JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES, 2017
VOL. 7, NO. 3, 185–189
https://doi.org/10.1080/20009666.2017.1343075

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CASE REPORT



# Nodular pulmonary amyloidosis with primary pulmonary MALT lymphoma masquerading as metastatic lung disease

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**ABSTRACT**

Nodular pulmonary amyloidosis is a very rare form of localized amyloidosis involving the lung, with very little known about its nature. It is usually associated with indolent B cell lymphoproliferative disorder and also connective tissue disorders. No definite treatment guideline exists. Many patients respond to chemotherapy with low risk of progression and a 'wait and watch' strategy is also considered a valid treatment option. In this report the authors present a case of nodular pulmonary amyloidosis with pulmonary mucosa associated lymphoid tissue (MALT) lymphoma that presented with features of metastatic malignant disease and after definitive diagnosis decided not to undergo treatment.

**ARTICLE HISTORY**
Received 21 January 2017
Accepted 8 June 2017

**KEYWORDS**
Oncology; lymphoma; MALT; observation; pulmonary

## 1. Background

Mucosa associated lymphoid tissue derived (MALT) lymphoma is one of three types of marginal zone lymphoma, which was first described more than 30 years ago [1]. It constitutes almost 8% of all non-Hodgkin's lymphomas in the Western world [2]. Since then, MALT lymphoma has been reported to involve almost all the organs although the stomach is the most commonly affected organ [3]. Lung involvement in MALT lymphoma is uncommon and is frequently associated with systematic autoimmune illnesses [4]. Helicobacter pylori is known to cause gastric MALT lymphoma [5].

Three morphological forms of localized amyloidosis mostly affects the lung: nodular pulmonary amyloidosis (NPA); diffuse alveolar septal amyloidosis; and tracheobronchial amyloidosis [6]. Primary systemic amyloidosis is the most common form of amyloidosis affecting the lung [6]. Few case reports and case series have shown an association between nodular pulmonary amyloidosis and MALT lymphoma [7–9]. Nodular pulmonary amyloidosis and primary pulmonary MALT lymphoma can be separated using histologic and immunohistochemical characteristics [10].

We have a large body of evidence that pulmonary MALT lymphoma does not always need to be treated due to the indolent nature of the disease. In this report we are presenting a case of NPA presenting as metastatic lung disease.

## 2. Case presentation

A 78-year-old Caucasian woman with past medical history of chronic obstructive pulmonary disease came to the emergency room with a chief complaint of shortness of breath for one week, which was progressively getting worse. The patient denied orthopnea or paroxysmal nocturnal dyspnea. Social history is significant for smoking 1.5 packs per day for almost 30 years, having quit 20 years ago. Vital signs were within normal limit. On general appearance the patient was in no distress at rest. Head and neck examination was unremarkable. Chest auscultation was significant for decreased aeration and prolonged expiration. No additional sounds were appreciated. The rest of the examination was normal.

Complete blood count was essentially normal. The chest x-ray showed a 2.4 cm lobular right middle lobe non-calcified mass, highly suspicious for carcinoma. It also showed predominant changes of emphysema with calcified granulomas in both lung fields (Figure 1). Computed tomography (CT) of the chest with contrast showed three spiculated non-calcified lung masses likely representing either metastatic disease or, more likely, lung carcinoma with metastasis along with emphysematous changes (Figure 2). CT abdomen-pelvis with contrast was normal.

Core biopsy of the lung nodule was obtained. Congo red stain was positive with tinctorial characteristics typical of amyloid. Immunohistochemical stains showed predominant population of cluster of differentiation (CD) 138 positive plasma cells with focal staining form CD20 and paired box (PAX) 5 in small lymphocytes and minor background population of small CD3 positive T cells (Figure 3). Immunohistochemical stains and in-situ hybridization studies showed a polytypic pattern of light

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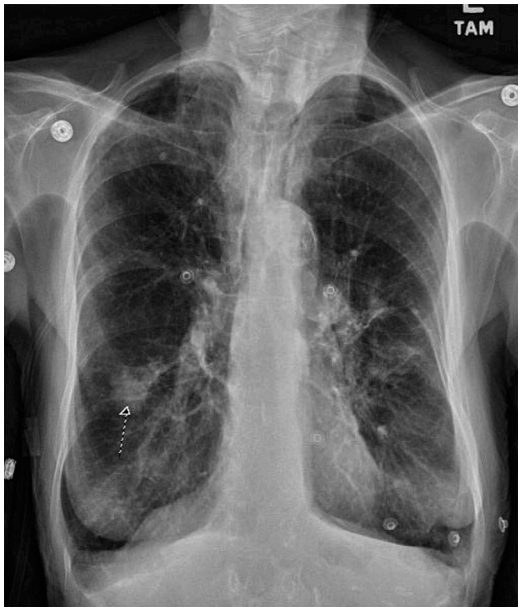


Figure 1. Chest x-ray showing predominant emphysematous changes along with a nodular non-calcified mass in right lung.

chain expression with focal mild lambda preponderance. Pan-cytokeratin stains were negative. All evidence suggested nodular amyloidosis with an atypical lymphoplasmacytic infiltrate suspicious for marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Lactate dehydrogenase level was 221 unit/litre [reference range 100 – 225 unit/litre]. Beta 2 microglobulin level was 3 milligram/litre [reference range 1 – 2.6 milligram/litre]. Bone marrow was negative for malignancy. Cytogenetics analysis was negative for any numerical or structural chromosome abnormalities. Positron emission tomography (PET) CT neck to thigh was done, which showed two right lung and one left lung area of increased opacity. There was increased uptake of 3.3 standardized uptake value (SUV) in the right middle lobe, 5.1 SUV in the right lower lobe, and 5.2 SUV in the left lower lobe with no other abnormal uptake identified in the axial or appendicular skeleton (Figure 4). No abnormal uptake was identified in the mediastinum or hilum or elsewhere.

The working diagnosis was metastatic lung disease with differential diagnosis including primary metastatic lung cancer and benign diseases including infectious process and amyloidosis. Core biopsy of the lung was done due to high-risk malignant features of the nodules on radiological examination. In light of the indolent nature of the tumor, the patient decided to not to undergo treatment. She remains under active surveillance. Clinical and radiological follow up at six months showed stable disease.

## 3. Discussion

Amyloidosis refers to extra-cellular accumulation of the amyloid, insoluble fibrillar protein, which exhibit characteristics of apple-green birefringence under polarized light after Congo red staining [7]. Biopsy is the only way to confirm the diagnosis of amyloidosis. Pulmonary amyloidosis can lead to nodules, trachea-bronchial infiltration, and rarely pleural effusions [6]. The Mayo Clinic published case series of 55 patients with pulmonary amyloidosis diagnosed by biopsy from 1980 to 1993 [6]. Thirty-eight out of 55 had either primary systemic amyloidosis or secondary amyloidosis. Only 17 had localized amyloidosis, and among them were seven cases of nodular pulmonary amyloidosis [6]. Tracheobronchial amyloidosis was the least common type of localized pulmonary amyloidosis in this series. Most of the patients with NPA had multiple nodules. Another series of 48 patients with pulmonary amyloidosis also had NPA as the most common subtype [8]. A recently published case series of 25 years duration, which examined the histopathological features of 18 patients with NPA, showed kappa chain being predominant in 13 of the cases; also 14 of them showed monotypic plasma cells by immunohistochemistry [9]. Tracheobronchial

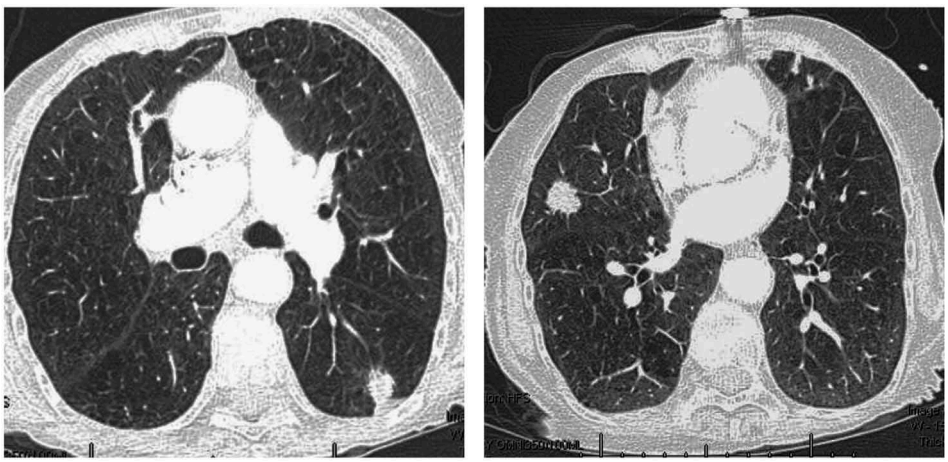

Figure 2. CT chest showing speculated multiple nodules in lung.

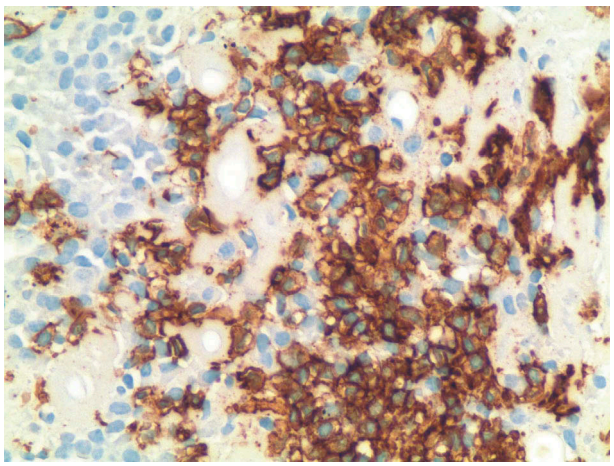

Figure 3. Histological slide showing predominant staining with CD 20 in the biopsy tissue.

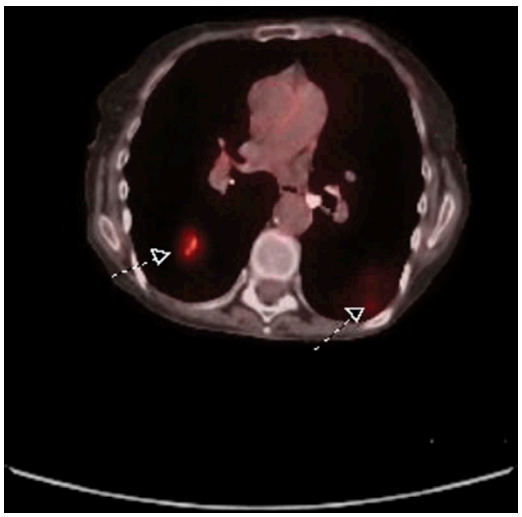

Figure 4. PET scan showing masses with increase opacity and increase uptake in lung.

amyloidosis is a rare form of localized pulmonary amyloidosis with mean age of presentation ranging from the 50s to the 60s in different series [6, 7]. Many patients are asymptomatic, and the symptoms range from cough to recurrent pneumonia. Diffuse interstitial pattern is the rarest form of localized pulmonary amyloidosis, but many of these patients either had no search for systematic amyloidosis or were later found to have features of systematic amyloidosis. NPA patients are usually asymptomatic and mostly are detected as incidental findings. Calcification or ossification can be seen in as many as 50% of the cases of nodular amyloidosis [11]. On literature review, NPA associated with MALT lymphoma has been reported very rarely [9, 12–17]. It is sometime difficult histologically to differentiate the associated malignancies from the amyloidosis. Few of the immunological cues to help diagnose the associated indolent B cell lymphoma include presence of light chain restriction and predominant CD20 and 79a expression [18].

No treatment guidelines exist for the treatment of MALT lymphoma of the lung. One retrospective study involving 11 patients with MALT lymphoma of the lung did not find any significant difference in terms of time for progression in between the wait-and-watch group and the treated group [19]. In addition, six of the 11 patients showed spontaneous regression of the MALT lymphoma in the wait-and-watch group. In another series of 18 patients with NPA, about 36% had evidence of connective tissue disorder [6]. Sojgren's syndrome was the most common associated diagnosis. Twelve out of 18 had immunoglobulin (Ig) kappa peptide dominance, with four cases showing lambda predominance. All the cases of NPA had lymph-plasmacytic infiltrates [6]. None of the cases in this series had translocation of MALT1 gene. Various studies have shown the prevalence of this translocation being up to 60%. On follow-up, none of the cases developed systemic amyloidosis. Two of the patients had recurrent pulmonary amyloidosis and another two had cutaneous MALT lymphoma. Recurrence rate in this study was about 33%. One series showed significantly increased incidence of Achromobacter xylosoxidans infection in MALT lymphoma group compared to non-lymphoma lung biopsies ranging up to 46% in the lymphoma group to 18% in the control group [20]. Chlamydia species has also been associated with pulmonary MALT lymphoma, but this does not prove a causal relationship [21]. More data and research is required to establish the causal relationship.

One of the largest series of patients with pulmonary MALT lymphoma followed 63 patients who were treated with different treatment modalities including abstention. It showed a three-year progression-free survival of 66% in the abstention group, with 83% in the local therapy group, 75% in the chlorambucil group, 40% in the cyclophosphamide group, and 25% in the anthracyclin/flurdarabine group [4]. This retrospective analysis showed significantly better outcome for patients in the chlorambucil group. However, overall survival was mainly dependant on age and performance status in multivariate cox analysis. None of the patients in the wait-and-watch group showed progression during median follow up of 12.5 months.

It is important to diagnose co-existing MALT lymphoma in cases of NPA, since patients with MALT lymphoma will require regular follow-up and also have high rates of recurrence or relapse after initial treatment [22]. NPA has been reported with increased risk of fatal hemorrhage secondary to amyloid deposition in the pulmonary arteries [23].

Several phase II trials have been done in patients with MALT lymphoma using single agents including bortezomib, entospletinib, everolimus, and lenalidomide with overall response rate less than 60%

with the highest complete remission rate being only 33% [24–28]. Similarly, many phase II trials using combination therapy including rituximab plus bortezomib (number of patients: 8, overall response rate: 50%) and lenalidomide plus rituximab (number of patients: 27, overall response rate: 89% and complete remission: 67%) [28, 29]. The sample size of these studies is considered small to generalize the finding and also the remission rate is not high enough. However, the largest phase III randomized control trial (number of patients: 252, event-free survival with hazard ratio, 0.52 and progression-free survival with hazard ratio 0.63) which compared chlorambucil with combination therapy of chlorambucil and rituximab showed increased complete remission in the combined group and event-free survival, but similar five-year overall survival in both groups [30]. A recently published review of the management of MALT lymphoma concluded that the treatment should be individualized as per nature and extent of disease [28].

In summary our case of nodular pulmonary amyloidosis with pulmonary MALT lymphoma was treated with watchful waiting after confirming the diagnosis.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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