



Pulmonary nodules associated with pulmonary embolism: A rare and misleading presentation of amyloidosis

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ABSTRACT

Amyloidosis is a rare disease especially the localized form involving pulmonary parenchyma. We report the case of a 74 years old woman who presented with chest pain and dyspnoea. CT scan showed pulmonary embolism and bilateral nodules. Laboratory examinations highlighted circulating Kappa IgM. 18F-FDG PET/CT showed intense activity of the nodules. Histological investigation supported the diagnosis of nodular pulmonary amyloidosis. There were no sign of systemic amyloidosis or autoimmune disease. No treatment was initiated: the patient remains asymptomatic after one year. Localized pulmonary amyloidosis related to MGUS was the most likely diagnosis. Malignancy, a differential diagnosis of pulmonary amyloidosis, must be excluded: histological examinations are overriding. Difference between systemic and localized amyloidosis conditions treatment and prognosis. This observation emphasizes the difficulty to establish the diagnosis of pulmonary nodular amyloidosis and the complex relationship between amyloidosis and thromboembolism.

1. Introduction

Amyloidosis is an extra-cellular deposit of amyloid, an insoluble fibrillary protein. Primary and secondary forms are described based on the presence of other diseases. Amyloidosis can be systemic or limited [1]. Nodular pulmonary amyloidosis is one of the potential localized form and refers to an aggregation of amyloid proteins in pulmonary parenchyma. Gillmore and Hawkins categorized pulmonary amyloidosis as tracheobronchial, parenchymal, nodular or diffuse alveolar septal [2].

The incidence of pulmonary amyloidosis is unclear: it is usually a silent disease diagnosed incidentally. Quaia et al. identified one case of pulmonary amyloidosis in 76 patients with pulmonary lesions suspected of malignancy between 2004 and 2006 [3]. This radiological pattern raises the concern of the differential diagnosis with other lung diseases such as lung neoplasm or granulomatosis. We present an original case of pulmonary nodular amyloidosis fortuitously revealed by a pulmonary embolism that highlights the complexity of the relationship between amyloidosis and thromboembolism.

2. Case report

A 74 years old woman was admitted to emergency room because of dyspnoea and bilateral chest pain for two days. It was the first episode. Symptoms were continuously present but more important during exercise. Cough or haemoptysis were not reported. Patient said she was asthenic but maintained normal appetite. No other symptom was found including fever, night sweats or slimming. Regarding her case history, nobody of her acquaintances was sick and she declared no recent foreign travel. Her last admission to hospital was many years before.

She had medical history of glaucoma, bilateral hip arthrosis and surgical treatment of a cystocele. No relevant information was found regarding her family medical history. She was non-smoker and did not report any occupational or pet exposure. She did not consume drug or alcohol. She had no known allergy. Her usual treatment only included Boric acid and Timolol eye drops for glaucoma.

The physical examination revealed no abnormal finding. Breath and heart sounds were totally normal. Abdominal palpation was painless. She had no digital clubbing or cutaneous lesion. Neurological

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assessment did not show any motor or sensory deficit. There was no argument for any neuropathy or cognitive impairment.

Laboratory examinations were within normal limits: white blood cell count of 4860/ μ l with neutrophil rate of 52.5%, eosinophil 4.3%, lymphocyte 35%. We found a haemoglobin level of 133 g/l, haematocrit 39.3% and platelet count of 205 000/ μ l. Prothrombin value, activated partial thromboplastin time were normal. D-dimer were elevated to 5360 ng/ml. Biochemical analysis revealed 2.35 mEq/l of calcium, 4.3 U/l of albumin, 4.3 mEq/l of potassium, 3.4 mg/l of C-reactive protein. Serum creatinine value was normal with a level of 0.852 mg/dl. Lactate dehydrogenase value was 306 UI/l. There were no abnormal results of liver aminotransferase level, total bilirubin, gamma-GT or alkaline phosphatase.

Chest X-Ray showed several bilateral nodules. No other lesion was identified.

A computerised tomography pulmonary angiography was performed and showed bilateral pulmonary embolism associated with multiples pulmonary nodules on both sides (Fig. 1). Some nodules were calcified and the largest one, in the right middle lobe measured 35mm. She was given enoxaparin and was referred to our service to assess these suspicious lesions.

Flexible bronchoscopy showed a normal endobronchial aspect without any suspicious lesion. Broncho-alveolar lavage was nonspecific and did not contain neoplastic cell. There was no acid fast bacilli on microscopic exam and cultures were negative for common bacteria, nocardia, mycobacteria or fungus.

CT guided-transparietal lung biopsy was performed and showed amorphous eosinophilic substance with plasma cells around these lesions. No neoplastic cell was found. Amyloidosis was suspected but malignancy had to be excluded.

Abdomen and pelvis were normal on injected tomography. A fluorine-18-FDG Positron emission tomography-computed tomography (18F-FDG PET-CT) was performed and showed intense activity for all nodules. The maximum standardized uptake value (SUV max) was 8.8 on the largest nodule. There were about ten lesions on each lung. No suspicious hypermetabolic lesion was detected throughout the rest of the body.

Etiological assessment for amyloidosis was as follows: rheumatoid factor <10 UI/ml, anti-citrullinated peptide antibodies 11 UI/ml. Anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. Complement dosing was normal and there was no immunoglobulin deficiency. No systemic disease was found including granulomatous pathology: Angiotensin-Converting Enzyme was normal with a value of 33UI/l. Serum and urine protein electrophoresis values were within normal limits. We only found an isolated monoclonal Kappa Immunoglobulin M on immunofixation. Bone marrow examination was normal with 3% of plasma cells and 9% of lymphocytes. Bone marrow richness was slightly reduced but without dystrophy.

Pulmonary function testing and blood gas examination were within

normal ranges.

The patient underwent surgical exploration with wedge resection of nodules in left lower lobe, lingula and apical segment in order to obtain final diagnosis. Architecture of pulmonary parenchyma were completely modified on biopsies. Homogenous eosinophilic amorphous deposits were found and the Congo red stain was positive with apple-green birefringence under polarized light (Fig. 2). Ossifications and fibrosis lesions were also found. Identification of amyloid protein type was difficult: pathologists reached the conclusion of amyloid localized form.

Cardiac, cutaneous and kidney localisation of amyloidosis were looked for. Echocardiogram and cardiac MRI were normal. Subcutaneous fat and salivary glands biopsies were also negative. Kidney biopsy was not performed because of normal laboratory examinations and normal computed tomography of the abdomen.

The diagnostic of localized nodular pulmonary amyloidosis, associated with MGUS was confirmed and we have scheduled a clinical, biological and radiological supervision. A lifelong treatment by RIVAXORABAN was initiated and follow up continue with periodic chest CT.

3. Discussion

In most of cases of nodular pulmonary amyloidosis described in the literature, patients were in their sixth decade and presented to clinicians with medical history of dry cough [4], dyspnoea, haemoptysis [5], chest pain. Asymptomatic patient like our case are also mentioned. Quan et al. [6] published a case report with a literature review: they found 41 patients between 2000 and 2014 with nodular pulmonary amyloidosis who underwent 18F-FDG PET/CT. Radiologically, amyloid lesion were single or multinodular with calcifications, up to several centimetres, in any lobe. Ground glass opacities and septal thickening were also found. In another case report with literature review [7], authors identified 58 patients between 1970 and 2011. They found the same radiological pattern and clinical presentation.

Metastatic neoplasms, Granulomatous, auto immune and infectious diseases are differential diagnosis of lung amyloidosis. In our case, because of imaging findings mimicking metastatic lesions and increased FDG uptake, malignancy was the first hypothesis [8]. 18F-FDG PET/CT takes an important place to characterize nodules, to detect possible malignancy and to reduce inappropriate invasive investigation [6,7,9]. Histological confirmation is necessary for final diagnosis and to exclude neoplasm. Open lung biopsy is the most used method and the gold standard. This exploration attested the presence of homogenous eosinophilic amorphous deposits with positive Congo red stain, pathognomonic of amyloidosis. In all case we found on the literature review, Congo red stain was positive with apple green birefringence under polarized light and confirmed nodular pulmonary amyloidosis [6,7,10-13].

Once the diagnosis confirmed, the differentiation between systemic

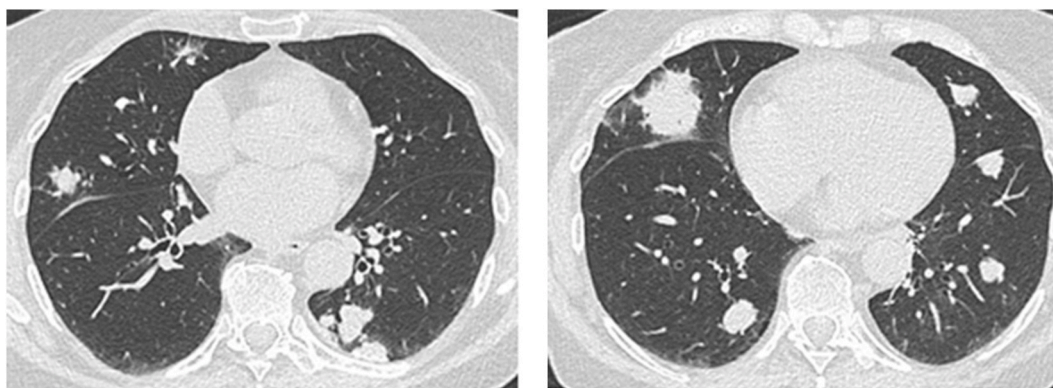


Figure 1. Chest CT Scan, parenchymal window showing multiple bilateral nodules.

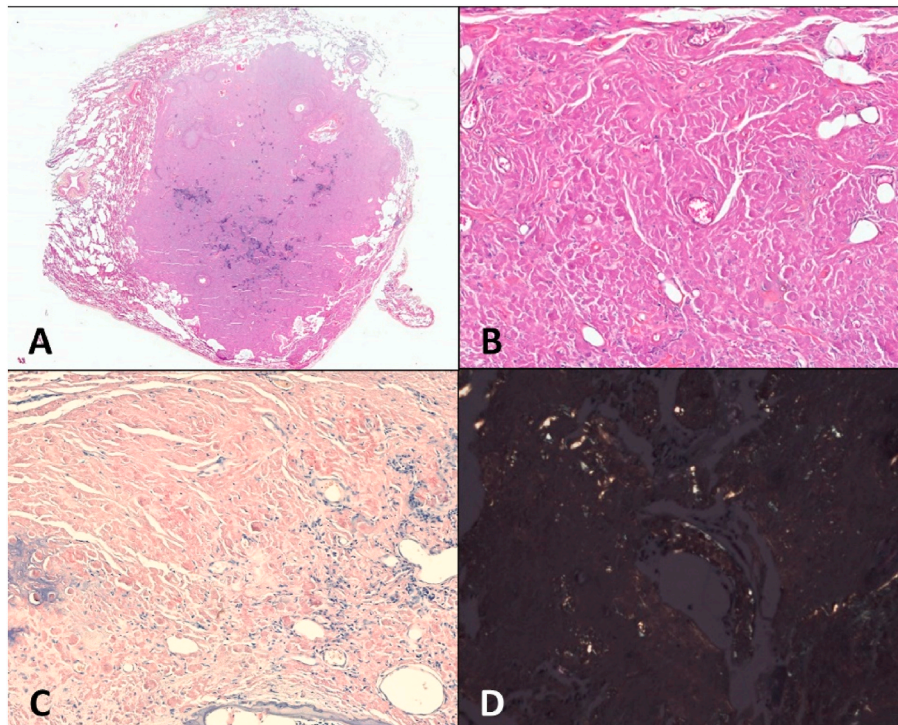


Fig. 2. Pulmonary amyloidosis. Homogenous eosinophilic amorphous extracellular deposits with standard staining (A: x10 and B: x100). Amyloid deposits on Congo red stain (C) with apple green birefringence under polarized light (D).

or localized form of amyloidosis is essential. In contrast with systemic amyloidosis which is fatal in 80% of patients, localized pulmonary amyloidosis follows a benign course in most cases [6,7,14–18]. More than thirty-five proteins have been identified to induce amyloid lesions [2]. The most common type, AL amyloidosis, can be primary or associated with multiple myeloma. AA amyloidosis is a secondary form occurring after chronic inflammation, neoplasia or infectious disease. Senile systemic amyloidosis (SSA) and hereditary amyloidosis also exist. These ones are called ATTR, AFib and AApoAI amyloidosis. Many organs are involved in systemic form depending on the type of proteins such as heart, kidney, liver, skin or nerves. For the diagnosis of limited amyloidosis, clinicians must investigate for other site of amyloid deposits. By consensus, labial salivary glands biopsies and subcutaneous fat aspiration are recommended. These explorations may confirm amyloid lesions in respectively fifty and ninety percent of patients [19]. In literature, studies showed that nodular pulmonary amyloidosis usually remains localized [20]. Glaudemans et al. [21] showed that 18F-FDG PET/CT could be useful to differentiate systemic and localized amyloidosis. In their study, all patients with localized amyloidosis had an increase FDG uptake. Concerning patients with systemic amyloidosis, increased FDG uptake was not found in any case. In our case, amyloid deposits were not found in other site like subcutaneous fat or salivary glands. Heart MRI was completely normal and also laboratory explorations. There was no sign of other organs involvement. Histopathologic examinations and increased FDG uptake supported the diagnosis of localized AL amyloidosis. Plasma cells were found near amyloid lesion on biopsies indicating a possible local production of amyloid proteins [2]. Ossifications found on CT scans and on the biopsies results were also in favour of amyloid disease [22].

Nodular pulmonary amyloidosis can be associated with monoclonal gammopathy of undetermined significance (MGUS) [19,23], MALT lymphoma [22,24,25], multiple myeloma [26] or other malignancy [27, 28]. In our case, an isolated monoclonal Kappa IgM on immunofixation was found: haematological disease like multiple myeloma or MGUS had to be ruled out. Bone marrow examination was normal. There was no evidence for a multiple myeloma: no sign of lytic bone lesions, no

laboratory abnormalities including hypercalcemia or anemia. Renal function and free light chains examination were completely normal. Localized AL amyloidosis of the lung with MGUS was the most likely diagnosis.

Pulmonary nodules were fortuitously discovered on CT scan associated with pulmonary embolism. Some studies showed an increased risk of thromboembolic disease in AL amyloidosis [29,30] and especially those with cardiac involvement [31]. Correlation between these two pathologies is unclear in the literature: raised blood viscosity because of circulating immunoglobulin and hypercoagulable state are suspected mechanisms [31,32]. For our patient amyloid deposits were atypical and could be induced by pulmonary embolism. No study or similar case report was found in a review of literature: there was no argument for post embolism amyloid deposits.

This pathology is very rare: no randomized trials are available to assess treatment. By consensus, periodic follow-up without surgical intervention is recommended for asymptomatic patients and localized forms. Nodular pulmonary amyloidosis followed a benign course in the majority of described cases. For symptomatic patients or systemic amyloidosis, chemotherapy and autologous stem cells could be required [33,34].

4. Conclusion

This is an original case of pulmonary amyloidosis fortuitously revealed by a pulmonary embolism that highlights the complex relationship between amyloidosis, thromboembolism and haematological disease. Malignancy, a differential diagnosis, must be considered.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.rmcr.2020.101095>.

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