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Transbronchial biopsies safely diagnose amyloid lung disease

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Abstract

Background—Autopsy identifies lung involvement in 58–92% of patients with the most prevalent forms of systemic amyloidoses. In the absence of lung biopsies, amyloid lung disease often goes unrecognized. Report of a death following transbronchial biopsies in a patient with systemic amyloidosis cautioned against the procedure in this patient cohort. We reviewed our experience with transbronchial biopsies in patients with amyloidosis to determine the safety and utility of bronchoscopic lung biopsies.

Methods—We identified patients referred to the Amyloidosis Center at Boston Medical Center with lung amyloidosis diagnosed by transbronchial lung biopsies (TBBX). Amyloid typing was determined by immunohistochemistry or mass spectrometry. Standard end organ assessments, including pulmonary function test (PFT) and chest tomography (CT) imaging, and extra-thoracic biopsies established the extent of disease.

Results—Twenty-five (21.7%) of 115 patients with lung amyloidosis were diagnosed by TBBX. PFT classified 33.3% with restrictive physiology, 28.6% with obstructive disease, and 9.5% mixed physiology; 9.5% exhibited isolated diffusion defects while 19% had normal pulmonary testing. Two view chest or CT imaging identified focal opacities in 52% of cases and diffuse interstitial disease in 48%. Amyloid type and disease extent included 68% systemic AL disease, 16% localized (lung limited) AL disease, 12% ATTR disease, and 4% AA amyloidosis. Fluoroscopy was not used during biopsy. No procedure complications were reported.

Conclusions—Our case series of 25 patients supports the use of bronchoscopic transbronchial biopsies for diagnosis of parenchymal lung amyloidosis. Normal PFTs do not rule out the histologic presence of amyloid lung disease.

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Disclosure statement

The authors report no conflicts of interest.

Keywords

Lung biopsy; amyloidosis; interstitial lung disease

Introduction

The amyloidoses are a family of diseases that result from the misfolding, aggregation and extracellular deposition of beta-sheet-rich insoluble proteins, disrupting organ function. Although >27 different proteins can misfold and form amyloid fibrils, three proteins – immunoglobulin light chain (AL), transthyretin (ATTR) and serum amyloid A (AA) – constitute the preponderance of worldwide amyloid cases [1]. Clinically apparent lung involvement complicates 28% of AL amyloidosis cases [2], fewer than 1% of ATTR amyloidosis cases, and is rarely reported in AA amyloidosis [3,4]. In contrast, autopsy studies reveal alveolar–septal wall amyloid deposition in 92% patients with AL and 58–100% of patients with TTR amyloidoses [5–8]. These data suggest that amyloid lung disease may be underdiagnosed in patients with amyloidosis.

For many interstitial lung diseases, histologic diagnosis requires surgical biopsies under general anesthesia – procedures poorly tolerated by patients with multi-organ dysfunction due to AL or ATTR amyloidosis. Transbronchial lung biopsies (TBBX) first diagnosed pulmonary amyloid deposition in 1985 [9]. Two years later, Strange et al. [10] reported hemorrhage, pneumothorax, air embolism and death complicating transbronchial biopsies in a patient with alveolar–septal amyloid deposition. The authors cautioned against the use of transbronchial biopsies in the amyloidosis patient population. We report on a case series of 25 patients with amyloid lung disease diagnosed by transbronchial biopsies, examining disease demographics and procedure complications.

Methods

Patients

We identified patients with biopsy-proven amyloid lung disease referred to the Amyloidosis Center at Boston Medical Center between 1994 and 2013. Institutional Review Board at Boston Medical Center approved record review and manuscript preparation from the data of patients with biopsy proven amyloid lung disease. Written informed consent was obtained from each patient in accordance with the Declaration of Helsinki. We reviewed records of all patients with amyloidosis diagnosed by TBBX. Patients with lung biopsies obtained by surgical techniques or transthoracic needle aspiration were excluded from the analysis.

All patients diagnosed by TBBX underwent plasma cell dyscrasia evaluations including quantitative immunoglobulin levels, serum and urine immunofixation electrophoreses, serum-free light chain measurement (after 2003), abdominal fat pad aspirates to identify systemic amyloid deposits by Congo red stain, and bone marrow biopsy if indicated. End organ assessments included echocardiograms, electrocardiograms (ECG), brain natriuretic peptide (BNP) and troponin I levels (after 2006), serum and urine chemistries, 24-h urine protein excretion, radiographic imaging of the chest, pulmonary function test (PFT), and

arterial blood gas (ABG) measurement. Typing the amyloidogenic protein of lung deposits involved immunohistochemical staining with anti-AA, lambda and kappa immunoglobulin light chain and TTR antibodies. After 2007, amyloid typing methodology included laser capture micro-dissection and tandem mass spectrometry (Mayo Medical Laboratories, Rochester, MN) when necessary.

Localized lung amyloidosis was defined as amyloid deposits confined to the lung parenchyma with no evidence of other major end-organ dysfunction attributable to amyloidosis and without evidence of a systemic plasma cell dyscrasia. Systemic amyloidosis was diagnosed when amyloid deposits were identified both within the lung and outside the thorax – in the presence or absence of plasma cell dyscrasia, variant TTR genopositivity or AA immunoreactivity. Cardiac involvement was defined as interventricular wall thickening (>12 mm) in the absence of valvular disease or chronic hypertension. Otherwise unexplained albuminuria (>500 mg/day) in the presence or absence of decreased creatinine clearance constituted kidney involvement. Signs of peripheral sensorimotor neuropathy by clinical examination or nerve conduction testing or manifestations of autonomic neuropathy were categorized as neurologic involvement. Diagnosis of gastrointestinal amyloidosis required histologic evidence of disease [11].

All lung tissues were stained with Congo red dye and viewed under polarized light by one pathologist with expertise in amyloidosis (COH).

Pulmonary function test

Forced spirometry (FVC and FEV1) and the diffusing capacity of the lung for carbon monoxide (DLCO) were measured using the single-breath method (SensorMedics; Yorba Linda, CA) according to American Thoracic Society guidelines [12,13]. Static lung volumes were determined using constant volume, whole-body plethysmography, as described by Dubois et al. [14]. Obstructive physiology was defined as FEV1/FVC ratio <0.70 and total lung capacity (TLC) ≥ 80% predicted; restrictive physiology was defined as FEV1/FVC ratio >0.70 with TLC <80% predicted [15].

Statistical analysis

Demographic, laboratory and PFT data were compared among subgroups of patients by *t*-test for continuously measured variables and by χ^2 test for dichotomous variables. All analyses were calculated (SAS for Windows; SAS institute Inc., Cary, NC) using a two-tailed significance value of 0.05.

Results

Demographics

Between 1994 and 2013, 3192 new patients were evaluated in Amyloid Clinic, 115 (3.6%) of whom had histologic evidence of amyloid deposition in the lung prompting referral to the Amyloidosis Center at Boston Medical Center. Twenty-five (21.7%) of the 115 patients with lung amyloidosis were diagnosed by bronchoscopic TBBX, forming the basis of this report. All biopsies were performed to evaluate new radiographic lung opacities, establishing the

first diagnosis of amyloidosis in each case. Lung pathology was reviewed by one pathologist. The median age of the cohort diagnosed by transbronchial biopsy was 63 years (range, 38–79), 56% were men, with a median body mass index (BMI) of 27 (range 18–35) (Table 1). The preponderance of cases (21/25) represented systemic amyloidosis; 16% constituted localized disease.

Pulmonary physiology

Our cohort of patients with TBBX documented lung amyloid had a median forced expiratory volume in 1 s (FEV1) of 80% predicted (range: 38–129) and FEV1/FVC ratio of 76% (range: 45–92) with low normal median TLC of 82% predicted (range: 31–135%). According to American Thoracic Society criteria, 33.3% exhibited restrictive disease, 28.6% obstructive parameters, and 9.5% mixed physiology. Isolated diffusion defects occurred in 9.5%, with 19% demonstrating completely normal PFTs. Although median gas diffusing capacity (DLCO) was moderately decreased (52%), median ABG data were within normal limits (Table 2). Systemic amyloid cases exhibited greater restrictive physiology while localized disease cases had obstructive character; however, neither trend reached statistical significance.

Chest imaging

All 25 patients with TBBX-proven amyloidosis had abnormalities identified by standard planar chest X-ray confirmed and characterized by chest tomography (CT). Thirteen patients (52%) had focal opacities (ground glass, atelectasis, tree-in-bud) limited to one or two lobes (RUL 1, RML 1, RLL 4, LLL 4, RLL/LLL 2, RML/lingual 1). Twelve patients (48%) exhibited diffuse interstitial opacities (Table 3). Notably, cases with systemic disease presented equally with focal versus diffuse radiologic abnormalities. Localized disease cases exhibited various focal lung opacity patterns.

Bronchoscopic approach

In 17/25 (68%) bronchoscopies, transbronchial biopsies were performed without anatomic targeting; focal radiographic signs directed transbronchial sampling in 7/25 (28%) cases. One procedure report did not comment on the approach used. Fluoroscopy guidance was not used in any of the procedures. Hemoptysis, pneumothorax or respiratory failure did not occur during or immediately after these 25 bronchoscopic biopsies. No delayed complications were reported.

Amyloid type and disease extent

Twenty-one (84%) of our 25 patients diagnosed by TBBX had systemic amyloidosis; 4 patients (16%) had lung-limited (localized) disease. Among the systemic disease cases, 81% of the TBBX patients had clinical and/or histological evidence of systemic AL amyloidosis; 14% had transthyretin amyloidosis (2 cases of V122I ATTR, 1 case of wild-type TTR (ATTRwt) amyloidosis) and 5% had secondary (AA) amyloidosis (Table 1). All localized lung amyloid cases proved to be derived from aggregation of immunoglobulin light chain (localized AL). Patients with TBBX-proven systemic AL amyloidosis almost exclusively

expressed monoclonal lambda light chain (94%) by immunofixation electrophoresis of serum or urine or serum free light chain assay.

Extra-thoracic organ involvement

Amyloid cardiomyopathy was diagnosed by echo features in 28% of the cohort, including all three of the transthyretin (ATTR) amyloid cases and 4 of the 17 systemic AL cases (23.5%). Neither the AA amyloid patients nor the patient with ATTRwt amyloidosis had evidence of cardiomyopathy (Table 4).

Echocardiographically, left ventricular ejection fraction (LVEF) (median 51.5%, 10–65% range) and right ventricular systolic pressure (RVSP) (30 mmHg, range: 21–76) were normal for the complete case series; however, the data ranges were wide. Median cardiac troponin I and BNP values were mildly increased (0.040 ng/mL and 205 pg/mL, respectively).

Amyloid-related renal disease, manifest as proteinuria (>500 mg/day) due to glomerular disease, occurred in 24% of the population; one case had AA amyloid, all others had AL disease (Table 1). While the median serum creatinine and 24-h urine protein excretion were normal, patients exhibited a range of renal dysfunction and urinary protein loss (Table 5).

Neurological, gastric or soft tissue involvement was diagnosed in 16%, 12% and 12% of the cases, respectively (Table 1). No abnormalities in coagulation parameters or platelet counts were detected in the cohort (data not shown).

Discussion

We present a case series of 25 bronchoscopic TBBX successfully diagnosing amyloidosis. In contrast to a single case report [10] of hemorrhage, air embolism, respiratory failure, and death complicating transbronchial biopsies in a patient with pulmonary amyloidosis, there were no reported complications in our series, regardless of other organ disease or body habitus based upon BMI. Although patients with AL amyloidosis have a propensity to bleed [16], significant pulmonary hemorrhage did not complicate any of the TBBX in our cohort.

Each of the patients in this series had radiographic findings suggestive of lung involvement on standard plain chest films. In patients with systemic amyloidosis, CT abnormalities were distributed evenly between diffuse interstitial opacities and focal lung changes. Two-thirds of the biopsies were obtained in an anatomically undirected fashion without fluoroscopy to guide forceps deployment; in one-third of the cases, biopsies targeted the abnormal radiographic findings.

The physiologic significance of the biopsy-proven amyloid lung disease varied widely. The majority of our cases exhibited restrictive, obstructive or combined restrictive–obstructive lung disease. Nearly 10% had depressed DLCO as their only physiologic deficit, and fully 19% of patients had normal spirometry, lung volumes and gas diffusion.

The majority of patients (82%) with amyloid deposits demonstrated by transbronchial biopsy proved to have AL amyloidosis, 80% with systemic and 20% with localized AL lung disease. Lambda light chain deposition dominated the AL disease, occurring in 94% of cases

as reported in large series of systemic AL disease [17]. Interestingly, 18% of our TBBX cases had TTR or AA amyloidosis despite the fact that alveolar–septal amyloid is rarely clinically recognized in these types of systemic amyloidosis. A 14-year review of pulmonary amyloidosis at the Mayo Clinic identified only 2 cases with radiographic signs of interstitial lung disease in the setting of AA amyloidosis; histologic confirmation was not pursued in either case [18]. Similarly, an autopsy series from Johns Hopkins Hospital involving 113 cases of AA amyloidosis demonstrated interstitial deposits in only one case [3]. ATTRwt cases, on the other hand, have interstitial lung amyloid deposits in an age-related, escalating fashion at autopsy [19]. In a separate series, Pitkanen et al. [20] reported ubiquitous vascular and alveolar wall amyloid in autopsies of 13 patients with ATTRwt disease.

Prior publications emphasize the coexistence of heart and lung amyloid deposition [7]. Smith et al. [21] analyzed autopsy findings in 26 patients with AL amyloidosis, reporting significant correlation between heart and lung involvement by pair-wise analysis. In contrast, 54% of our cohort had amyloid deposition in the lungs without clinical signs of amyloid cardiomyopathy, indicating that amyloid deposition can selectively occur in the lung.

Our cohort was selected for the presence of amyloid on TBBX. Therefore, ascertainment bias is an inherent weakness of our report. The data generated by our retrospective review cannot address the sensitivity or negative predictive power of transbronchial biopsies in detecting amyloid parenchymal lung disease. A prospective study would be needed to generate those results.

Our results, based upon the largest reported case series of transbronchial biopsies in patients with interstitial lung amyloidosis, have significant implications. Our data support the use of bronchoscopic transbronchial biopsies for diagnosis of parenchymal lung amyloidosis in patients with typical physiologic and radiographic signs of disease. Although AL amyloidosis dominated our case series, our results confirm that TTR and AA amyloidoses can involve the lung and may be diagnosed by TBBX. Finally, the data establish that normal PFTs should not dissuade bronchoscopists from performing TBBX to diagnose interstitial lung amyloidosis.

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Table 1

Demographics[a].

	Systemic (*n* =21)	Localized (*n* =4)	Total (*n* =25)
Age (years, range)	63 (38–77)	70 (63–79)	63 (38–79)
Gender			
Men	13	1	14 (56%)
Women	8	3	11 (44%)
Body habitus			
BMI, kg/m^2		27 (18–35)	
Disease			
AL systemic		17 (68%)	
AL localized		4 (16%)	
AF transthyretin		3 (12%)	
AA		1 (4%)	
IFE monoclonal light chain expression			
Kappa		1 (6%)	
Lambda		16 (94%)	
Quantitative Ig levels, mg/dL			
IgG		862 (416–5060)	
IgA		80 (15–739)	
IgM		44 (9–320)	
Serum-free light chains, mg/L			
Kappa		9.2 (0.2–105)	
Lambda		32.9 (4.1–1127.5)	
K:L ratio		0.6 (0.01–25.6)	
Organ involvement			
Cardiac		28%	
Renal		24%	
Gastric		12%	
Neurologic		16%	
Soft tissue		12%	

[a]Values given as median (range), unless otherwise indicated.

BMI: body mass index.

Table 2

Lung characteristics[a].

	Systemic (*n* =17)	Localized (*n* =4)	Total (*n* =21)
Pulmonary function test			
FEV1, %	75 (38–129)	91 (71–114)	80 (38–129)
FEV1/FVC, %	76 (45–92)	62 (51–80)	76 (45–92)
TLC, %	79 (31–108)	89 (80–135)	82 (31–135)
DLCO, %	49 (25–105)	61 (46–70)	52 (25–105)
	Systemic	Localized	Total
Physiologic profiles, %			
Normal	3	1	4 (19%)
Isolated DLCO	2	0	2 (9.5%)
Obstructed	3	3	6 (28.6%)
Restricted	7	0	7 (33.3%)
Mixed	2	0	2 (9.5%)
Arterial blood gas			
pH		7.44 (7.28–7.49)	
$PaCO_2$, mmHg		37.6 (33–56)	
PaO_2, mmHg		81 (55–97)	

[a]Values given as median (range), unless otherwise indicated.

DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expira tory volume in 1 s; FEV1/FVC: forced expiratory volume in 1 s/forced vital capacity; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure oxygen; TLC: total lung capacity.

Table 3

Chest imaging.

	Systemic	Localized	Total
Diffuse			
Interstitial	11	1	12
Focal			
Interstitial	7	1	8
Atelectasis	2	1	3
Ground glass	1	1	2

Table 4

Cardiac profile[a].

Parameter	Data
IVS, mm	11.0 (8–17)
LVEF, %	51.5 (10–65)
RVSP, mmHg	30 (21–76)
Troponin I, ng/mL	0.040 (0.006–0.098)
BNP, pg/mL	205 (33–1249)

[a]Values given as median (range), unless otherwise indicated.

BNP: brain natriuretic protein; IVS: interventricular septal wall thickness (diastole); LVEF: left ventricular ejection fraction; RVSP: right ventricular systolic pressure.

Table 5

Renal characteristics[a].

Parameter	Data
Serum creatinine, mg/dL	1.0 (0.6–3.9)
BUN, mg/dL	19 (10–36)
24-h urine protein, mg	208 (55–10,805)
Serum albumin, g/dL	4.0 (1.7–4.8)

[a]Values given as median (range), unless otherwise indicated.

BUN: blood urea nitrogen.