Pulmonary Amyloidosis

The Mayo Clinic Experience from 1980 to 1993

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Objective: To define the prognosis for and radiographic presentation of patients with pulmonary amyloidosis.

Design: Retrospective review of the Mayo Clinic experience with biopsy-proven pulmonary amyloidosis from 1980 to 1993.

Setting: Tertiary care center.

Patients: Patients with pulmonary biopsy specimens showing amyloid deposition.

Measurements: Medical records were reviewed, and pertinent information was recorded, including demographic data, type of pulmonary biopsy, results of biopsies of nonpulmonary sites and of immunoelectrophoresis, and other clinical, radiographic, and laboratory information necessary for distinguishing localized pulmonary amyloidosis, primary systemic amyloidosis, secondary amyloidosis, and familial amyloidosis.

Results: 35 of 55 patients with pulmonary amyloidosis had primary systemic amyloidosis that presented radiographically as an interstitial or reticulonodular pattern with or without pleural effusion. The median survival after diagnosis was 16 months. Nodular pulmonary "amyloidomas" (nodular amyloid lesions) were not associated with systemic disease and were associated with a benign prognosis. Three of 4 patients with localized tracheobronchial amyloidosis required Nd:YAG (neodymium:yttrium-aluminum-garnet) laser therapy for obstructive symptoms. "Senile" amyloid deposition was an incidental finding in some patients at autopsy.

Conclusions: Localized amyloidomas are characterized by a benign course and are not associated with systemic amyloidosis. Despite its localized nature, tracheobronchial amyloid deposition may be asymptomatic or may result in significant morbidity due to obstructive phenomena. Pulmonary amyloidosis associated with primary systemic amyloidosis generally presents as a diffuse interstitial pattern with or without pleural effusion. Complete survival data indicate that long-term outcome is poor after diagnosis. We describe the largest series of patients diagnosed by bronchoscopic lung biopsy. Despite reports to the contrary, we have found bronchoscopic lung biopsy to be a safe and effective diagnostic technique.

Ann Intern Med. 1996;124:407-413.

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The term amyloidosis refers to a group of conditions characterized by the deposition of abnormal protein material in extracellular tissue. Amyloid protein takes up Congo red stain and exhibits apple-green birefringence under polarized microscopy. 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. Many classification schemes have evolved and are discussed in detail elsewhere (1–4).

Virchow first described amyloid involving the lungs in 1857. The first case of amyloidosis confined to the lower respiratory tract was described by Lesser in 1857, based on an autopsy study. Pulmonary amyloidosis may be localized to the respiratory tract or may be part of a widespread process involving many organs. We present our experience at the Mayo Clinic with pulmonary amyloidosis involving the respiratory tract.

Methods

We began our retrospective study of the Mayo Clinic experience with pulmonary amyloidosis by doing computer-assisted and manual searches of pathology records to identify patients with pulmonary biopsy specimens showing amyloidosis that were obtained at the Mayo Clinic from 1980 to 1993. We reviewed patients' medical records and examined chest radiographs, tomograms, and computed tomographic scans. We recorded pertinent clinical details, including demographic information, type of pulmonary biopsy, and results of other biopsies and of immunoelectrophoresis. We also obtained other clinical and laboratory information needed to distinguish localized pulmonary amyloidosis from pulmonary amyloidosis that is part of primary systemic amyloidosis (including cases accompanied by multiple myeloma), secondary amyloidosis, or familial amyloidosis. No patient was lost to follow-up.

Results

We identified 55 patients (28 men and 27 women) with pulmonary biopsy specimens showing amyloidosis (age range, 35 to 94 years).

Table 1. Pulmonary Amyloidosis, Mayo Clinic 1980–1993: Type of Biopsy

Type of Biopsy	Number of Patients (n = 55)
Autopsy	21
Open lung biopsy	17
Bronchoscopic lung biopsy	11
Tracheal or bronchial biopsy	3
Closed pleural biopsy	2
Thoracoscopic lung biopsy	1

Various types of biopsy were done (Table 1). Bronchoscopic lung biopsies ("transbronchial lung biopsies") were done without major complications in all 11 patients who had this procedure. An estimated 100 mL of blood was lost in 2 of 11 patients who had bronchoscopic lung biopsy. No other complications were reported.

Table 2 summarizes the types of amyloid deposition. Of the 35 patients with primary systemic amyloidosis and histologic evidence of pulmonary involvement, 18 were women and 17 were men (mean age, 64 years; range, 41 to 90 years). The diagnosis of pulmonary amyloidosis was made before death in 21 of these patients and at autopsy in 14 others. Patients had a monoclonal light chain in serum or urine or both (30 patients), autopsy evidence of primary systemic amyloidosis (3 patients), or biopsy and other clinical evidence (2 patients) confirming the diagnosis of primary systemic amyloidosis. Figure 1 shows typical findings of the pulmonary involvement that occurs with primary systemic amyloidosis.

Two patients (a 42-year-old man with longstanding bronchiectasis and a 49-year-old woman with familial Mediterranean fever) had pulmonary deposition of amyloid associated with secondary amyloidosis. One 69-year-old patient had familial amyloidosis.

Eleven patients had localized pulmonary amyloid deposition without evidence of systemic amyloidosis. Seven of these patients (mean age, 67 years; range, 43 to 78 years) had localized nodules often referred to as "amyloidomas." Four patients (35, 51, 79, and 85 years of age) had localized tracheobronchial amyloid. Six patients had localized senile pulmonary amyloid deposition at the time of autopsy (mean age, 87 years; range, 80 to 94 years).

Table 2. Pulmonary Amyloidosis, Mayo Clinic 1980–1993: Distribution of Patients

Condition	Number of Patients (n = 55)
Primary systemic amyloidosis	35*
Secondary or familial amyloidosis	3
Localized amyloidosis	17
Nodular	7
Tracheobronchial	4
Senile	6

* Includes 5 patients with multiple myeloma.

We observed various radiographic presentations of pulmonary amyloidosis. Table 3 outlines those seen in patients with systemic amyloidosis, and Table 4 shows those seen in patients with localized pulmonary amyloidosis. Figure 2 shows a typical chest radiograph of a patient with diffuse infiltrates related to primary systemic amyloidosis, and Figure 3 shows a computed tomographic scan of a patient with a localized pulmonary amyloidoma.

Follow-up data were available for all 21 patients with primary systemic amyloidosis diagnosed before death. Long-term survival was poor (median survival, 16 months) (Figure 4). Fourteen other patients with primary systemic amyloidosis and biopsy-proven pulmonary involvement were diagnosed at autopsy. In the secondary amyloidosis group, the 42-year-old man with bronchiectasis was alive at 87 months, and the diagnosis of the 49-year-old woman with familial Mediterranean fever was established at autopsy. The 69-year-old patient with familial amyloidosis was alive at 16 months.

In the localized pulmonary amyloidosis group, three of the four patients with tracheobronchial amyloidosis had died by the time of the last follow-up. One died of recurrent major airway obstruction and pneumonitis at 79 months (diagnosed at age 51 years); one died of a stroke at 28 months (diagnosed at age 79 years); and one died of unknown cause at 42 months (diagnosed at age 85 years). The remaining patient was alive at 156 months (diagnosed at age 35 years).

Discussion

Pulmonary amyloid may be classified according to the anatomic site of involvement, but it may also be discussed with reference to its associated condition. Some authors classify pulmonary amyloid according to the anatomic site of involvement and exclude cases in which systemic amyloidosis is present (5, 6). Others classify it according to the site of involvement and the presence or absence of systemic amyloidosis (7, 8). Further confusion in classification stems from the unfortunate similarity between the terms primary systemic amyloidosis and primary pulmonary amyloidosis. In the context of our study, the term primary pulmonary amyloidosis refers to amyloidosis that is confined to the pulmonary system, and it excludes patients with primary systemic amyloidosis. We use a categorization system differentiating systemic amyloidosis (Table 3) from localized pulmonary amyloidosis (Table 4). Using this initial division as a basis, we can discuss

other features, including the gross anatomic distribution of amyloid deposition and the radiographic pattern.

Pulmonary Amyloidosis Associated with Systemic Amyloidosis

Primary Systemic Amyloidosis

Primary systemic amyloidosis may involve the lung with amyloid deposition in an alveolar septal pattern. Although it has long been known that primary systemic amyloidosis has a propensity to involve the lung (9), cases have been infrequently reported. Cordier and colleagues (8) described several patients with primary systemic amyloidosis with diffuse pulmonary deposition of amyloid, but the incidence of pulmonary involvement with primary systemic amyloidosis cannot be calculated from their data. Other case reports (10, 11) show that pulmonary involvement does occur in these patients, but no incidence figures can be calculated. Celli and colleagues (12) 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, and Smith and colleagues (13) found that 23 of 26 patients who had primary systemic amyloidosis had pulmonary involvement. These autopsy series show that pulmonary involvement with primary systemic amyloidosis is the rule. Pleural involvement occurring with primary systemic amyloidosis has been diagnosed by closed-needle pleural biopsy (14–16).

To our knowledge, our series, which included 35 patients who had primary systemic amyloidosis with pulmonary involvement, is the largest such series reported. This clustering of cases is probably the result of referral patterns rather than a reflection of the relative prevalences of primary amyloidosis compared with secondary amyloidosis in the general population. Our series also includes the only large group of patients with pulmonary amyloidosis related to primary systemic amyloidosis diagnosed before death. Follow-up data on the entire group are complete. For the 21 patients diagnosed before death, the median survival was 16 months, which is consistent with the poor survival rates of patients with primary systemic amyloidosis (Figure 4).

Table 3. Pulmonary Amyloidosis Associated with Systemic Disease*

Type	Radiographic Pattern
Primary systemic amyloidosis (n = 35)	Interstitial (20 patients) Reticular (12 patients), reticulonodular (8 patients) Diffuse (14 patients), predominantly lower lobes (4 patients), upper lobes (1 patient), nonspecific/patchy (1 patient) Coexisting pleural effusion (4 patients) (2 unilateral, 2 bilateral) Pleural effusion without infiltrate (10 patients) Unilateral (2 patients), bilateral (8 patients) Pleural thickening (1 patient) Unremarkable chest radiograph (4 patients)
Secondary amyloidosis (n = 2)	Bibasilar interstitial infiltrate (1 patient with bronchiectasis) Diffuse interstitial infiltrate with bilateral hilar adenopathy (1 patient with familial Mediterranean fever)
Familial amyloidosis (n = 1)	Diffuse fine nodular pattern

* n = 38.

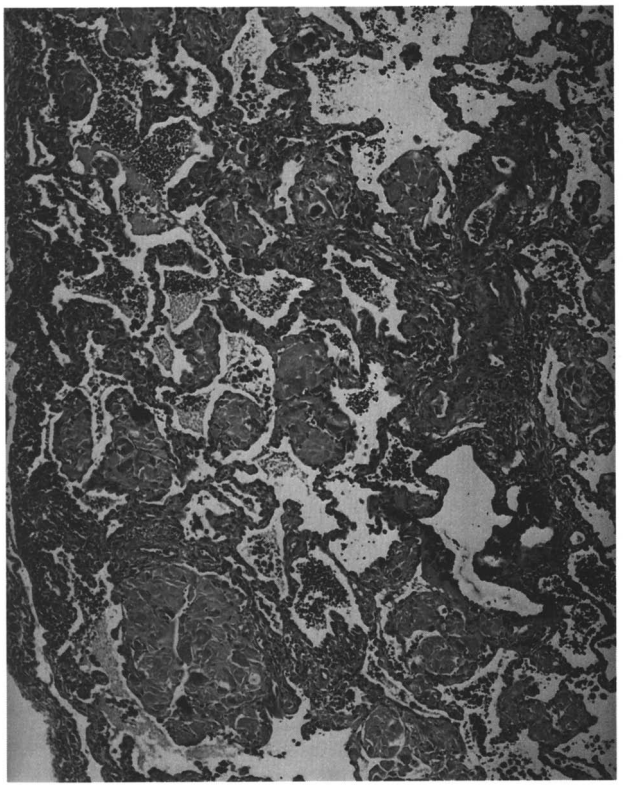

Figure 1. Low-magnification photomicrograph showing diffuse alveolar septal amyloidosis. Alveolar septa show patchy, nodular thickening by waxy, acellular amyloid deposits. The remainder of the lung shows mild, nonspecific abnormalities, including a chronic pleuritis.

Celli and colleagues (12) believed that the pulmonary involvement was a major contributor to death in only 1 of 12 cases of pulmonary amyloidosis related to primary systemic amyloidosis, and Cordier and colleagues (8) estimated that only about 10% of their patients died as a result of the pulmonary involvement. Because of the frequent incidence of concomitant cardiac amyloidosis, it is not always possible to determine the degree to which pulmonary amyloid involvement contributes to symptoms (13). The presence of pulmonary amyloidosis in patients with primary systemic amyloidosis is a harbinger of a poor outcome, whether the pulmonary component of the disease is directly related to death or is simply a marker of an otherwise fatal disease.

A substantial number of patients with pulmonary

Table 4. Localized Pulmonary Amyloidosis*

Location	Distribution	Radiographic Pattern
Tracheobronchial (4 patients)	Localized (1 patient) Diffuse (3 patients)	Thickened airway Shadows or no significant finding
Parenchymal (7 patients)	Nodular (7 patients) Diffuse† (0 patients)	Single nodule (5 patients) Multiple nodules (2 patients)
Senile (6 patients)	Scattered/diffuse	Normal or minimal nonspecific findings

* $n = 17$.
† Reported to have occurred but not seen in our series.

amyloidosis associated with systemic amyloidosis also have multiple myeloma. Five of the 35 patients (14%) in our series who had systemic amyloidosis had associated multiple myeloma, and, in the Johns Hopkins series (13), 8 of 31 patients with systemic amyloidosis had multiple myeloma, most of whom had pulmonary amyloid deposition. In the Johns Hopkins series, 11 of 90 patients (12%) with multiple myeloma who had had an autopsy at that institution were found to have amyloidosis.

Secondary Amyloidosis

Conditions associated with secondary amyloidosis include tuberculosis, chronic renal disease, syphilis, osteomyelitis, inflammatory bowel disease, bronchiectasis, chronic inflammation, rheumatoid arthritis, leprosy, and certain cancers (13). The incidence of pulmonary amyloidosis associated with secondary amyloidosis is low. Mild pulmonary parenchymal involvement was noted in only 1 of 113 patients with secondary amyloidosis in the Johns Hopkins series (13). We noted only two cases of pulmonary amyloidosis related to secondary amyloidosis during a 14-year period.

Familial Amyloidosis

Familial amyloidosis is a rare condition that may result in pulmonary amyloidosis. Only a single case was found in our 14-year series. In the Johns Hopkins experience of almost 90 years, only three cases of familial amyloidosis were found, two of which had pulmonary involvement (13).

Localized Pulmonary Amyloidosis

Localized pulmonary amyloidosis is defined as amyloid deposition isolated to the respiratory tract and does not include amyloidosis associated with systemic deposition (primary, secondary, or familial). Localized pulmonary amyloidosis may involve the tracheobronchial tree or pulmonary parenchyma in a localized or diffuse distribution (Table 4).

Tracheobronchial Amyloidosis

Localized pulmonary amyloidosis involving the tracheobronchial tree is relatively uncommon; we found only 4 cases in our series, and only 5 cases were reported by Cordier and colleagues (8) during a 15-year period. The largest single series of patients with localized pulmonary amyloidosis from one institution was reported by Hui and coworkers (5) from the Armed Forces Institute of Pathology: Of the 48 cases of localized pulmonary amyloid, 14 were classified as tracheobronchial. Thompson and Citron (7) reviewed the world literature in 1983 and found 126 cases (67 tracheobronchial and 59 pulmonary parenchymal) of primary localized amyloidosis. Of the 67 patients with tracheobronchial disease, 57 had multifocal submucosal plaques and 10 had amyloid tumorlike masses.

The mean age of patients with localized tracheobronchial amyloidosis was 62 years (range, 35 to 85 years) in our series and 54 years in the series by Hui and coworkers (5). In a review of the world literature, Rubinow and colleagues (6) reported the mean age of such patients to be 53 years. In patients with tracheobronchial amyloidosis, relatively flat plaques of amyloid material or a tracheobronchial nodule that has the appearance of neoplasm may be seen. These findings may be localized or diffuse or multifocal and are not associated with systemic amyloidosis (5–8, 12, 17–19). Patients may be asymptomatic or may have dyspnea, hemoptysis, recurrent pneumonia, cough, or atelectasis (5–7).

Although primary localized tracheobronchial amyloidosis is not associated with primary systemic amy-

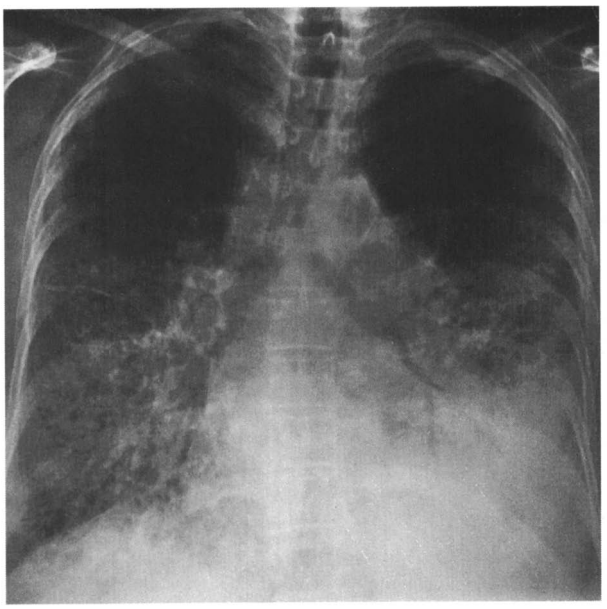

Figure 2. Chest radiograph in a patient with primary systemic amyloidosis showing a diffuse reticulonodular infiltrate with unilateral left pleural effusion.

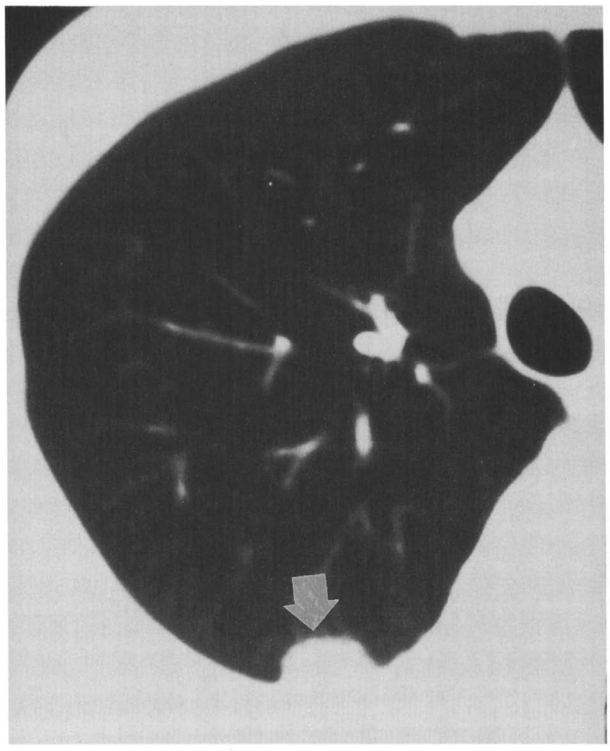

Figure 3. Computed tomographic scan showing a 2-cm uncalcified amyloidoma in the right upper lobe abutting the pleura (*arrow*).

loidosis, its course may not be benign. In the study by Hui and colleagues (5), follow-up data were available for 7 of 14 patients with tracheobronchial amyloidosis, and 3 of these patients died of respiratory failure or recurrent pneumonia secondary to bronchial obstruction. Management has included observation, intermittent bronchoscopic resection, and surgical resection (18, 20–22). Recently, carbon dioxide laser ablation has been used in several cases (23), and we have used Nd:YAG (neodymium: yttrium-aluminum-garnet) laser therapy in 3 patients.

Tracheobronchial amyloidosis has been associated with the uncommon condition tracheobronchopathia osteoplastica, a disease of unknown cause characterized by the presence of calcified or cartilaginous submucosal nodules within the tracheobronchial tree (24–26). These nodules usually spare the posterior membrane of the trachea and may be an incidental finding at the time of bronchoscopy or autopsy. Other patients may have respiratory symptoms related to luminal narrowing of the tracheobronchial tree. Some authors have suggested that tracheobronchial amyloidosis leads to tracheobronchopathia osteopathica (27, 28), whereas others disagree (4, 25, 26).

Nodular Amyloid Lesions

Nodular amyloid lesions ("amyloidomas") are uncommon and are not associated with primary systemic amyloidosis. Only three cases of isolated nodular pulmonary parenchymal amyloidosis were found in a review of autopsy files at the Johns Hopkins Hospital from 1889 to 1977 (13). However, because autopsies only of patients diagnosed with "amyloidosis" were reviewed, and because this diagnosis is often reserved for patients with systemic disease, this study may have underestimated the true incidence of localized pulmonary amyloid nodules. We found 7 cases over a 13-year period, and Hui and colleagues (5) reported 28 cases over an unspecified period. Some authors have reported that localized amyloid nodules are more common than tracheobronchial amyloid (5); others have reported the reverse (6). Our study shows that localized pulmonary amyloid nodules may be single or multiple; this is consistent with previous findings (5, 6). The largest reported nodule was 15 cm; the size of most nodules ranges from 0.4 to 5 cm; and the average nodule is 3 cm (5). Pulmonary amyloid nodules may occur more frequently in the lower lobes (5) and may be asymmetric when bilateral nodules are present (29, 30). Often, they are incidentally found on chest radiograph or at autopsy (5, 7). They are frequently seen in older patients, with an average age in the sixth decade (5, 31). They may calcify, or metaplastic bone or cartilage formation may occur (5, 32).

Diffuse Interstitial Pattern

A diffuse interstitial pattern is rare in localized pulmonary amyloidosis. In our series, this radiographic presentation was not seen in any patient with localized pulmonary amyloidosis. Hui and colleagues (5) noted a diffuse interstitial pattern in 6 of 48 cases of local pulmonary amyloidosis. In a series reported by Cordier and colleagues (8), amyloidosis of the lower respiratory tract included both localized pulmonary amyloidosis and pulmonary amyloidosis related to systemic amyloidosis. In the group of 15 patients with a radiographically diffuse process, most had evidence of amyloid deposition in

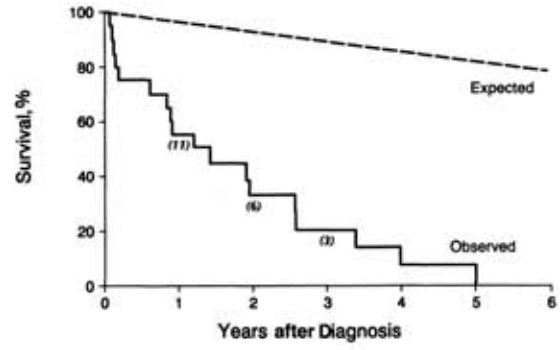

Figure 4. Survival curve for patients after diagnosis of pulmonary amyloidosis related to primary systemic amyloidosis. The numbers in parentheses are the numbers of patients at risk at 1, 2, and 3 years after diagnosis.

other organs or of a monoclonal gammopathy in the urine or serum, suggesting systemic amyloidosis rather than localized pulmonary amyloidosis. The remaining patients had had neither biopsies of other organs nor the urine or serum immunoelectrophoresis studies necessary to distinguish systemic amyloidosis from localized pulmonary amyloidosis.

Senile Pulmonary Amyloidosis

It is estimated that approximately 10% of patients older than 80 years of age and 50% of patients older than 90 years of age have senile pulmonary amyloidosis, which parallels senile cardiac involvement and is usually present without significant symptoms (33). On the basis of random autopsies, Kunze (34) found that the incidence of senile pulmonary amyloidosis was 10% in patients older than 80 years of age and 20% in patients older than 85 years of age. Our series includes six patients with senile pulmonary amyloidosis that, in all six patients, was found incidentally at autopsy.

Mediastinal and Hilar Amyloidosis

Discussions of pulmonary amyloidosis sometimes include hilar or mediastinal adenopathy or mediastinal masses secondary to amyloidosis. Although not precisely pulmonary, they are thoracic manifestations. Hilar adenopathy may be unilateral or bilateral, and it may be calcified; it may be a localized phenomenon, or it may be associated with primary systemic amyloidosis (29, 35–38). Intrathoracic amyloidosis may present as an isolated mediastinal mass (39), and tracheobronchial amyloidosis has also been found to occur in conjunction with hilar adenopathy (40).

Biopsy Techniques

We used various biopsy techniques in our series (Table 1). Although patients with amyloidosis probably have a generalized increased risk for bleeding (41), cases have been reported of diagnosis of pulmonary amyloid nodules by fine-needle aspiration without bleeding complications (42–45). However, a case of hemorrhage after bronchoscopic lung biopsy in a patient with pulmonary parenchymal amyloidosis, which resulted in respiratory compromise, intubation, and massive air embolism, has also been reported (46). The authors of this report suggested that patients may be at increased risk for substantial complications after bronchoscopic lung biopsy (46). Others have reported several cases diagnosed without complication (47, 48). Our series of 11 patients diagnosed by bronchoscopic lung biopsy is the largest reported series. Two of these 11 patients lost approximately 100 mL of blood. On the basis of these findings, it appears that pulmonary amyloidosis can be diagnosed by bronchoscopic lung biopsy with reasonable safety, although the bronchoscopist should be prepared to manage hemorrhage after biopsy.

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The great doctor Hermes was sent for from Memphis, and he came to Babylon with a numerous retinue. He visited the sick man and said he would lose his eye. He even predicted the day and the hour when this disastrous accident would happen. "If it had been the right," he said, "I should have cured it, but wounds in the left eye are incurable."

All Babylon, while bemoaning Zadig's fate, marveled at Hermes' profound knowledge. Two days later the abscess burst of its own accord, and Zadig was completely cured. Hermes wrote a book in which he proved that Zadig should not have been cured. Zadig did not read the book.

Voltaire
Zadig

Submitted by:
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