



## Review

## Pulmonary AL amyloidosis: A review and update on treatment options

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## ABSTRACT

Amyloidosis is a rare disease that involves the extracellular deposition of abnormally folded proteins, precipitating organ dysfunction. Pulmonary amyloidosis is frequently characterized by the AL amyloid subtype and can be localized or associated with systemic involvement, presenting in a nodular, diffuse alveolar-septal, or tracheobronchial pattern. Presentation of disease can vary from clinically silent to severe. Pulmonary amyloidosis is typically first suspected on CT scan of the chest. Diagnostic workup requires tissue biopsy and identification by immunohistochemical staining. Systemic treatment has evolved over recent years to include the combination of daratumumab, bortezomib, cyclophosphamide, and dexamethasone (dara-VCD) as first-line therapy, with the goal of quickly attaining complete hematologic response. Through clinical vignettes, we review pulmonary AL amyloidosis and discuss current treatment options.

## 1. Introduction

Amyloidosis is a disease wherein proteins are abnormally deposited into extracellular tissue, leading to disruption of existing structures and manifesting in a variety of clinical presentations depending on the organ involved. They lead to progressive malfunction and potential failure of the affected structure [1]. Mortality is often attributed to cardiac involvement [1]. Amyloidosis can be classified based on quantity, type, and location of these proteins. Disease may be systemic or localized [2]. The most common types of amyloidosis are systemic AL (primary), systemic AA (secondary), systemic wild-type ATTR (senile), systemic hereditary ATTR (familial amyloid polyneuropathy), and localized AL [2]. AL amyloidosis is a plasma cell proliferative disorder, and may be associated with an underlying monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, or another plasma cell dyscrasia [1,2]. It involves the deposition of an excess amount of protein light chains that arrange in beta-pleated sheets forming organized fibrils [2,3]. Systemic AA amyloidosis occurs in patients with chronic inflammatory conditions, such as rheumatoid arthritis or inflammatory bowel disease, and involves the deposition of inflammatory protein serum amyloid A [2]. Systemic wild-type ATTR and systemic hereditary ATTR are age-related or familial, respectively, and involve the deposition of

transthyretin protein [2]. Locations that can be affected by amyloidosis include the kidneys, heart, nerves, liver, spleen, gastrointestinal tract, skin, lungs, and joints; however, this is by no means an exhaustive list. For diagnosis, a tissue sample is required for histologic evaluation. Treatment options are based on the type of amyloidosis and the patient's functional status.

AL amyloidosis is a rare disease with an annual incidence of 4000 cases per year in the United States and an increasing prevalence [4,5]. In the lung, there are three predominant types of amyloidosis which are classified by location: nodular, diffuse alveolar-septal, and tracheobronchial [2,6]. Each of these are commonly comprised of AL amyloid [2,6]. For pulmonary amyloidosis, bronchoscopy with biopsy is the mainstay of diagnosis [7]. Subtypes of amyloidosis are identified using immunohistochemistry staining [2,6]. Classically, when using Congo red stain, amyloid displays apple-green birefringence under polarized light [2,6]. Crystal violet and thioflavin-T fluorescence staining may also aid in identifying amyloid [8]. Additionally, mass spectrometry can be used for subtyping and has been noted to have a higher sensitivity and specificity [2,6]. Serum immunofixation and protein electrophoresis help in determining the type of underlying immunoglobulin light chain responsible for disease, and furthermore, for monitoring treatment response [7]. Bone marrow biopsy may be used as well to further

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differentiate between kappa and lambda light chain immunoglobulins. Computed tomography (CT) imaging is useful for establishing the extent of disease and for monitoring progression after diagnosis [3]. As AL amyloidosis is considered a type of plasma cell dyscrasia, treatment has historically been based off of chemotherapies used for multiple myeloma [1]. While societal costs have been reported on the impact of hereditary transthyretin amyloidosis polyneuropathy, the impact of primary amyloidosis, and more specifically pulmonary amyloidosis, have not been examined [9,10].

The objective of this review is to focus on pulmonary AL amyloidosis and the treatment options that are currently available. It appears that the last comprehensive review of pulmonary amyloidosis was completed over a decade ago and several therapeutic advancements have since been made. We will present three illustrative cases seen in our clinic as examples of pulmonary amyloidosis and their treatment approaches.

## 2. Case presentations

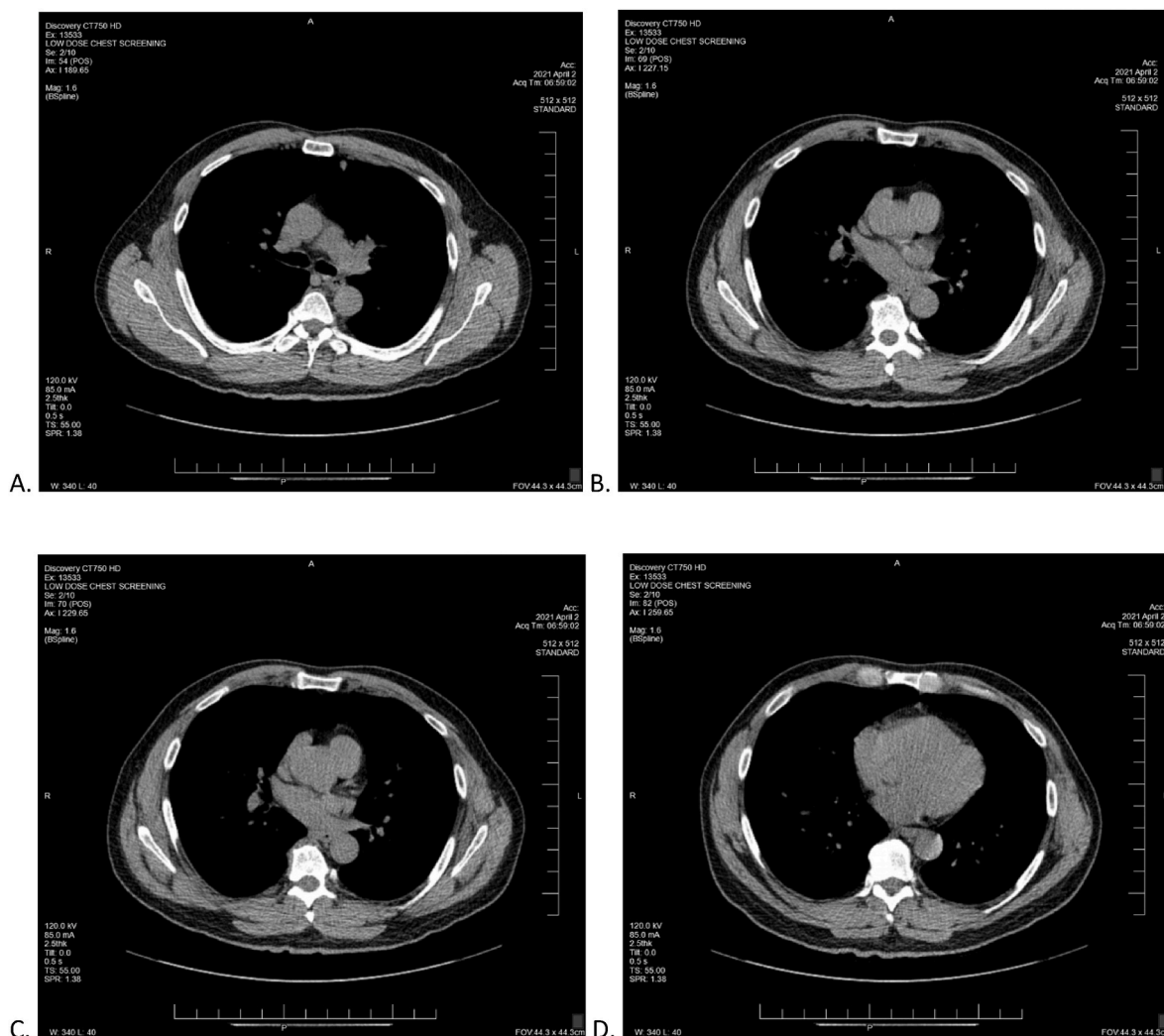
### 2.1. Nodular amyloidosis

A 57-year-old male with a past medical history of tobacco use presented in March 2021 for a routine physical exam without pulmonary complaints. Due to his smoking history, he was referred for lung cancer screening with low dose CT scan, which revealed a left upper lobe

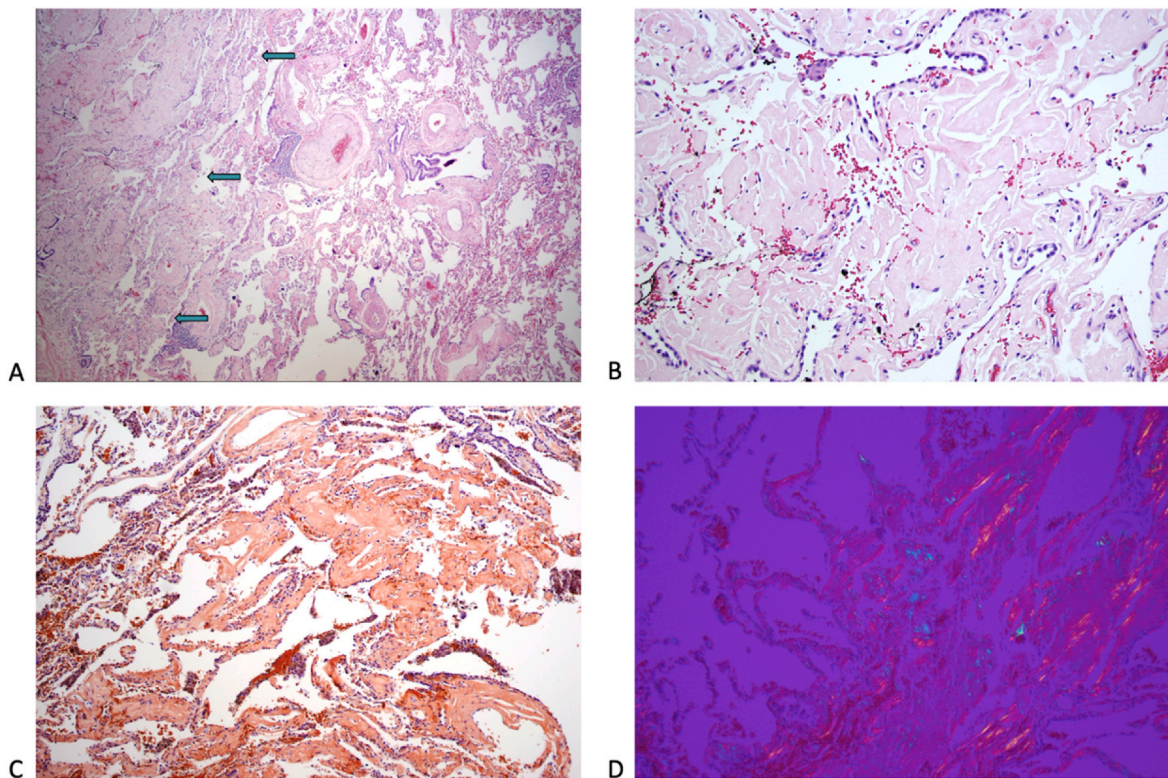
nodule measuring 1.3 cm (cm) in size and other small nodules in the right middle lobe (Fig. 1). He underwent additional imaging to further evaluate these findings. Positron emission tomography-computed tomography (PET/CT) scan demonstrated a  $0.8 \times 0.7$  cm faintly fluoro-deoxyglucose (FDG) avid nodule (standardized uptake value [SUV] 1.28) in the left upper lobe, a  $0.4 \times 0.41$  cm right middle lobe nodule (SUV 0.52), and a few mildly FDG avid lymph nodes in the right axilla which were presumed to be reactive or inflammatory.

The patient was referred to a thoracic surgeon who discussed options of a CT-guided biopsy versus primary surgical resection. At the conclusion of the consultation, the patient elected to have the pulmonary nodule resected. Left upper lobe wedge resection was done in May 2021 and subsequent pathology revealed a nodular amyloidoma with calcification and cystic changes (Fig. 2). Immunostaining for kappa and lambda light chains was equivocal. The specimen was sent to Cleveland Clinic for subtyping which confirmed AL amyloidosis. The patient's serum plasma cell profile and protein electrophoresis were essentially normal.

Based on these studies, he was diagnosed with localized AL amyloid, consistent with nodular pulmonary amyloidosis. A follow up chest CT performed in January 2022 demonstrated no new or recurrent pulmonary nodules. The patient remains asymptomatic and has quit smoking since the left upper lobe resection. He will undergo surveillance CT scans every six months.



**Fig. 1.** Initial CT scan of the chest from March 2021. (A) Slightly irregular left upper lobe pulmonary nodule measuring 1.3 cm (B, C, D) Three 0.5 cm subpleural nodules in the right middle lobe which are likely intrapulmonary lymph nodes.



**Fig. 2.** Histopathology of nodular amyloidosis. (A) Left upper lobe wedge: the right side shows preserved lung parenchyma; the left side shows abnormal deposition of homogenous acellular eosinophilic material within the lung parenchyma (green arrows). (B) Deposition of amorphous acellular pale eosinophilic material. (C) Congo red showing positive bright brick staining. (D) Congo red stain showing apple green birefringence under polarized light. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

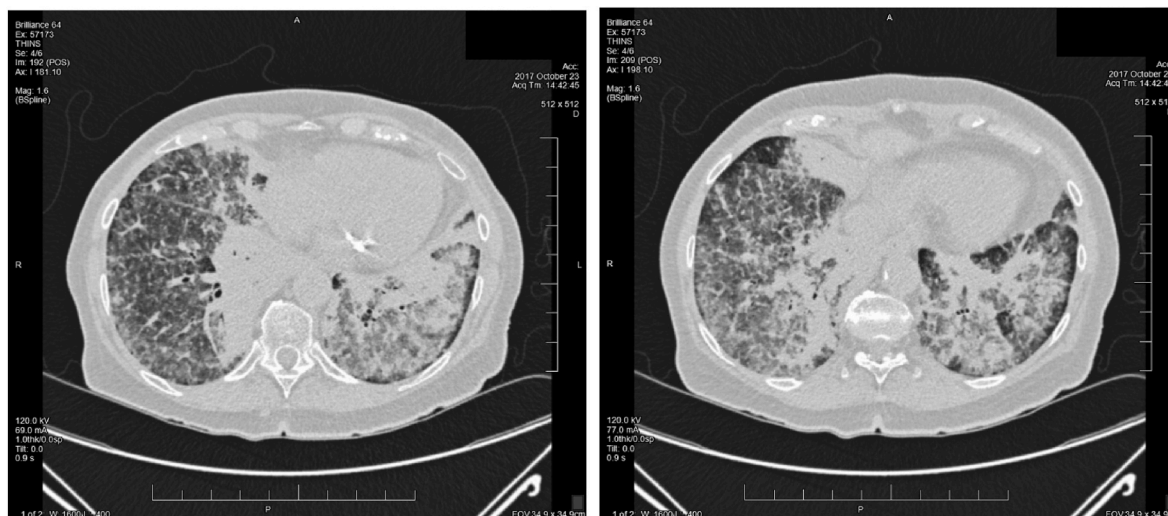
**2.2. Diffuse alveolar-septal amyloidosis**

A 75-year-old female presented in September 2017 for progressive shortness of breath with minimal exertion. She had a past medical history significant for cystic-bullous disease of the lung, breast cancer status post lumpectomy, cervical cancer status post hysterectomy, and a smoking history of greater than 50 pack years. She underwent CT scan of the chest that revealed chronic-appearing nonspecific diffuse interstitial opacities (Fig. 3).

The patient was referred to a pulmonologist who diagnosed AL

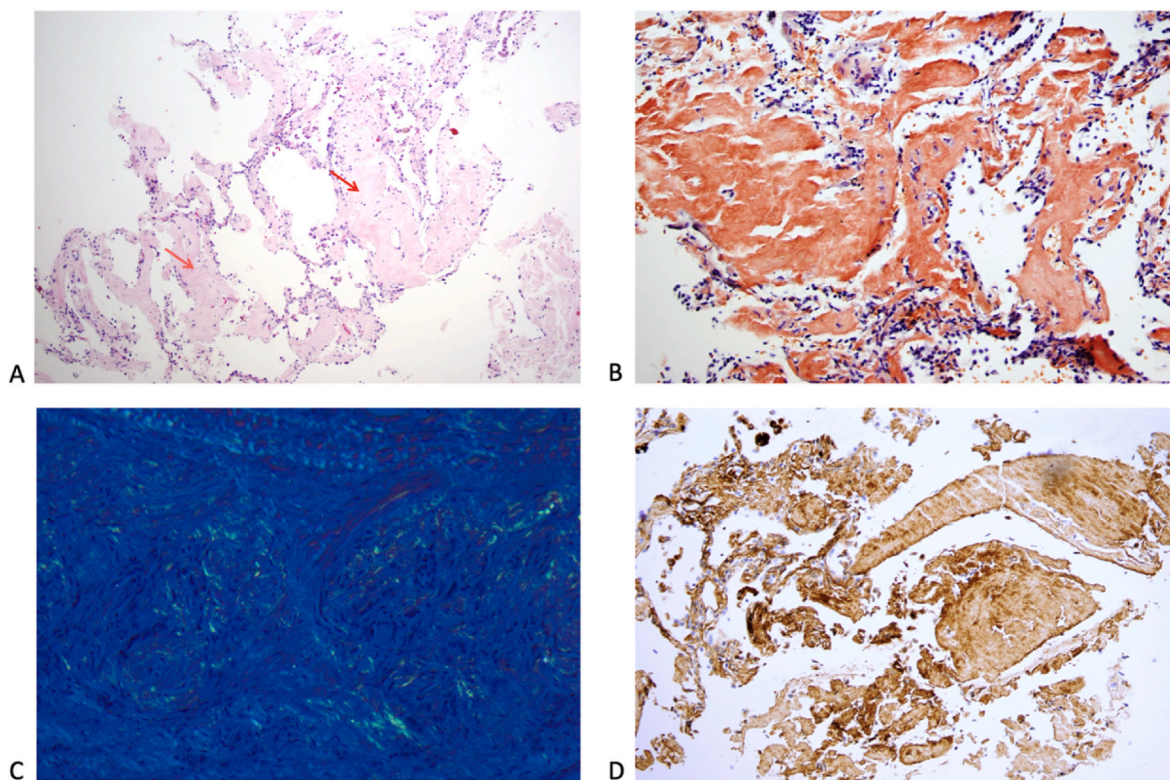
amyloidosis from lung biopsy. The pathology showed interstitial and vascular amyloid deposits (Fig. 4). Serum immunofixation showed a normal free kappa light chain (0.78 mg/dL) and an elevated free lambda light chain (39.5 mg/dL).

She received systemic therapy with cyclophosphamide, bortezomib, and dexamethasone (CyBorD). Following her second cycle of CyBorD, the patient only had intermittent shortness of breath and was able to climb a flight of stairs without issue. A significant decrease in serum free lambda light chains was also documented (1.36 mg/dL). Her treatment course was complicated by several congestive heart failure



**Fig. 3.** Initial chest CT from October 2017. Imaging shows diffuse interstitial and airspace opacities appearing in a nonspecific pattern that can be seen with chronic lung diseases.





**Fig. 4.** Histopathology of diffuse alveolar-septal amyloidosis. (A) Fragment of lung parenchyma showing abnormal amorphous material deposition (red arrows). (B) Abnormal material stain positive with Congo red. (C) Congo red stain showing apple green birefringence under polarized light. (D) Kappa immunohistochemical staining. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exacerbations, shingles, influenza, and bacterial pneumonia. However, she completed six cycles of CyBorD and has been in complete remission for over four years as evidenced by clinical improvement of symptoms, subsequent CT scans of the chest for other indications, and surveillance bloodwork.

### 2.3. Tracheobronchial amyloidosis

A 72-year-old female presented in November 2011 with complaints of a persistent dry cough that started two years prior. She had seen multiple specialists including otolaryngology, allergy & immunology, and pulmonology. Chest CT showed diffuse tracheal wall thickening

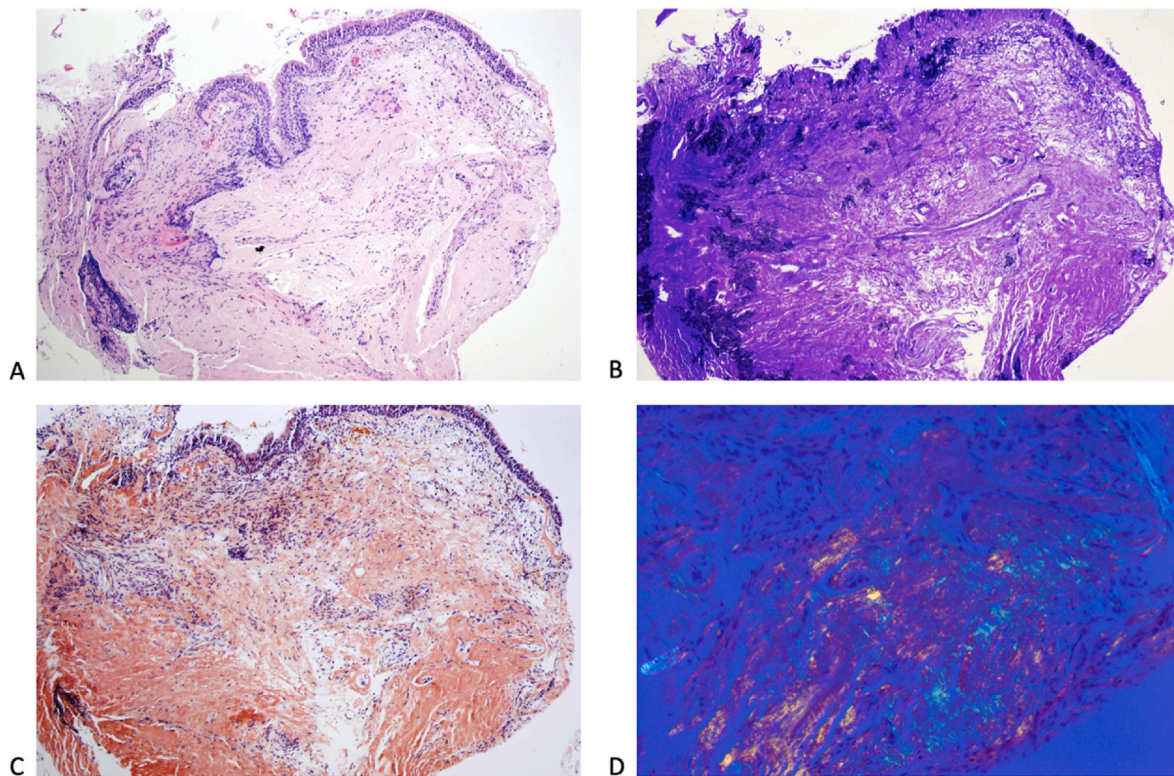
(Fig. 5). Her pulmonologist initially suspected the etiology of her cough to be multifactorial, possibly due to reactive airway disease and gastroesophageal reflux disease. She underwent a repeat CT scan of the chest in February 2014 that confirmed unchanged tracheal wall thickening and she subsequently had a bronchoscopy for further investigation.

The biopsies of the trachea and bronchus intermedius revealed interstitial amyloid deposition (Fig. 6). The biopsy specimens were sent to Cleveland Clinic for further subtyping, where liquid chromatography with tandem mass spectrometry (LC-MS) showed predominantly kappa immunoglobulin light chains. Her initial serum immunofixation showed an elevated free kappa light chain (2.63 mg/dL) and a normal free



**Fig. 5.** Chest CT from (A) November 2011 and (B) February 2014. Imaging shows stable diffuse tracheal wall thickening.





**Fig. 6.** Histopathology of tracheobronchial amyloidosis. (A) Fragment of bronchial mucosa showing abnormal homogenous acellular material deposition. (B) Abnormal material stain positive with Crystal violet. (C) Abnormal material stain positive with Congo red. (D) Congo red stain displaying apple green birefringence under polarized light. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

lambda light chain (0.69 mg/dL).

Bone marrow biopsy was performed and was negative for amyloid deposition. During this time, she also developed bilateral ptosis, which raised suspicion for systemic amyloidosis. Given these findings, she was started on CyBorD. After four cycles of treatment, she had a notable decrease in serum free kappa light chains (0.89 mg/dL). A repeat chest CT again showed no change in her tracheal thickening. The patient elected to stop chemotherapy at this time due to subjective symptomatic improvement. However, a few months later, she developed a worsening cough. CT scan of the chest in December 2014 showed a new 2.3 cm nodule and repeat biopsy confirmed amyloidosis. The recommendation was that she receive high dose melphalan and undergo autologous stem cell transplantation (ASCT). Her course was complicated by a subsegmental pulmonary embolism for which she had an inferior vena cava filter placed, delaying her transplant. Echocardiogram and cardiac magnetic resonance imaging (MRI) were negative for cardiac involvement. She eventually underwent ASCT with high dose melphalan induction therapy in 2015 without any major complications. Follow up bloodwork showed good hematologic response with a decrease in her serum free kappa light chains (0.31 mg/dL). She has remained disease free for the past seven years without cough or any evidence of AL amyloidosis.

### 3. Discussion

The three cases we presented are indicative of the ways pulmonary amyloidosis can manifest itself, from an asymptomatic incidental finding to a chronic respiratory malady. The lungs are commonly affected by AL amyloid, whether it be systemic or localized [2,6]. Nodular amyloidosis typically responds well to simple excision [6]. Diffuse alveolar-septal and tracheobronchial amyloidosis require a systemic approach [6]. Of note, in some cases of tracheobronchial amyloidosis, wherein disease is localized and nonprogressive, systemic

treatment may be avoided and debridement or radiation may be an option [6]. The aim of systemic treatment is to rapidly reach complete hematologic response in order to enhance survival [1,7]. Complete hematologic response is often defined as the absence of monoclonal protein and a normal free light chain ratio on protein electrophoresis and immunofixation [7]. If the patient has refractory disease, other therapies should be considered.

Historically, due to the rarity of amyloidosis, it had been difficult to perform randomized controlled trials. Therefore, therapies were modeled after treatment algorithms for multiple myeloma [1]. Initially, patients were treated with melphalan, an alkylating agent that disrupts DNA synthesis, and dexamethasone (MDex) [1,7]. Then, bortezomib, a proteasome inhibitor, was introduced as a possible treatment option due to its success as a treatment for myeloma [1]. A phase III, randomized, open-label trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT01277016) conducted between January 2011 to February 2016 showed a better hematologic response and overall survival rate using bortezomib, melphalan, and dexamethasone (BMDex) as compared to MDex [11]. However, there were notable adverse effects including cytopenia, neuropathy, and heart failure [11]. For some time, the treatment of choice was CyBorD, which uses a different alkylating agent, cyclophosphamide, in place of melphalan [1,7,12,13]. CyBorD is what our diffuse alveolar-septal and tracheobronchial patients received.

Since then, new treatment recommendations have been proposed. The current recommendation is that CyBorD be administered with daratumumab (dara-VCD) as first-line therapy due to its efficacy in producing rapid and profound hematologic responses [1,7,14]. Daratumumab is a human monoclonal antibody targeting CD38, a glycoprotein that is abundant on malignant plasma cells, such as those involved in AL amyloidosis [1,7,14]. The ANDROMEDA trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT03201965), a phase III, randomized, open-label trial conducted May 2018 to August 2019, found that treatment with dara-VCD induced a greater number of complete hematologic responses

as compared to treatment with CyBorD in a shorter median time frame [14]. Additionally, the group of patients that received dara-VCD experienced less disease progression as evidenced by surveillance of bloodwork and major organ damage [14]. Treatment with dara-VCD is currently recommended for at least three cycles [1]. If there is an inadequate response at the end of three cycles, the treatment plan should be reassessed [1]. As in the case of our tracheobronchial amyloidosis patient, the next step may be to undergo ASCT. However, this involves the use of high dose melphalan. Depending on patients' functional status and medical comorbidities, this may or may not be a suitable option. If patients are ineligible for ASCT, treatment with second-generation selective proteasome inhibitors, such as carfilzomib and ixazomib, are promising next-line options [1]. Or, depending on patients' overall clinical status, a palliative approach may be more appropriate. Fig. 7 depicts a treatment algorithm for pulmonary amyloidosis.

Despite its rarity, there is a substantial amount of research currently underway regarding therapy for AL amyloidosis. There is an ongoing phase II, open-label trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT04131309) exploring daratumumab monotherapy in stage 3B AL amyloidosis patients [15]. These patients have cardiac involvement and a poor prognosis [15]. If this trial supports the use of daratumumab monotherapy, it would be worthwhile to investigate its efficacy in patients with predominantly pulmonary amyloidosis. Other anti-CD38 medications are also being explored, such as isatuximab [1]. Targeted therapies against amyloid fibrils, like Cael-101, are being examined as well [1,7]. It will be interesting to see what therapeutic advancements will be made in the next decade.

#### 4. Conclusion

Pulmonary amyloidosis is a rare disorder that has the potential to cause significant morbidity and mortality. It is essential to accurately diagnose and properly treat the disease. The current standard therapy for nodular amyloidosis is surgical removal. For diffuse alveolar-septal and tracheobronchial amyloidosis, the standard of care is systemic treatment with dara-VCD. The focus of treatment is to produce a

complete and rapid hematologic response. As mentioned previously, this is the first comprehensive review of pulmonary amyloidosis completed in over ten years. Though uncommon, amyloidosis is a recognized disease for which there is a burgeoning field of research.

#### Ethical approval

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#### Author contribution

All authors had access to the data and a role in writing the manuscript.

#### Please state any conflicts of interest

There are no actual or potential conflicts of interest in relation to this manuscript. There are no relationships with industry.

#### Registration of research studies

Not applicable to this manuscript.

#### Guarantor

All authors are guarantors of this manuscript.

#### Consent

Not applicable to this manuscript.

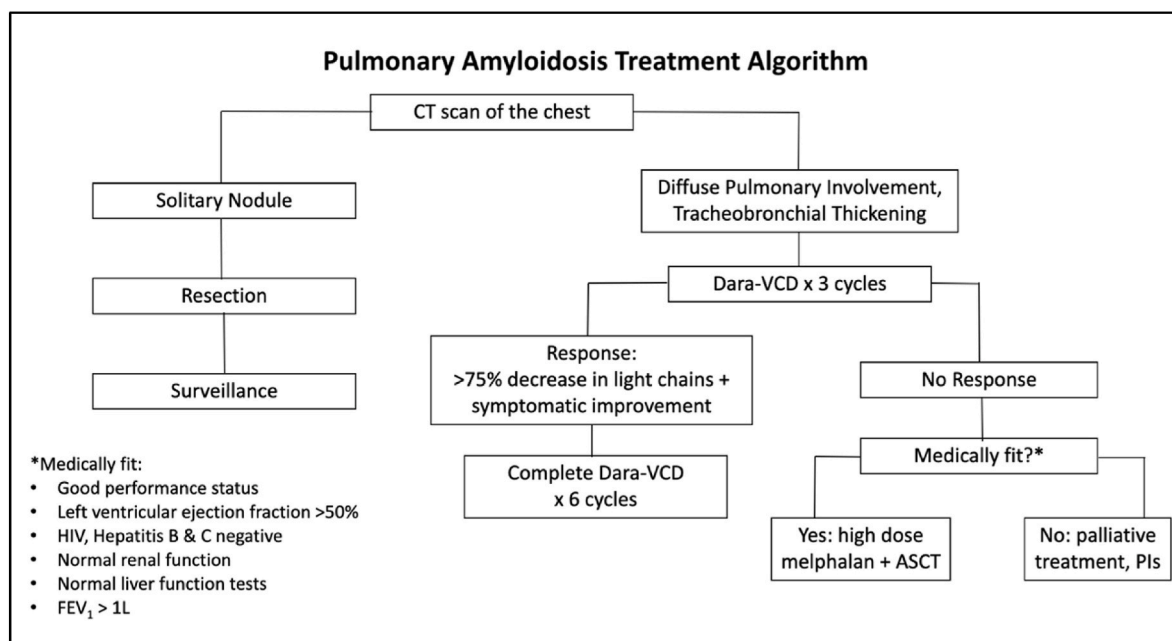


Fig. 7. Treatment strategy for pulmonary amyloidosis. Management begins with classifying the type of pulmonary amyloidosis that is present. CT scan findings of a solitary nodule are suggestive of nodular amyloidosis. Treatment is resection and surveillance. CT scan findings of diffuse or tracheobronchial disease are suggestive of diffuse alveolar-septal or tracheobronchial amyloidosis. Initial treatment is systemic with dara-VCD for 3 cycles. If patients display >75% decrease in serum light chains and have symptomatic improvement, dara-VCD is continued for 6 total cycles. If patients display a less robust response, ASCT with melphalan induction therapy may be an option. If patients are not considered medically fit, proteasome inhibitors or a palliative approach may be pursued.



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## Access to data

All authors had access to the data and a role in writing the manuscript.

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