Effective Radiation Therapy for Isolated Apical Pulmonary Amyloidoma: A Case Report and Treatment Insight

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Patient: Male, 68-year-old
Final Diagnosis: Amyloidoma
Symptoms: Shortness of breath
Clinical Procedure: —
Specialty: Pulmonology

Objective: Rare disease
Background: Amyloidosis refers to an assortment of diseases characterized by the accumulation and deposition of misfolded proteins in the extracellular matrix of tissues and organs. It may present systemically, affecting multiple organs, or locally by affecting a single organ. When the lungs or mediastinal structures are involved, the term pulmonary amyloid is used. Sole pulmonary involvement with amyloid is extremely rare. There is no definitive treatment for this disease, but proposed treatment options include surgery, cytotoxic medications, and external beam radiation therapy (EBRT).

Case Report: A 68-year-old man with a left apical lung mass presented with subacute shortness of breath. Comprehensive evaluation of the patient’s symptoms and findings, including infectious and oncologic evaluation, were performed. Infectious evaluation revealed positive acid-fast bacilli sputum cultures with *Mycobacterium chimerea intracellulare*. Biopsy of the mass revealed a Lambda restricted amyloidoma, which is usually seen in lymphoproliferative diseases and disorders. Bone marrow biopsy did not reveal any monoclonal cell lines or neoplasms. Abdominal fat pad biopsy was performed to rule out systemic amyloid and the results were negative. The diagnosis of isolated apical pulmonary amyloidoma was made. EBRT was performed over 12 fractions in 24 mGy, with improvement in the patient’s symptoms.

Conclusions: The diagnosis of pulmonary amyloid necessitates comprehensive evaluation. There is no specific treatment for pulmonary amyloid; however, there has been success with surgical intervention, cytotoxic medications, and EBRT. Successful treatment of the amyloidoma is based on its anatomic location. We suggest EBRT in fractionated doses for optimal treatment of rare isolated apical pulmonary amyloidoma.

Keywords: Amyloidosis • Hematology • Pulmonary Medicine • Radiotherapy

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Introduction
Amyloidosis refers to an assortment of rare diseases characterized by the accumulation and deposition of misfolded proteins in the extracellular matrix of tissues and organs. The identity of the abnormal protein determines its classification. It may present systemically, affecting multiple organs throughout the body, or locally by affecting a single organ. The most common types of amyloid diseases are systemic amyloidosis, including light-chain amyloidosis (primary AL), hereditary or mutated transthyretin amyloidosis (ATTRmt), and wild-type transthyretin amyloidosis (ATTRwt), followed by less common systemic amyloidoses, including reactive (AA) amyloidosis and B2-microglobulin amyloidosis (AB2M) [1]. Each subtype has a predilection for specific tissues and organs.

When the lungs or mediastinal structures are involved, the term pulmonary amyloid is used. The characterization is further divided by the anatomic involvement, including laryngeal, alveolar-septal/parenchymal, tracheal-bronchial, and nodular [2]. Pulmonary amyloidosis can present asymptptomatically or as dyspnea with or without extrapulmonary symptoms. Sole pulmonary involvement with amyloid is extremely rare. It is sometimes secondary to an underlying hematologic process [2]. When a thorough diagnostic evaluation yields no identifiable origin of the amyloid, isolated pulmonary amyloidosis is the resulting diagnosis [3]. There are few reported occurrences in the general population, and these rare cases have been treated with a variety of therapies as there are no professional guidelines to assist physicians in managing this condition. Proposed treatments include surgery, cytotoxic medications, and external beam radiation therapy (EBRT). We present a case of isolated apical pulmonary amyloidoma and discuss the benefit of EBRT over other options in the treatment of pulmonary amyloidosis.

Case Report
A 68-year-old man with a past medical history of hypertension initially presented to an outside hospital with pleuritic chest pain, dyspnea, and cough. Initial evaluation revealed a left apical lung mass. The patient was transferred to our institution for a higher level of care. On presentation, he was afebrile, normotensive, and had a normal pulse rate that was regular in rhythm. The chest X-ray (CXR) demonstrated the mass and a moderate left-sided pleural effusion (Figure 1). Pulmonary exam revealed decreased breath sounds throughout the left lung field and dullness to percussion in the left posterior thorax. An electrocardiogram (EKG) revealed nonspecific T wave inversions in the anterior and lateral leads (Figure 2). CT thorax with contrast was performed, which revealed a posterior left upper-lobe heterogeneous mass with cystic features and coarse calcifications (Figure 3A, 3B). The mass measured 6×7 cm in the coronal plane (Figure 3C, 3D). These findings were concerning for infectious or malignant processes.

Infectious evaluation included acid-fast bacilli (AFB) sputum cultures, *Mycobacterium tuberculosis* (MTB) PCR, and QuantiFERON gold assay, as well as inflammatory markers, C-reactive protein (CRP), and procalcitonin. The CRP level was 0.8 mg/dL (normal <0.8 mg/dL) and procalcitonin was 0.2 ng/mL (normal <0.07 ng/mL). A diagnostic thoracentesis of the pleural fluid yielded an exudative effusion that grew *Haemophilus influenzae*. Initial analysis revealed a negative MTB PCR, but a positive QuantiFERON gold blood assay. Cytopathology evaluation of the pleural fluid revealed no malignant cells. A CT-guided biopsy of the mass was performed to evaluate for a potential underlying malignancy. While the infectious work-up was pending, the patient was isolated with airborne precautions and started on empiric therapy for suspected active MTB. Appropriate antimicrobials were also started to treat the underlying pneumonia.

Biopsy results of the mass revealed necrosis and inflammatory cells in the background of amorphous, waxy, and eosinophilic deposition that was positive with Congo red staining and negative with AFB staining. Additionally, significant focal lymphoplasmacytic infiltration that was Lambda restricted was visualized in the histological specimen, suggesting lymphoma, plasmacytoma, amyloidoma, or underlying hematologic malignancy. Given the biopsy findings and absence of AFB on stains, empiric MTB treatment was discontinued, and the patient was transitioned to latent MTB treatment.
Further oncologic evaluation was pursued, which revealed a normal Kappa-to-Lambda ratio, as well as a nonspecific serum and urine protein electrophoresis with no M spike. Bone marrow biopsy did not reveal any monoclonal plasma cell populations nor any immunophenotypic findings of lymphoproliferative neoplasms. Malignancy evaluation was negative.

Amyloid was present in the lung. Evaluation for primary amyloidosis (AL) was negative, as was the malignancy and infectious evaluation. An abdominal fat pad biopsy was performed to evaluate for systemic amyloid and yielded negative results. The lack of other findings supported the diagnosis of isolated pulmonary amyloidoma.

The patient had cardiac evaluation for dyspnea and chest pain via a transthoracic echocardiogram, which showed heart failure with reduced ejection fraction (HFrEF) with moderate diastolic dysfunction. Coronary angiography revealed non-ischemic cardiomyopathy (NICM). Endomyocardial biopsy and bone scintigraphy were considered; however, given the lack of echocardiographic and electrophysiographic features of cardiac amyloid, this procedure was deferred.

Treatment options considered were surgical intervention versus EBRT. Pulmonary function testing (PFTs) revealed normal spirometry and lung volumes. Thoracic Surgery deemed the patient to be at high risk for postoperative morbidity and mortality given his underlying HFrEF. Therefore, with the assistance of Radiation Oncology, palliative EBRT was pursued.

At initiation of EBRT, AFB sputum cultures from 6 weeks prior (2 of 3 specimens) ultimately grew *Mycobacterium chimerea intracellulare*. The patient began appropriate antimicrobial therapy. Seven weeks after initial presentation, he received radiation therapy with 24 Gy given over 12 fractions with no complications. The patient was discharged on an antimicrobial regimen for his MAC infection as well as a follow-up CT thorax to assess the resolution of the isolated apical pulmonary amyloidoma. At 4-month follow-up, the patient reported mild improvement in his shortness of breath, but had ongoing fatigue with minimal activity. At 10-month follow-up, his shortness of breath and fatigue had resolved, as he was able to ambulate farther without the need for intermittent rest. Furthermore, he did not have hemoptysis, cough, or gastroesophageal symptoms at follow-up to suggest EBRT complications. Radiographic response to treatment was not able to be assessed due to loss of follow-up for CT thorax evaluation after treatment. However, it is important to highlight the

**Figure 2.** Electrocardiogram obtained on presentation. As shown by the rhythm strips, the patient had a normal sinus rhythm and normal rate. It is important to note the good R wave progression in the precordial leads as well as the normal amplitude of the QRS complexes. The dark black arrows in leads V3, V4, V5, and V6 represent the nonspecific T wave inversions that were visualized upon presentation.
patient’s profound improvement in functional capacity and resolution of symptoms at 10-month follow-up.

**Discussion**

Given the various manifestations of amyloid, the diagnosis and management are challenging. Classification of pulmonary amyloid reflects anatomic involvement. Our patient’s amyloidoma involved the left upper lobe without encasement of surrounding structures. Despite a thorough literature review, to the best of our knowledge, this is the first report of isolated apical pulmonary amyloidoma.

Cytopathology revealed amyloid with lymphocytic infiltrate, suggestive of AL amyloid. However, tests for neoplasms were negative and were confirmed via bone marrow biopsy; AL amyloid was ruled-out. Fat pad biopsy did not confirm systemic amyloid; thus, a diagnosis of isolated pulmonary amyloidoma was made. After diagnosis, treatment considerations include clinical significance, functional capacity, prognosis, and comorbidities. Although we considered surgery or cytotoxic medications as options for treatment, EBRT is safer and non-inferior to alternative therapies [4].

The most prevalent type of amyloidosis is systemic AL amyloid, which most commonly affects the heart and kidneys. In contrast, localized light-chain amyloid deposition represents 7-12% of all amyloidosis and may occur in any organ; however, respiratory, skin and soft tissue, gastrointestinal, and urinary system involvement are most common [5,6]. Literature review identified patients across the world with local light-chain amyloidoma with respiratory tract involvement noted to be 52% of cases [5]. The frequency of respiratory tract amyloidoma includes involvement of the lung (59%), nasopharynx (58%), larynx (45%), and lower airways (45%) [5]. Our literature review found no randomized controlled trials, as this presentation is rare. Isolated pulmonary amyloidoma, as in this case, with no AL amyloid identified is even rarer. Cases similar to our patient’s presentation describe negative infectious, oncologic, and cardiac workups [1,2].

In patients with local respiratory tract amyloidomas, local progression is noted to occur in 29% of cases, with local

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**Figure 3. Axial and coronal views of the CT thorax with contrast obtained on presentation.** Panel A shows the axial section of the thorax and visualization of the heterogeneous composition of the posterior left upper lobe mass while visualized in the abdominal window. Panel B shows the same image as panel A, but in the bone window. Panel C shows the CT thorax findings in the coronal view and abdominal window. Panel D shows the same image as panel C, but in the bone window. Thick black arrows in all panels point to the necrotic left apical mass. Blue stars in panels C and D indicate the left pleural effusion that was visualized. Additionally, a moderate pleural effusion was noted in the right lung field. CT – computed tomography.
progression-free survival (PFS) of about 90% at 1 year and 66% at 5 years and median overall survival (OS) of 79% at 5 years. Moreover, in symptomatic and asymptomatic patients who responded to treatment, local PFS was greater and there was no significant difference in local PFS observed among treatment strategies [5]. Therapeutic modalities include radiotherapy with or without surgical removal, or systemic therapy with cytotoxic medications such as cyclophosphamide and melphalan. Overall, treatment results in improvement or stability of the disease in 75% and 24% of cases, respectively. Not all patients are optimal surgical candidates; therefore, other modalities such as EBRT in multiple fractions are offered.

Treatment selection depends on the subtype of amyloid present. This is vital, as specific types of amyloid have better outcomes with different treatment options. Specifically, AL amyloid responds more robustly to systemic therapies and stem cell therapies. On the other hand, AA amyloid requires treatment of the underlying inflammatory etiology. In a patient with an isolated pulmonary amyloidoma, surgical resection, cytotoxic medications, or EBRT may be considered.

Surgical intervention requires identifying the pathology and selecting optimal surgical candidates. Localized amyloid and endotracheal/endobronchial amyloid are generally amenable to surgical intervention and have an excellent prognosis [7]; this approach was suggested due to their local occurrence as compared to the other subtypes of pulmonary amyloid [1]. Additionally, reports of endoscopic surgical removal of laryngeal and tracheal-bronchial amyloid have been published [2]. Lastly, surgery has been proposed as the optimal treatment modality for pulmonary amyloid that comprises a majority of a lobar section [3]. Patients with multiple comorbidities that predispose them to high surgical morbidity and mortality may not be ideal surgical candidates. Clinical assessment is needed to determine the patient’s likelihood of surgical mortality. Factors to consider before surgery include the potential mass effect of the amyloidoma, spirometry to assess ventilatory reserve, patient age and comorbidities, and other clinical factors.

CT imaging is an important component of the surgical approach as it provides orientation of the mass with respect to other structures in the thoracic cavity. A cohort study that assessed respiratory tract amyloidoma and their association with CT findings found that local parenchymal amyloid and nodular amyloid with ≥10 nodules had a higher frequency of mass-like lesions on CT compared to tracheal-bronchial amyloid – 41% vs 0%, P=0.002 and 56% vs 0%, P<0.001, respectively [8]. Tracheal-bronchial amyloid had bronchial wall thickening and tracheal calcifications compared to parenchymal amyloid – 100% vs 0%, P<0.001 and 100% vs 27%, P<0.001, respectively [8]. Overall, these features can aid clinicians in determining the ideal treatment for these patients.

In a case described by Kapoor et al [9], an isolated pulmonary amyloidoma was identified; EBRT was used rather than surgery due to encasement of the pulmonary artery by the amyloidoma. In our patient, the amyloidoma was isolated and had no impact on surrounding vasculature, nerves, or airways. His spirometry and lung volumes were normal. Thoracic Surgery was part of the multi-disciplinary assessment of the patient and suggested that the patient was not an optimal surgical candidate as his HFrEF put him at a high risk of surgical complications.

Systemic cytotoxic medications have shown to have good outcomes in patients with AL amyloid as well as diffuse pulmonary amyloid. Specifically, patients with alveolar-septal or parenchymal pulmonary amyloid have had complete remission with cyclophosphamide, bortezomib, and dexamethasone (CyBoR) after a few years [7]. Other treatment options suggested by the literature include melphalan, an alkylating agent. In a case series by Moy et al [7], a patient with tracheal-bronchial pulmonary amyloid initially underwent CyBoR therapy; however, this treatment was stopped due to symptomatic improvement. After a brief period of no treatment, the patient developed worsening symptoms and was found to have recurrence of tracheal-bronchial amyloid [7]. The patient had induction with melphalan as well as underwent autologous stem cell transplantation, with clinical success. It is important to note that in both situations, the patient’s initial oncologic work-up yielded positive results for either the Kappa-to-Lambda ratio or monoclonal spike on electrophoresis. In our patient, initiation of chemotherapy was deferred pending completion of oncology work-up and ultimately was not pursued due to his significant response to EBRT alone, localized pathology, limited evidence for additive benefit, and preference to avoid chemotherapy-related toxicities such as cardiac dysfunction and neutropenia.

EBRT was first used to treat pulmonary amyloid in 1998 [10]. Tracheal-bronchial pulmonary amyloid was initially treated with bronchoscopic laser debulking; however, this was shown to be ineffective as patients had worse pulmonary function as well as progression of symptoms [10]. The utilization of EBRT was initially approached with caution given the concern for potential adverse effects, such as esophagitis and pneumonitis. Many subsequent case series have shown the efficacy of EBRT as well as the low incidence of these reported adverse effects [11-13]. Time to symptomatic improvement varied in these cases as some patients had resolution of symptoms at 1 month after treatment, while others had resolution of their symptoms by 12 months. EBRT has been used for tracheal-bronchial pulmonary amyloid and parenchymal pulmonary amyloid, with significant reduction in the size of the mass and fewer adverse effects with the use of lower doses of radiation [4]. Ultimately, our patient received 24 Gy in 12 fractions, with profound improvement in his functional capacity and resolution of symptoms at 10 months after completing treatment.
This patient’s evaluation occurred over several weeks. Approximately 6 weeks after obtaining AFB sputum cultures, there was growth of *Mycobacterium chimaera intracellulare* in 2 of 3 specimens. *Mycobacterium chimaera intracellulare* belongs to the mycobacterium avium complex (MAC). The patient started an antibiotic regimen of azithromycin, ethambutol, and rifampin. After completion of EBRT, he was discharged with non-tuberculosis (NTB) Mycobacterium treatment. At the 4-month follow-up, he had slight improvement in his symptoms; however, by the 10-month follow-up his shortness of breath and exertional fatigue had resolved. Outpatient CT thorax imaging was ordered for reevaluation of the isolated apical pulmonary amyloidoma. MAC could have caused an inflammatory reaction leading to the amyloid; however, it is important to restate the negative AFB stain visualized upon histology of the biopsy of the mass. It is also important to illustrate the limitation of single-foci biopsy sampling and the potential for false negatives. Additionally, it is important to note that radiographic response to EBRT could not be assessed in our case and this is a limitation. Nonetheless, our patient had an isolated apical pulmonary amyloidoma and received EBRT given its risks and benefits as stated over other treatment modalities with significant improvement in symptoms at the 10-month follow-up.

Conclusions

A thorough work-up is essential in evaluating pulmonary amyloidoma. Despite reports in the literature suggesting surgery and cytotoxic medications for treatment, there is no standardized management for patients with pulmonary amyloidoma; thus, treatment should be individualized. We suggest EBRT in fractionated doses for treatment of rare isolated apical pulmonary amyloidoma, particularly in poor surgical candidates.

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