Clinical relevance of pulmonary amyloidosis: an analysis of 76 autopsy-derived cases

To the Editor:

Amyloidosis refers to a group of diseases characterised by the extracellular tissue deposition of insoluble misfolded proteins that disrupt the function of the involved organs [1]. The principal types of systemic amyloidosis include immunoglobulin light-chain amyloidosis (AL) due to an underlying monoclonal B-lymphocyte/plasma cell disorder, serum amyloid A amyloidosis (AA) due to chronic inflammatory diseases, and transthyretin amyloidosis (ATTR) from variations (mutations) in the transthyretin gene (mut-ATTR) or acquired form, *i.e.* wild-type ATTR (wt-ATTR) [1].

Deaths related to amyloidosis are usually attributed to cardiac involvement with AL. The prevalence of pulmonary deposition in AL patients has ranged from 36% to 90% based on histopathologic studies, but clinical correlation has been sparse [2, 3]. To shed additional insights on this issue, we analysed autopsy cases of amyloidosis to ascertain the clinical relevance of pulmonary involvement, including its role in the death of these patients.

We used a computer-assisted search of medical records to identify all patients diagnosed by autopsy to have pulmonary amyloidosis at our institution between January 1, 1997 and September 30, 2014. We reviewed relevant medical records, radiologic studies, and autopsy slides. Congo red and/or sulfated Alcian blue staining was used to identify amyloid deposition. The type of amyloid was determined by nanoflow liquid chromatography–tandem mass spectrometry as previously described [4].

The demographics of the 76 patients with autopsy-proven pulmonary amyloidosis are summarised in table 1. AL accounted for 76% of cases; nearly all were diagnosed to have amyloidosis antemortem. ATTR was mostly diagnosed at autopsy.

Chest radiographs obtained within 1 year of death (n=70) were abnormal in 64 patients (91%) and demonstrated bilateral or unilateral/focal lung infiltrates (40%) or basilar atelectasis (20%), which was usually related to the presence of pleural effusion; bilateral lung infiltrates were usually attributed to oedema. Pleural effusion (63%) and cardiomegaly (47%) were also common. Chest computed tomography (CT) images obtained within 1 year of death (n=29) were abnormal in 28 (97%) and revealed focal/unilateral or bilateral parenchymal opacities in 21 subjects (72%); pleural effusion was seen in 59%. The chest CT findings were mostly judged nonspecific.

At autopsy, cardiac involvement was found in 75 cases (99%; 57 AL, 14 wt-ATTR, three mut-ATTR and one apolipoprotein A-IV type amyloidosis (AApoAIV)). Pulmonary vascular involvement was present in 74 cases (97%; 58 AL, 12 wt-ATTR, three mut-ATTR and one AApoAIV); two cases without pulmonary vascular involvement comprised those with wt-ATTR type. Alveolar septal involvement was seen in 59 cases (78%; 44 AL, 11 wt-ATTR, three mut-ATTR and one AApoAIV) and tracheobronchial in 22 cases, (29%; 21 AL and one mut-ATTR). An antemortem diagnosis of pulmonary amyloidosis was rendered in only one patient (1%), who manifested bilateral pulmonary nodules and masses; bronchoscopic biopsy demonstrated AL. Pulmonary amyloidosis was clinically unsuspected in the remaining 75 patients (99%).

Cardiac disease (51 patients, 67%) was the most common cause of death, and included cardiac amyloidosis (86%), ischaemic heart disease (12%), and acute rejection after cardiac transplantation for AL (2%). 50 of

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Pulmonary involvement was common in amyloidosis but was not the immediate cause of death in most of these patients http://ow.ly/WK3N307cbE6

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TABLE 1 Demographic and clinical characteristics

Characteristics	Patients (n=76)	Known amyloidosis before autopsy (n=58)	Diagnosis of amyloidosis at autopsy (n=18)
Median time in days between diagnosis and autopsy		109 (2 days to 131 months)[#]	
Age years	64±15	59±12	79±12
Female	27 (36)	24 (41)	3 (17)
Presenting symptoms			
Respiratory symptoms			
Dyspnoea	24 (32)	22 (38)	2 (11)
Haemoptysis	2 (3)	2 (3)	0
Cardiac symptoms			
Chest pain	11 (15)	8 (14)	3 (17)
Oedema	8 (11)	7 (12)	1 (6)
Syncope	2 (3)	2 (3)	0
Hypotension	2 (3)	1 (2)	1 (6)
Gastrointestinal symptoms			
Abdominal pain	6 (8)	3 (5)	3 (17)
Gastrointestinal bleeding	2 (3)	2 (3)	0
Nausea, vomiting	2 (3)	2 (3)	0
Neurologic symptoms			
Loss of consciousness	7 (9)	2 (3)	5 (28)
Neuropathy	1 (1)	1 (2)	0
Miscellaneous			
Anorexia, fatigue	2 (3)	2 (3)	0
Fever	2 (3)	2 (3)	0
Fall	2 (3)	0	2 (11)
Mouth dryness	1 (1)	1 (2)	0
Type of amyloid			
AL	58 (76)	54 (93)	4 (22)
ATTR	17 (22)	4 (7)	13 (72)
AApoAIV	1 (1)	0	1 (6)

Data are presented as median (range), mean±SD or n (%). AL: immunoglobulin light chain amyloid; ATTR: transthyretin amyloid; AApoAIV: apolipoprotein A-IV amyloid. [#]: date of diagnosis was available in 57 of 58 patients.

these patients (98%) had histopathologic cardiac involvement with amyloidosis; the remaining patient had AL but suffered sudden cardiac death caused by ischaemic heart disease. Among 39 patients who had undergone echocardiography within 1 year prior to death, 23 (45%) exhibited abnormal findings suggestive of infiltrative cardiomyopathy.

Respiratory disease was the second most common cause of death (13 patients, 17%) but only one death was directly attributable to pulmonary AL. This patient died from respiratory failure related to diffuse pulmonary alveolar septal amyloidosis complicated by recurrent pleural effusions. Among other respiratory causes of death were pneumonia, pulmonary embolism and aspiration, among others.

Six patients (8%) died from gastrointestinal causes; five were directly related to AL of the gastrointestinal tract. Three patients (4%) died from AL-associated kidney disease resulting in renal failure. The remaining three deaths were caused by sepsis in AL patients.

In our large cohort of patients proven to have pulmonary amyloidosis at autopsy, the majority had systemic AL. However, pulmonary amyloidosis was rarely recognised antemortem nor did it directly cause death. Vascular (97%) and alveolar septal patterns (78%) of pulmonary involvement were more frequently observed than tracheobronchial pattern (29%). The most common cause of deaths in our patients with pulmonary amyloidosis was cardiac, most of which were amyloid-related. Previous studies reported the cause of death to be cardiac in 30%–50% of patients with systemic amyloidosis [5–7].

Amyloidosis can affect the respiratory tract in various patterns. The isolated pulmonary amyloidosis is more commonly recognised antemortem than pulmonary involvement in systemic amyloidosis [2, 8, 9]. Prior autopsy studies of AL noted lung involvement to be common, although usually not of clinical consequence. For example, Dahlin [10] reported amyloid deposition in or around the small vessels of the lungs in five of

six patients but did not accord this finding "apparent clinical importance". Another autopsy study reported amyloid involvement of the lung parenchyma and vasculature in 11 of 12 patients with AL but only four were symptomatic, including one patient who died from pulmonary amyloidosis [2].

Smith *et al.* [8] speculated that pulmonary amyloidosis in AL patients was principally a marker for severe cardiac infiltration, as no pulmonary deposition was seen in the absence of cardiac amyloidosis [8]. In our study, all cases with alveolar septal involvement exhibited cardiac involvement but there was one patient with pulmonary vascular amyloid deposition in the absence of cardiac involvement.

All 14 wt-ATTR patients in our series had evidence of cardiac amyloidosis. 12 (87%) of these patients also had pulmonary vascular involvement while 10 (71%) patients exhibited alveolar septal involvement; none died from pulmonary amyloidosis.

Pulmonary involvement in mut-ATTR amyloidosis is rare. Our current study includes three patients with mut-ATTR amyloidosis; all had alveolar septal amyloid deposits but their deaths were unrelated to pulmonary involvement. One patient with AApoAIV systemic amyloidosis had progressive dyspnoea and exhibited both cardiac and pulmonary amyloid deposits but did not die from pulmonary amyloidosis.

Factors that influence the pattern of pulmonary deposition in amyloidosis remain unclear. However, in patients with systemic amyloidosis, pulmonary involvement is commonly demonstrable histopathologically at autopsy but generally not diagnosed clinically [11]. Recognition of pulmonary amyloidosis antemortem might be facilitated by novel imaging techniques such as positron emission tomography using radiolabelled florbetapir [12]. 99m-Technetium-labelled pyrophosphate scanning (myocardial radiotracer uptake on bone scintigraphy) was recently demonstrated to diagnose cardiac ATTR amyloidosis reliably [13].

The primary limitation of the current study is the retrospective design. This study was restricted to amyloidosis patients who underwent autopsy with associated selection bias and limitations. Because autopsy is more likely to be performed in patients with unclear cause of death, our results may underestimate the frequency of clinically overt causes of deaths, *e.g.* renal failure, while overestimating that of clinically occult forms of involvement, *e.g.* sudden cardiac deaths related to undiagnosed cardiac amyloidosis.

In conclusion, we observed cardiac disease as the most common immediate cause of death in patients with pulmonary amyloidosis confirmed at autopsy. Pulmonary alveolar septal and vascular involvement was prevalent in all types of amyloidosis but pulmonary involvement was not suspected clinically and not the immediate cause of death in most of these patients.

Kamonpun Ussavarungsi[1], Eunhee S. Yi[2], Joseph J. Maleszewski[2], Paul J. Kurtin[3], Surenda Dasari[4], Jason D. Theis[3], Angela Dispenzieri[5] and Jay H. Ryu[1]
[1]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA. [2]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA. [3]Division of Hematopathology, Mayo Clinic, Rochester, MN, USA. [4]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. [5]Division of Hematology, Mayo Clinic, Rochester, MN, USA.

Correspondence: Kamonpun Ussavarungsi, Division of Pulmonary and Critical Care Medicine, Gonda 18 South, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA. E-mail: kamonpun@live.com

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