>15</sup>

Amino acid analyses of localized amyloid deposits reveal AL protein with  $\kappa$ I and  $\lambda$ III light-chain subgroups predominating.<sup>16-18</sup> In contrast to systemic disease, monoclonal proteins constituting localized amyloid deposits arise from a small number of plasma cells surrounding the lesion. Skin, urethra and urinary bladder, eye, larynx and supraglottic area, tracheobronchial tree, and lung parenchyma are sites most commonly involved by localized amyloid. Monoclonal light-chain does not circulate or deposit outside the target organ.

### SYSTEMIC AL LUNG DISEASE

At autopsy, AL amyloid is found in the walls of most blood vessels, including the lung. The extent of extravascular amyloid deposition varies widely among organs, determined in part by the precursor light-chain fragment. Five forms of extravascular lung involvement are seen in systemic AL disease: (1) diffuse interstitial or alveolar-septal disease, in which amyloid deposits between vascular endothelium and alveolar epithelium in the lung interstitium; (2) nodular disease; (3) intra- and extrathoracic adenopathy; (4) pleural disease; and, rarely, (5) diaphragm deposition.

**Alveolar-Septal Disease** In the lung, the degree of amyloid infiltration and the level of functional compromise do not correlate directly. Celli et al<sup>3</sup> reviewed the clinical course and autopsy data in 12 AL patients. Excluding one patient without biopsy evidence of amyloidosis, all AL patients had amyloid demonstrated by congo red birefringence in the walls of alveoli, vessels, and airways. Despite extensive histologic evidence of AL disease, 64% had no signs nor symptoms of lung

disease. In only 1/12 cases did pulmonary involvement appear to dictate clinical outcome. Similarly, Cordier et al<sup>19</sup> reported that AL lung disease was the cause of death in only 10% of patients.

To explain the discrepancy between amyloid burden in the lung and the course of disease, pathologists at the Johns Hopkins Hospital examined the association of cardiac and pulmonary amyloid infiltration in autopsy data from 26 patients with systemic AL disease.<sup>4</sup> Ninety-two percent of patients had moderate to severe amyloid deposits in the interstitium of the myocardium, whereas 73% had similar degrees of alveolar-septal lung disease. Pairwise statistical analysis was highly significant ( $p < 0.01$ ). No patient had pulmonary amyloid deposition in the absence of cardiac disease. In most cases, amyloid deposition in the heart exceeded levels found in the lung. The authors concluded that histologic and clinical pulmonary disease in AL patients were principally markers of severe cardiac infiltration, not the determinant of survivorship. Kaplan-Meier analysis of organ-specific disease burden further demonstrate the vital role of cardiac infiltration in AL disease. In AL patients with systolic heart failure (LVEF [left ventricular ejection fraction]  $< 40\%$ ), median survival is 12 weeks, whereas patients with diffuse alveolar-septal infiltrates and normal cardiac function live approximately 16 months.<sup>5,20</sup>

Contemporary clinical experience in amyloid centers supports these findings. Among 474 AL patients presenting to the Mayo Clinic between 1981 and 1992, kidney disease (28%), congestive heart failure (17%), and peripheral neuropathy (17%) were the most prominent clinical manifestations of AL disease; pulmonary presentations were not reported.<sup>20</sup> Over the past 5 years, we evaluated 492 new cases of AL disease in the amyloid program at Boston University, 138 (28%) of whom manifested signs of pulmonary involvement. Despite higher numbers, only 9% of these patients had pulmonary disease in the absence of cardiac dysfunction.

Reported pulmonary complications of systemic AL disease include hemoptysis due to medial dissection of amyloid-infiltrated pulmonary arteries,<sup>21</sup> massive pulmonary embolism related to extensive thrombosis of the inferior vena cava,<sup>22</sup> chylous pleural effusions,<sup>23</sup> and air embolism following transbronchial biopsy.<sup>24</sup>

**Nodular Disease** The presence of nodular amyloid deposits in systemic AL disease is controversial. Review of published autopsy, open lung biopsy, and radiologic data from the Mayo Clinic, Boston University, and the Johns Hopkins Hospital failed to identify any nodular lung disease in 70 patients with systemic AL amyloidosis.<sup>3-5</sup> In contrast, Hui et al reported 3 cases of nodular lung disease in patients expressing monoclonal protein in serum or urine.<sup>25</sup> We, too, have recently diagnosed an amyloidoma by excisional biopsy in a patient with pri-

mary (AL) systemic disease. Although nodular lung disease occurs in systemic AL, it is sufficiently rare to warrant biopsy identification.

**Adenopathy** Generalized adenopathy occurs in approximately 8% of patients with systemic AL disease.<sup>26</sup> Mediastinal or hilar adenopathy, although less common than extrathoracic adenopathy, occurs in systemic AL—with or without accompanying pulmonary disease. Occasionally adenopathy will antedate expression of monoclonal protein by several years. Throughout the clinical course, cervical nodes in particular will periodically enlarge, become tender, and recede, mimicking the glandular fever of sarcoidosis. The histologic presence of giant cells surrounding involved nodes may suggest the diagnosis of sarcoidosis. Although longstanding sarcoidosis may induce secondary (AA) amyloidosis, no definite relationship with systemic AL has been established.<sup>27-29</sup>

**Pleural Disease** Several small series and numerous case reports document pleural effusions in patients with systemic AL disease.<sup>30-33</sup> Large, recurrent effusions occur in the setting of significant cardiac dysfunction and pleural amyloid.<sup>34</sup> The effusions present in equal numbers in the left and right hemithorax and are occasionally bilateral. Although congestive heart failure plays a significant role in the generation and maintenance of the effusion(s), exudative chemistries are reported as frequently as transudative profiles.<sup>32</sup> Lymphocyte-predominant white blood cell counts range from 50 to 400/cm<sup>3</sup>. Rarely, chylous effusions occur in patients with extensive amyloid burden. Patients with nephrotic syndrome and serum albumin levels  $< 2.5$  gm/dL do not frequently manifest pleural effusion in the absence of congestive heart failure. Thoracoscopic views reveal amyloid deposits studding the parietal pleural surface, supporting the diagnostic utility of closed needle pleural biopsies.<sup>32,35-37</sup>

**Diaphragm Deposition** A case report of acute respiratory insufficiency and absent diaphragm excursion on sniff testing describes extensive amyloid infiltration of the diaphragm leaflets at autopsy.<sup>38</sup> The amyloid protein was not characterized, and assays for monoclonal proteins were incomplete. Nonetheless, the presence of macroglossia identifies this as primary (AL) systemic amyloidosis. In a separate case, a patient with  $\kappa$  light-chain multiple myeloma had low maximal voluntary ventilation and maximal inspiratory pressures in association with abundant amyloid deposition on and within the diaphragm.<sup>39</sup> The phrenic nerves were spared of amyloid infiltration. Despite these reports, we have not recognized significant amyloid involvement of the diaphragm in over 50 autopsies at Boston University School of Medicine.

**Table 2 Radiographic Manifestations of Systemic Amyloidosis**

Type	Parenchymal Findings	Extrapulmonary	Treatment
AL	Reticular nodular opacities	Adenopathy	Chemotherapy
	Reticular opacities	Mediastinal	(A) cyclic oral melphalan + prednisone
	Diffuse alveolar opacities	Hilar	(B) high dose melphalan + stem cell rescue
		Cervical, inguinal, axillary	
		Pleural effusions	(1) diuresis (2) serial thoracenteses (3) pleurodesis
		Cardiomegaly	(1) avoid digitalis + calcium channel blockers
		Kerley B lines	(2) diuresis
		Cephalization	(3) assess for atrial thrombi (4) mechanical pacing
AA	Rare interstitial opacities	No CHF	(1) excise bronchiectasis, osteomyelitis, IBD (2) colchicine for FMF (3) aggressively treat underlying disease
		Adenopathy	
		Hilar	
		Mediastinal	
		Retroperitoneal	
ATTR	Rare interstitial opacities	Cardiomegaly	Liver transplantation
		Kerley B lines	
		Cephalization	
		Pleural effusions	
		Adenopathy	

AA, secondary amyloidosis; AL, immunoglobulin light-chain amyloidosis; ATTR, hereditary amyloidosis; CHF, congestive heart failure; IBD, inflammatory bowel disease; FMF, familial Mediterranean fever.

## RADIOLOGY

Two patterns of disease dominate chest x-ray findings in systemic AL disease: (1) diffuse or reticulonodular opacities, and (2) nodular opacities. Other findings include recurrent pleural effusions, intra- and extrathoracic adenopathy, pleural thickening, and, rarely, a pattern of lymphatic obstruction (Table 2).

**Systemic AL Disease** Although not frequently seen, diffuse reticulonodular opacities on chest x-ray signal alveolar-septal amyloid deposition, which is almost exclusively manifest in systemic AL disease (Fig. 1A). In 35 AL patients with biopsy-proven lung involvement, Utz et al<sup>5</sup> reported reticulonodular opacities in 23%, reticular pattern in 33%, isolated pleural effusion(s) in 29%, and pleural thickening in < 1%. Computed tomographic (CT) imaging of patients with diffuse disease revealed nodules (75%), honeycombing (38%), heterogeneous ground-glass alveolar filling (38%), and interlobular septal thickening (75%) (Fig. 1B).<sup>40</sup> Additionally, small (2–4 mm), variably calcified, well-defined nodules have been described in several reports.<sup>40,41</sup>

**Adenopathy** Patients with adenopathy generally exhibit global changes in lymph node size. CT studies detect

noncalcified node enlargement in the cervical, retroperitoneal, inguinal, hilar, axillary, and mediastinal regions.<sup>40</sup> Amyloid-infiltrated nodes frequently calcify in a popcorn pattern or, rarely, an eggshell conformation.<sup>42</sup> One CT report noted high attenuation adenopathy in the mediastinum and retroperitoneal space, postulated to be due to increased vascularity of the node.<sup>43</sup> Hilar nodes, the least involved site, typically enlarge bilaterally.<sup>44</sup>

**Pleural Disease** In a large series, pleural effusions without infiltrates occurred in 29% of systemic AL cases, predominantly in bilateral distribution. Only 11% of cases had diffuse interstitial opacities and pleural effusions, one half of which were unilateral.<sup>5</sup> Pleural thickening was detected in 3% of AL cases.

**Diaphragm Disease** No radiographic signs have been associated with amyloid infiltration of the diaphragm.

## LOCALIZED AL LUNG DISEASE

Three forms of pulmonary disease exist in localized AL amyloid: (1) nodular opacities, (2) diffuse opacities, and (3) tracheobronchial disease. A 1983 literature review identified 126 cases of localized amyloid lung disease,



**Figure 1** Radiologic and histologic features of alveolar-septal amyloid in systemic AL disease. (A) Chest film of a woman with AL amyloidosis expressing IgG  $\lambda$  monoclonal protein. (B) Chest computed tomographic image of same patient. (C) Lung biopsy obtained at autopsy of the patient (H&E 250 $\times$  magnification). Massive replacement of alveolar-septal structures with amorphous salmon pink matrix, exhibiting apple green birefringence under polarizing light (not shown).

44% having nodular disease, 3% with diffuse opacities, and 53% exhibiting tracheobronchial amyloid (Table 3).<sup>45</sup>

**Nodular Opacities** The presence of amyloid nodules on chest imaging or histologic sampling almost uniformly indicates localized disease. The incidence of nodular disease is undefined because many are diagnosed incidentally at open lung biopsy or at autopsy. Among 223 autopsies of patients with amyloidosis between 1889 and 1979, only three cases with isolated nodular lung disease were identified.<sup>4</sup> More recently, Utz et al<sup>5</sup> reported seven cases of nodular disease over a 13-year period, whereas Hui et al described 25 patients with lung nodules in the absence of plasma cell dyscrasia.<sup>25</sup> The lesions range in size from 0.6 to 9 cm (mean of 3 cm), present as multiple nodules of varying size in 58% of cases, and often appear peripherally in the lower lobes.<sup>25,46</sup> The amyloid deposit is typically surrounded by plasma cells, lymphocytes, and giant cells; small amounts of amyloid can be found in contiguous blood vessels.<sup>4,25</sup> Dystrophic calcification and

bone formation were seen in over one third of lesions.<sup>25</sup> Amyloid nodules grow slowly, if at all, and can cavitate.<sup>46-48</sup> Unless densely calcified, all nodules should expand at similar rates. Dyssynchronous growth of one lesion warrants investigation to rule out carcinoma. Typically, nodular disease does not impair lung function nor impact survivorship.<sup>25</sup>

**Diffuse Opacities** Diffuse parenchymal opacities is the rarest form of localized AL lung disease, with none seen over a 13-year period at the Mayo Clinic<sup>5</sup> or over nearly 90 years of autopsies at Johns Hopkins Hospital.<sup>4</sup> Hui et al reported five cases of lung-limited amyloidosis with diffuse radiographic opacities.<sup>25</sup> Although counterintuitive, diffuse opacities may be restricted to one lung. Over 55% of reported cases died of respiratory insufficiency.<sup>24,46</sup> In our experience, diffuse opacities limited to the lung may enter a stable phase with longer survivorship, or may even regress spontaneously.

**Table 3 Radiographic Manifestations of Localized Amyloidosis**

Type	Parenchymal Findings	Extrapulmonary	Treatment
Tracheobronchial	(53% of local AL)	Calcified tracheobronchial wall (including posterior membrane) Airway wall thickening Airway lumen narrowing Lobar atelectasis	(1) Nd:YAG + rigid bronchoscopic debridement (2) oral antibiotics + steroids (3) balloon dilatation + stenting
Parenchymal	(3% of local AL)		Supportive care
Diffuse opacities			
Unilateral opacities			
Nodular disease	(44% of local AL)		Biopsy nodules with unusual growth kinetics
Few lesions (< 10)			
Slow growing lesions			
Calcification (29%)			
Cavitation (11%)			

AL, immunoglobulin light-chain amyloidosis.

**Tracheobronchial Disease** Tracheobronchial amyloidosis (TBA) represents 0.5% of all symptomatic tracheobronchial lesions and 23% of benign symptomatic airway lesions referred for laser excision.<sup>49</sup> Less than 135 published cases exist. Analysis of the three largest series indicates that women are affected earlier (52 vs 59 years), slightly more often (10:9 ratio), and more extensively than men.<sup>49-51</sup> Cough, wheezing, dyspnea, and hemoptysis antedate histologic diagnosis by an average 17 months.<sup>50</sup> The precipitants of TBA are undefined; tobacco use is not a consistent predisposing factor.<sup>50</sup> Patients are often treated for recurrent pneumonia, tracheobronchitis, or asthma prior to diagnosis.

At bronchoscopy, two patterns of amyloid deposition are described: (1) nodular or unifocal disease, and (2) diffuse submucosal disease. The nodular form mimics endobronchial carcinomas, obstructing airways and inducing hemoptysis. The deposits, whether nodular or diffuse, are composed of immunoglobulin light chains produced and secreted by small numbers of plasma cells surrounding the involved airway.<sup>16,18</sup> Although autopsies of patients with systemic AL disease identified amyloid in the tracheobronchial walls,<sup>3</sup> endobronchial disease was not described nor did patients manifest antemortem signs or symptoms of airway involvement. In our experience with 15 TBA patients, the disorder is limited to the airways. None have expressed monoclonal protein, clonal plasma cell expansion, or congophilic deposits outside the airways. Two published cases of biopsy-proven TBA expressed serum monoclonal protein; however, neither had amyloid documented outside the airway.<sup>51,52</sup>

Three patterns of airway involvement occur: (1) proximal, (2) mid- or main-bronchial, and (3) distal disease.<sup>50</sup> Patients with proximal TBA have decreased air

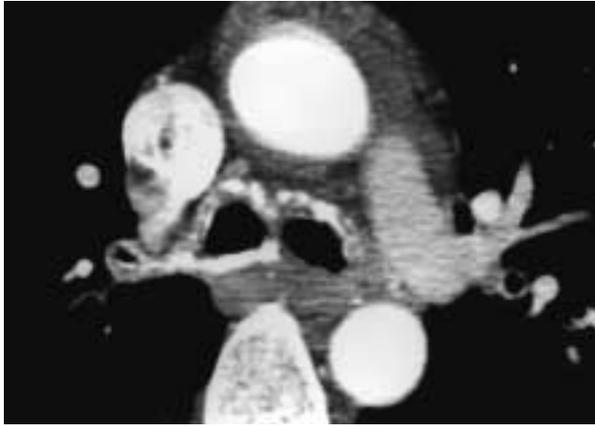
flows and, with progressive disease, may develop upper airway obstruction requiring tracheotomy. Over time, TBA circumferentially infiltrates the tracheal wall, blunting peak inspiratory and expiratory flows. Consequently, the flow-volume loop in proximal tracheal disease depicts fixed upper airway obstruction, a pattern not seen in mid- or distal-bronchial disease. Among noninvasive measures of airway disease, including CT imaging and pulmonary function tests, serial spirometry is most sensitive to progressive deposition of amyloid in the tracheobronchial tree.

#### RADIOLOGY

**Nodular Opacities** Among 28 cases of amyloid nodules, 29% calcified and 11% cavitated.<sup>53,54</sup> Pickford et al reported CT images of five patients with localized nodular AL<sup>40</sup>; 60% had one nodule, 20% had two nodules, and 20% had 10 nodules. A separate series observed multiple nodules in 67% of the cases.<sup>25</sup> Eighty percent of the nodules had smooth contours and were located in the subpleural region of the midzone; 20% of the nodules were spiculated. No associated adenopathy or pleural disease was detected.

**Diffuse Opacities** Reticular and reticulonodular patterns are reported,<sup>25</sup> although peripheral alveolar opacities occur as well. Despite reports of reticulonodular opacities in localized AL, this x-ray pattern should prompt thorough investigations for primary systemic (AL) disease.

**Tracheobronchial Disease** Chest x-rays are normal in 50% of cases. Findings in other cases include atelectasis or lobar collapse, calcified extraluminal amyloid deposits, bronchiectasis, or hilar adenopathy.<sup>50</sup> CT, un-



**Figure 2** Computed tomography of the main carina in tracheo-bronchial amyloidosis. The walls of both main bronchi are thickened and densely calcified, particularly along the posterior wall of the right main bronchus. The right upper lobe take-off is extensively infiltrated with amyloid.

like bronchoscopy, demonstrates the full extent of disease: (a) airway wall thickening, (b) irregular narrowing of airway lumen, and (c) heterotopic calcification of amyloid deposits in airway walls (Fig. 2).<sup>40,50,55</sup> Additionally, CT depicts airways beyond critical narrowings, affording full assessment of the airway.

#### DIAGNOSTIC ALGORITHM

Biopsy diagnosis of amyloidosis rests on apple-green birefringence conferred by congo red staining. Once amyloid has been identified, the extent of disease and the protein subunit must be defined. Extent of disease is most easily determined by performing a fat pad aspirate and staining with congo red dye. Electrocardiograms and echocardiograms identify cardiac infiltration, which frequently occurs in primary (AL) and hereditary

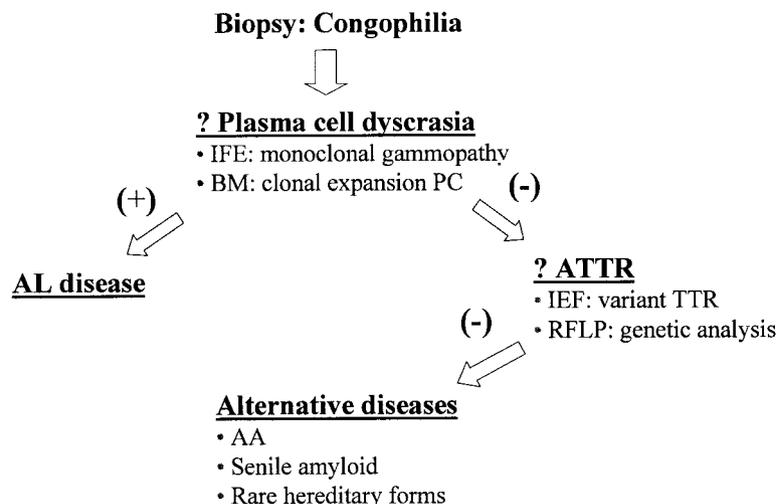
(ATTR) amyloidosis. Alternative biopsy sites will be defined by the spectrum of organ dysfunction.

Two approaches define subunit composition of amyloid: (1) direct testing of tissue samples, or (2) demonstrating a plasma cell dyscrasia or variant transthyretin (Fig. 3). Direct testing involves (a) treating amyloid tissue with potassium permanganate, which differentiates AA from AL, ATTR, or  $A\beta_2M$ ; or (b) immunohistochemical staining with antibodies directed against  $\lambda$  or  $\kappa$  light chains (AL), serum amyloid A protein (SAA), or transthyretin (TTR). Definitive diagnosis of ATTR disease requires amino acid sequencing or genotyping.

#### PROGNOSIS AND TREATMENT OF SYSTEMIC AND LOCALIZED AL DISEASE

**Systemic AL Disease** The median survival for patients with untreated systemic AL disease is 13 months; when complicated by heart failure, survival decreases to 16 weeks.<sup>20</sup> A small cadre of patients (< 5%) survive more than 10 years without treatment. Oral cyclic melphalan and glucocorticoids increase median survival to approximately 17 months, but rarely induce hematologic cure or regression of organ dysfunction.<sup>56,57</sup> To improve outcomes, the Amyloid Program at Boston University School of Medicine used high-dose intravenous melphalan with autologous stem cell rescue to treat systemic AL disease.<sup>58</sup> Hematologic cure was achieved in 62% of these patients, with 65% experiencing improved organ function.<sup>58</sup> The impact of dose intensive therapy on amyloid-related lung disease is unknown because patients with significant pulmonary compromise were excluded from this trial.

Symptomatic pleural effusions are a therapeutic challenge in systemic AL disease. Tenets of care are optimizing cardiac filling pressures, serial drainage of



**Figure 3** Algorithm for diagnosing different types of amyloidosis. IFE, immunofixation electrophoresis; BM, bone marrow biopsy; PC, plasma cells; IEF, isoelectric focusing; RFLP, restriction fragment length polymorphisms.

pleural fluid for symptomatic relief, and consideration of pleurodesis to decrease fluid reaccumulation.<sup>34</sup>

**Localized AL Disease** The published data addressing prognosis and treatment of amyloid localized to the lung are anecdotal. Nodular disease may slowly progress, with increasing size or number of lesions, but does not impact lung gas exchange nor patient survival. Diffuse parenchymal involvement can impair lung physiology and lead to death. Rubinow et al reported on four patients with diffuse lung involvement, three of whom died of respiratory failure.<sup>46</sup> Corticosteroids had no effect on the course of disease in two of these patients. Systemic chemotherapy is not advocated for treatment of localized disease; however, diffuse parenchymal involvement may warrant consideration of aggressive therapy given its inexorable course.

**Tracheobronchial Disease** In our experience, proximal and mid-bronchial TBA often progress to respiratory failure (7/15 patients). Proximal disease requires more frequent laser excision than does mid-bronchial disease (4.7 vs 2.0 treatments/yr, respectively). The deaths in our series all occurred approximately 9 years after presentation in patients with isolated proximal or combined proximal and mid-airways disease.<sup>50</sup>

Excisional therapy is the standard approach to managing TBA.<sup>46,49,50,59-62</sup> In some nodular forms of TBA, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser treatment removes tissue and eliminates further amyloid deposition in the field, perhaps by laser-induced thermal injury to underlying plasma cells. The diffuse form of TBA recurs after laser treatment. Repeated rigid bronchoscopies or laser treatments denude airways and promote collagen scar formation. Consequently, repeated airway debridement may trade one obstructing disease (TBA) for another (scar stenosis). Anecdotal experience with colchicine, oral glucocorticoids, and an iodinated isoform of doxorubicin (IDOX), have yielded disappointing results. Systemic chemotherapy has not been used to treat isolated tracheobronchial amyloidosis due to its toxic side effects and the low burden of clonally expanded plasma cells.

Because plasma cells are radiosensitive,<sup>63</sup> low-dose external beam radiation was attempted in five published cases of TBA.<sup>50,51,64-66</sup> Kurrus et al reported regression of endobronchial deposits after delivering 20 Gy in 10 fractions.<sup>64</sup> Five months later, disease had not progressed in the radiation port. No large series are available.

Supportive care should be directed at minimizing mucous production, which may further compromise airway lumen caliber. Antibiotics, regular nebulizer use, and occasional courses of oral or inhaled glucocorticoids are useful adjuncts to airway debridement.

## FUTURE TREATMENTS

Ideal treatment of amyloidosis would prevent formation of the insoluble  $\beta$ -pleated sheets, or render previously formed deposits susceptible to enzymatic destruction. Recent *in vitro* studies demonstrated that two ubiquitous chaperone molecules—serum amyloid P (SAP) component and heparan sulfate proteoglycan (HSP)—promote  $\beta$ -pleated sheet formation and prevent proteolytic digestion. Functionally removing these chaperones from fibril complexes inhibited amyloid formation and increased protease susceptibility.<sup>67,68</sup> The universal presence of SAP and HSP in all types of amyloid suggests that these diseases may be successfully treated with SAP- and HSP-adsorbing agents in the future.

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