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Original Research Paper

Pathology

PRIMARY PULMONARY NODULAR AMYLOIDOSIS WITH CO-EXISTING MICROFILARIAL INFESTATION: A CASE REPORT

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ABSTRACT Primary pulmonary amyloidosis is a rare disease characterized by the deposition of congophilic amyloid fibrils in extracellular tissue. The term "amyloid" was coined by Rudolph Virchow in 1854. It is can be hereditary or acquired, localized or systemic and potentially lethal or merely an incidental finding. Amyloidosis in lung was first recognized by Lesser in 1877. It can be primary or secondary to various hereditary, inflammatory or neoplastic pathogenesis. Till date, there are 27 known extracellular fibril proteins identified in humans. The extracellular deposits interfere with organ functions and may lead to death. The most common presentations of amyloidosis are unexplained nephrotic syndrome, cardiomyopathy. Primary pulmonary nodular amyloidosis should be considered in the differential diagnosis of pulmonary nodules or masses. Here we are presenting a case of coexistence of primary pulmonary nodular amyloidosis with microflarial infestation.

KEYWORDS : Primary pulmonary amyloidosis, microfilaria, pulmonary nodules, congo red

INTRODUCTION

Amyloidosis is an extracellular deposition of pathologic insoluble fibrillar proteins in organs or tissues. Nodular deposition of amyloid in the lung is an uncommon condition apparently first described by Lesser in 1877 (1). The diverse spectrum of amyloid related diseases is now recognized to include Alzheimer's disease, type II diabetes and transmissible spongiform encephalopathies. It may be hereditary or acquired potentially fatal or incidental finding. It can be subdivided into localized or systemic form. It can also be classified as primary or secondary.

The term amyloid (starch like) was coined by Rudolph Virchow in 1854, when he made the observation that corpora amylacea in the brain stained similarly to starch, that is, stained pale blue after treatment with iodine and violet upon the addition of sulfuric acid (2). Amyloid now consists of a wide variety of fibrillary proteins that exhibit similar tinctorial, ultrastructural, and x-ray diffraction properties. In hematoxylin-eosin stained sections, amyloid appears as homogeneous acellular, glassy, amorphous, eosinophilic material. Congo red staining shows apple green birefringence under polarization. This apple-green birefringence under polarized light is considered the gold standard for amyloidosis (3). Here we are presenting a case of primary pulmonary nodular amyloidosis with co-existing microfilarial infestation.

CASE REPORT

60-year male presented with right upper limb swelling since 2-3 days. On local examination, right upper limb showed ulcer extending from elbow to fingers with pus discharge. On examination patient was febrile and looking pale. General condition was poor with BP 100/60 mm of Hg and respiratory rate of 26/min. On respiratory system examination bilateral harsh breathing sounds were present. On investigation, the hemogram was showing total leukocyte count – 27200/cu.mm, hemoglobin – 11.4gm%, platelet 1,30,000/cu.mm. Other investigations include random blood sugar- 80 mg%, BUN- 45, creatinine – 0.62 mg%, sodium – 136 mEq/L, potassium – 4 mEq/L, chlorides – 94 mEq/L.

At autopsy, on external examination, there was swelling of right forearm with ulceration covered with exudate which on culture showed growth of Klebsiella Pneumonie. Bilateral lung weighed 500 grams each with pleura hazy and adherent pleura. On cut surface, lung showed multiple nodules ranging from 0.5 cm to 4 cms present throughout the lung parenchyma, predominantly in the subpleural areas. Nodules are waxy greyish yellow in colour with irregular borders, firm to hard in consistency and gritty to cut and easily shelled from surrounding lung parenchyma (figure - 1)

Imprint cytology of lung nodules showed large number of microfilaria of Wuchereria Bancrofti with background showing plenty of plasma cells, macrophages, lymphocytes and giant cells. (figure - 2)

On histopathological examination, section from lung nodule showed large areas of acellular, homogenous, amorphous, eosinophilic material surrounded by plenty of plasma cells along with lymphocytes, giant cells and presence of recognizable fragments of microfilaria (figure - 3, 4). Also showed areas of calcification and fibrin thrombi (figure – 5). On congo red staining showed presence of acellular material without polarization (figure – 6). It showed apple green bifringerence under polarized light (figure- 7). This amyloid material was resistant to potassium permanganate and retained the congophilia (figure -8) even after decolorization indicating primary pulmonary amyloidosis. Kidney showed hyalinized glomeruli without evidence of amyloid material. Section from liver, spleen, heart, brain and GIT were unremarkable. Final cause of death was given as sepsis with bilateral primary pulmonary nodular amyloidosis in a case of right upper limb cellulitis (natural).

Figure 1 - Multiple waxy greyish yellow nodules in lung parenchyma

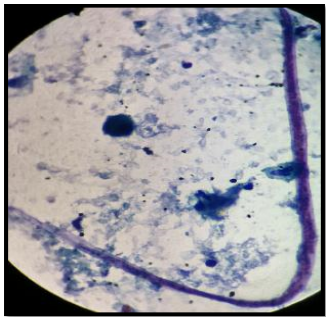

Figure 2 - Microfilaria of Wuchereria Bancrofti. (MGG stain - 400x)

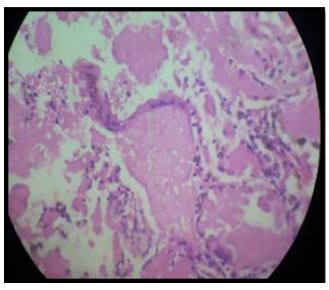

Figure 3 – Acellular eosinophilic material along with recognizable fragments of microfilaria. (HE - 400x)

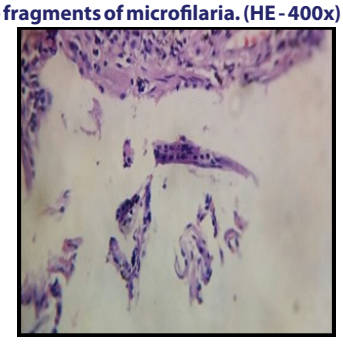

Figure 4 - Presence of recognizable fragments of microfilaria in lung nodules (HE - 400x)

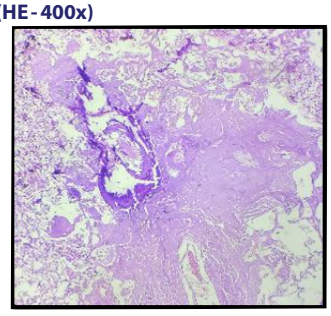

Figure 5 –Acellular, homogenous, amorphous, eosinophilic material and areas of calcification. Inset showing fibrin thrombi (HE – 400x

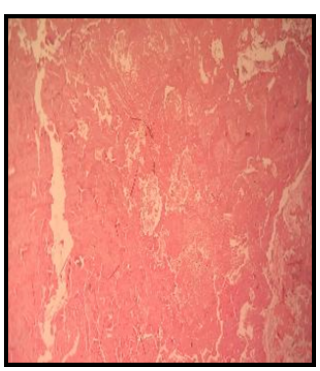

Figure 6 - Congo red without polarization (100x)

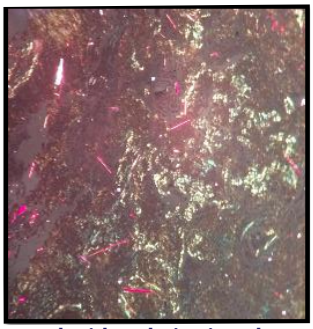

Figure 7 - Congo red with polarization showed apple green bifringerence (400x)

Figure 8 – Amyloid was resistant to potassium permanganate and retained congophilia(400x)

DISCUSSION

Amyloidosis is characterized by deposition of abnormal fibrillary protein material in extracellular tissue in variety of organs. Primary localized amyloidosis is divided into 3 forms including tracheobronchial amyloidosis, nodular parenchymal amyloidosis and alveolar-septal amyloidosis. The classification of amyloidosis was made depending upon nature of the precursor plasma proteins that form the fibril deposits. Rarely primary pulmonary amyloidosis presents as multiple nodular lesions or masses. Localized pulmonary amyloidosis may involve the tracheobronchial tree or pulmonary parenchyma in a localized or diffuse distribution (4).

Amyloidosis can be classified into three types: reactive (AA type), primary idiopathic (AL type) and transthyretin related amyloidosis (ATTR type). The great majority of patients with pulmonary impairment present as primary form of the disease. It is subdivided into localized and systemic forms. In also can be classified as primary or secondary (2)

Primary pulmonary amyloidosis is a rare disease which can be focal or systemic features. The secondary systemic form is related to neoplastic, infectious, or chronic inflammatory processes, including tuberculosis, chronic kidney disease, syphilis, leprosy, inflammatory bowel disease, osteomyelitis, parasitic infections, rheumatoid arthritis, and bronchiectasis (5). The presence of amyloid nodules located in the lung parenchyma is a finding that needs to be distinguished from neoplasm. Amyloid nodules are typically peripheral and sub pleural and in lower lobe, may be bilateral, and ranges from 0.4 to 15 cm in diameter waxy, with grey tan colour. They grow slowly and frequently calcify and form a cavity similar to this case. The nodular form is more common in patients aged 60 or older, who are typically asymptomatic, and is characterized by the presence of solitary or multiple nodules in the lung parenchyma. The nodules are frequently well-defined but vary in size, number, or shape. In approximately half of the cases foci of calcification or ossification are seen, as seen in this case. The nodules grow slowly for years without any regression. The differential diagnosis of the nodules includes primary or metastatic neoplasia and granulomatous diseases specially the hyalinizing granulomas. The most common finding in the nodular form are masses of amyloid,

surrounded by plasma cells, lymphocytes, and giant cells which were also seen in this case. On Congo red, shows apple green birefringence under polarized light as in this case.

Secondary amyloidosis can be distinguished from other forms by a simple procedure. Tissue sections incubated for 3 minutes with equal volume of potassium permanganate and 0.3% sulfuric acid, decolorized with 5% oxalic acid, washed twice in distilled water and stained with congo red. By potassium permanganate test, the secondary type of amyloidosis loses its affinity for congo red (6). It is important to distinguish secondary amyloidosis because treatment of underlying condition that has stimulated production of the amyloid may result in partial remission of the amyloidosis. Other special stains for amyloid are thioflavin T and metachromatic dyes, such as crystal violet. Electron microscopy scans of amyloid typically reveal haphazardly arranged nonbranching fibrils that measure 8 to 10 nm in diameter. The association of giant cells with primary amyloidosis is well documented but the role is still unclear. As per recent studies, giant cell participates in amyloid fibril formation by uptake and modification of precursor light chain or it can be foreign body giant cell response to the inert amyloid material.

Table 1. Comparison of various types of pulmonary amyloidosis

Amyloidosis type	Gross findings	Plasma cells /giant cells	Permanganate bleach
Primary localized	Single /Multiple nodules	Present	Resistant
Systemic AA	Diffuse	Absent	Sensitive
Systemic AL	Nodule or mass	Present	Resistant

Patterns of pulmonary amyloidosis: (7)

1)Diffuse alveolar-septal amyloidosis –

Also known as diffuse parenchymal amyloidosis, it is characterized by the presence of amyloid deposits in the alveolar septa and vessel walls. On gross examination the lungs are rubbery, and their cut surface show uniform sponge like appearance. The vessel walls are often involved, and small nodules may be formed. Histopathologically, amyloid material is seen in the visceral pleura. The lesions are typically hypocellular with scant plasma cells with absence of giant cells. Amyloid material shows apple-green birefringence under polarized light. As mentioned above, various forms of systemic amyloidosis are treated differently. Therefore, if diffuse alveolar-septal amyloidosis is diagnosed in a biopsy specimen, amyloid subtyping is pivotal. It can be done by immunohistochemistry. The Mass spectrometry based proteomic analysis has a higher sensitivity and specificity. In hematoxylin-eosin stained sections, amyloid and collagen looks similar in appearance. As a result, diffuse alveolar-septal amyloidosis is difficult to differentiate from fibrosing interstitial pneumonia, usual interstitial pneumonia or fibrosing nonspecific interstitial pneumonia. Congo red stain can be used to confirm the presence of perivascular glassy eosinophilic deposits for diagnosis of amyloidosis.

2) Nodular pulmonary amyloidosis –

Also known as nodular parenchymal amyloidosis or nodular amyloidoma, it is defined as one or more tumefactive amyloid deposits involving the lungs. In literature, nodular pulmonary amyloidosis and primary pulmonary lymphoma with amyloid production are thought to be two fundamentally different processes. Many cases of nodular amyloidosis lung are the outcome of lymphoproliferative disorder like extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.

Gross of the lungs reveals one or rarely more nodules, which typically measure 0.5 to 5 cms size. The cut surface of the nodules is waxy, gray-tan with irregular border firm to hard in consistency, gritty to cut and may show calcification or cavitation.

Histologically, the nodules are well circumscribed and consist of homogeneous, acellular glassy, densely eosinophilic material with plenty of lymphocytes and plasma cells usually found within or adjacent to the nodules. Foreign body giant cells, calcifications and bony or cartilaginous areas may also be seen. Congophilia with apple-green birefringence under polarized light is diagnostic of amyloidosis.

Amyloid subtyping to reveal an underlying localized lymphoproliferative disorder is done with mass spectrometry based proteomic analysis. Amyloid subtyping usually reveals monoclonal immunoglobulin light chains. The light chains in nodular pulmonary amyloidosis are more frequently of j than of k type, with a ratio of 3:1. In rare cases of nodular pulmonary amyloidosis, serum amyloid A or transthyretin may be detected. The clonality of the lymphoplasmacytic component can be evaluated by immunohistochemistry for j and k light chains or immunoglobulin gene rearrangement analysis. Exclusion of a plasma cell dyscrasia needs further investigations.

Differential diagnoses of nodular pulmonary amyloidosis include amyloid like nodules especially light chain deposition disease and pulmonary hyalinizing. Similar to nodular pulmonary amyloidosis, pulmonary hyalinizing granuloma often presents as incidental solitary or multiple nodules with the histologic features is composed of thick collagen bundles arranged in lamellae. Bony and cartilaginous areas are not seen in pulmonary hyalinizing granuloma. Congo red staining is negative. Amyloid-like nodules are histologically indistinguishable from nodular pulmonary amyloidosis. They are congo red negative usually composed of nonamyloid light chains (typically j), which means that the light chain fragments do not form fibrils and electron microscopy shows a granular material. Localized form nonamyloid light-chain deposition in the lungs is usually associated with systemic light chain deposition disease. Since most patients with light chain deposition disease show evidence of renal involvement and an underlying monoclonal plasma cell proliferative disorder, the presence of appropriate clinical features may also be helpful in separating light chain deposition disease from nodular pulmonary amyloidosis.

3) Tracheobronchial amyloidosis –

It is characterized by amyloid deposition in various segments of the tracheobronchial tree. Tracheobronchial amyloidosis is rare form of pulmonary amyloidosis. In individual cases, various segments of the tracheobronchial tree are involved to various extents. Three patterns of involvement includes proximal, mid, and distal airway disease. Bronchoscopy with transbronchial biopsy is most useful for establishing the diagnosis of tracheobronchial amyloidosis, whereas computed tomography is very helpful for determining the extent of the disease. Grossly, the walls of the affected airways are thickened with luminal narrowing. Deposits are located in the submucosa.

Histologically, the deposits are composed of homogeneous eosinophilic material and surrounding seromucous glands and cartilage with submucosal vessels with plasma cells, foreign body giant cells, calcifications, and ossification. Apple-green birefringence under polarized light is diagnostic of amyloidosis. Proximal and severe mid airway disease is usually treated with laser or forceps debridement, or external beam radiation therapy.

Filariasis is a major health problem in many endemic areas of India with majority of patients tending to be asymptomatic. The rare coexistence of primary pulmonary amyloidosis and microfilaria in this case. Microfilaria or recognizable fragments are present in lung nodules. Filarial parasites have been isolated only in few cases of lung nodules. Incidental finding of microfilaria in cytological smears are considered as that it is an opportunistic infection debilitating condition. Tropical pulmonary eosinophilia (TPE) is a form of occult filariasis characterized by pulmonary infiltrates on chest radiograph and peripheral eosinophilia. TPE results from a hypersensitivity response to the microfilariae of the lymphatic dwelling parasites are related to parasitic infestation like W. bancrofti or B. malayi infection. But in our case, there was no TPE or peripheral eosinophilia on

presentation. In literature, renal secondary amyloidosis due to chronic filariasis are known (8). Another case reported in literature is kidney amyloidosis with filariasis presenting as nephrotic syndrome (9)

CONCLUSION

Nodular pulmonary amyloidosis should be included in the differential diagnosis of multiple lung nodules, especially when the nodules fail to enlarge rapidly. The other differential diagnosis of multiple large pulmonary nodules would include metastatic neoplasm, especially the ones that occasionally calcify, fungal infection, tuberculosis, non-Hodgkin's lymphoma, multiple hamartomas and echinococcal cysts.

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