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Nodular Pulmonary Amyloidosis with Interstitial Lung Disease—Case Report and Literature Review

Efosa Imuetinyan[1], Irshad Soomro[2], Muhammad Hawari[1], Adnan Raza[1]

[1]Department of Thoracic Surgery, Nottingham University Hospital, Nottingham, UK
[2]Department of Pathology, Nottingham University Hospital, Nottingham, UK
Email: Efosa.imuetinyan@nuh.nhs.uk, Irshad.Soomro@nuh.nhs.uk, Mohammad.Hawari@nuh.nhs.uk, Adnan_Raza@hotmail.com

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Abstract

Amyloidosis is a rare spectrum of disease which involves deposition of misfolded extracellular proteins (amyloids) in various body organs leading to progressive organ dysfunction. Clinical presentation can be variable depending on the organ involved and type of protein. Amyloidosis can be classified based on quantity, type, and location of these proteins. Amyloid light-chain amyloidosis develops in the bone marrow, producing abnormal forms of light-chain proteins, which cannot be broken down. These proteins transform into amyloid fibrils and form amyloid deposits in different organs. Pulmonary amyloidosis is uncommonly diagnosed since it is rarely symptomatic. Diagnosis of pulmonary amyloidosis is usually made in the setting of systemic amyloidosis; however, it may present as localised pulmonary disease. Localized pulmonary Amyloidosis can present as nodular, cystic, or tracheobronchial amyloidosis. Depending on the degree of the interstitial involvement, it may affect alveolar gas exchange and cause respiratory symptoms. This is a case of a 47-year-old female with background history of interstitial lung disease presenting with progressive shortness of breath. Computed tomography scan revealed bilateral pulmonary nodules. The patient was referred to our thoracic surgery team with the suspicion of bronchogenic malignancy with metastasis. Diagnostic video assisted wedge resection was performed for this patient, and histology confirmed pulmonary amyloidosis of nodular type. Amyloid deposition simulates both inflammatory and neoplastic conditions. Definitive diagnosis requires biopsy confirmation therefore early detection and commencing the patient on appropriate treatment pathway may help in symptomatic relief and better outcome.

Keywords

Nodular Amyloidosis, Interstitial Lung Disease, Immunomodulatory Drugs

1. Introduction

Amyloidosis was first described in 1854 by Rudolph Virchow. It is a rare disease whereby abnormally folded proteins form amyloid fibrils which then accumulates in various organs leading to their dysfunction. Proteins usually fold into various shapes, which are vital to how they function. When abnormal shape accumulates, they are called amyloid fibrils or amyloid deposits.

Amyloidosis may be systemic or localised. In localised type, the amyloids are deposited in specific organs or tissue while systemic amyloidosis has various types depending on the type of amyloid protein that is produced. The most common types are:

(1) Primary amyloidosis—light chain (AL);

(2) Secondary amyloidosis—serum amyloid A (AA);

(3) Familial amyloidosis—Transthyretin amyloid (ATTR).

Light-chain (AL) amyloidosis is the most common type of systemic amyloidosis in the western world. In Europe, incidence ranges from 1/80,000 to 330,000 and prevalence between 1/17,000 and 50,000 [1]. Male to female ratio is 3:2. It begins in the plasma cells of the bone marrow where abnormal form of light chain proteins is produced. These proteins bind together and form amyloid fibrils and build up to form deposits in different organs [2]. It usually involves multiple organs but can affect one organ only. Symptoms related to the light-chain amyloidosis can vary, depending upon the organ involved however, patient can be asymptomatic. Generalised symptoms like fatigue, generalised weakness, weight loss, neuropathy, bruising and organ specific symptoms have been reported.

Clinical characteristics of different types of amyloidosis may be similar but treatment varies according to the type and pathogenic mechanism involved. In the lung, light chain (AL) Amyloidosis is of three different types: nodular pulmonary amyloidosis, diffuse alveolar septal amyloidosis and trachea-bronchial amyloidosis [3].

Treatment of AL amyloidosis is based to effectively control the condition, reducing the symptoms and improving the quality of life. Most of the treatment options are based on multiple myeloma therapy including steroids, proteasome inhibitors and immunomodulatory drugs. These drugs are often given in combination depending upon the symptoms, organ involved, general fitness and age of the patient. In selective cases stem cell transplantation is also considered.

2. Case Report

A 47-year-old female, presented with progressive shortness of breath on exertion and cough, which had gradually worsened since her diagnosis of interstitial lung

disease in 2016. She denies other symptoms such as fever, chest pain and haemoptysis. There was a background of previous exposure of the tuberculosis (TB) from one of her family members. There was no history of smoking. Physical examination showed reduced air entry at bases bilaterally, otherwise unremarkable. On investigations, her CT scan showed radiological findings of interstitial lung disease along with bilateral lung nodules with the largest nodule measuring 3cm in right middle lobe concerning for primary bronchogenic carcinoma with possible metastasis (**Figure 1**). Positron emission tomography (PET) scan revealed mild to moderately avid lung nodules with some activity in the sub-centimetre hilar and mediastinal lymph nodes. Her lung function test confirmed forced expiratory volume in the first second 1.13L (44% predicted), forced vital capacity 1.31 L (42% predicted), diffusing capacity of the lungs for carbon monoxide 45% predicted.

CT guided biopsy was planned due to suspicion of malignancy. Biopsy was attempted, but sample was insufficient to make a diagnosis, hence patient was referred for surgical biopsy. Patient underwent right video assisted (VATS) wedge resection of middle lobe nodule as a diagnostic procedure. Intra-operatively there were significant adhesions particularly around upper and lower lobe. After gentle dissection, mass was localised in the middle lobe and wedge resection performed. Additional biopsy was taken from another nodule in the apical segment of the lower lobe. Samples were sent for histology, which showed large nodular area of amorphous eosinophilic materials which stains positively with congo red (**Figure 2**) and shows apple green birefringence under polarising light, with equal number of kappa and lamda plasma cells consistent with amyloid. The background lungs show widening of the interstitium by a lymphoplasmatic cell infiltrate with scattered multinucleate giant cell, some of which contains cholesterol cleft and are centred on bronchioles. There was also focal interstitial fibrosis, smooth muscle hyperplasia and emphysematous changes. Further review of the sections shows focal neuroendocrine cell hyperplasia/tumourlet arising in a background of pulmonary fibrosis, which is most likely related to chronic interstitial lung disease. No evidence of malignancy, and Bone marrow biopsy using congo red staining showed no evidence of amyloidosis.

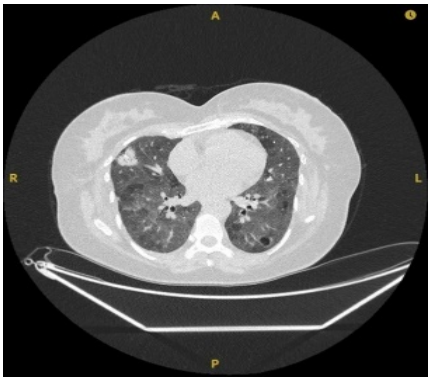

Figure 1. CT scan of the chest showing the mass in the right middle lobe.

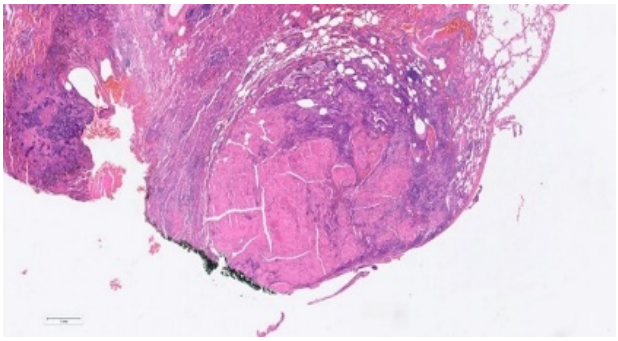

Figure 2. Section of the lungs shows a large nodular area of amorphous eosinophilic materials which stains positively with Congo red.

3. Discussion

Nodular pulmonary amyloidosis is mostly asymptomatic and diagnosed as an incidental finding on chest radiography. Our patient presented with symptoms of dyspnoea on exertion and cough which are present in common respiratory disorders and have a wide differential diagnosis. Several conditions can be suspected based on radiological evidence only, such as neoplasia and tuberculosis. Pulmonary hyalinising granuloma should also be considered and distinguished from the nodular amyloidosis [4]. Pulmonary hyalinising granuloma (PHG) have similar presentation and imagining shows pulmonary nodules which can be solitary or multiple, the diagnosis is confirmed on histology which shows lesions containing keloid-type coarse collagen [5].

Sarcoidosis is another differential. As opposed to amyloidosis, granuloma deposits in the lung and lymphatic systems. Bilateral hilar lymphadenopathy on imaging is characteristic of sarcoidosis and diagnosis is confirmed by identifying non caseous granuloma on biopsy samples in the presence of clinical and radiological findings [6]. Pulmonary involvement includes three main patterns: nodular parenchymal, tracheobronchial, and diffuse alveolar septal. Nodular pulmonary amyloidosis can also be associated with underlying lymphoproliferative disorder such as lymphoma or autoimmune disease process like Sjogren's Syndrome [7] [8]. On CT imaging, nodular amyloidosis can present as multiple lesions or less commonly as a single lesion with mostly lower lobe and subpleural predominance [9].

This patient presented with the nodular parenchymal pattern as evident on CT imaging. Biopsy with immunohistochemistry, which is the gold standard is needed and confirms nodular pulmonary amyloidosis by appearing eosinophilic with congo red stain and display green birefringence under polarised light with the presence of kappa and lambda plasma cells [9].

Treatment of pulmonary amyloidosis is directed towards the underline disease process and varies depending on the pattern, ranging from surgical resection with interval surveillance CT in nodular pattern, to systemic treatment for diffused alveolar septal and tracheobronchial pattern. In selected cases autologous stem cell transplantation may be considered.

Due to the rarity of amyloidosis, it had been difficult to perform randomized controlled trials. Therefore, therapies have revolved around treatment algorithms for multiple myeloma. Chemotherapy for the treatment of amyloidosis was introduced in 1972 in the form of melphalan and prednisolone [10]. Patient's age, comorbidities, frailty, extent of organ involvement and disease progression, personal and regional treatment preferences are taken into account when considering the treatment options. Risk stratification is pivotal before commencing any treatment. Immunomodulatory drugs have been introduced in the management of amyloidosis including thalidomide and Lenalidomide. Also, the bortezomib (proteasome inhibitor) have been increasingly used in treatment of systemic amyloidosis [11]. There have been several changes to systemic treatment evolved over the years. Many centres' advocates administering cyclophosphamide, bortezomib, dexamethasone with daratumumab as first line as it produces rapid response [3] [12] [13]. Due to the side effects of these medications, choice of management is tailored in view of the fitness, comorbidities, extent, and type of disease. Treatment with Daratumumab, bortezomib and dexamethasone has recently been recommended by National Institute of Health and Care Excellence (NICE) guidelines in the UK as an option for treating relapsing multiple myeloma in adults, only if they have had just one previous line of treatment [14]. In future, it may help to carve the way in getting integrated into amyloidosis management pathway in the National Health Service (NHS). There is already a draft scope published by NICE guidelines regarding the use of Daratumumab monotherapy for newly diagnosed systemic amyloid light-chain amyloidosis. In general, nodular pulmonary amyloidosis has better long-term prognosis as comparted to other types of lung amyloidosis. several factors such as smoking, comorbidities, age, presence of dyspnoea at presentation affect prognosis. There is a risk of respiratory infection which is responsible for the high prevalence of death in several studies [15].

4. Conclusion

Pulmonary amyloidosis is rare and should be considered as one of differentials along with other medical conditions like infection, malignancy, or vasculitis. Treatment should be based on the type of amyloidosis detected on histopathology amidst other factors. Early detection and commencing the patient on appropriate treatment pathway, depending on the pattern and type may help in better outcome and experience for the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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