

# Nodular Pulmonary Amyloidosis Mimicking Metastatic Pulmonary Nodules

## A case report and review of the literature

\*Rashid S. Al-Umairi,<sup>1</sup> Fatma Al-Lawati,<sup>2</sup> Fadhila M. Al-Busaidi<sup>3</sup>

### حالة داء النشواني العقيدي الرئوي مشابها للعقيدات الرئوية السرطانية تقرير حالة و استعراض الأدبيات العلمية

راشد العميري، فاطمة اللواتية، فضيلة محمد البوسعيدية

**ABSTRACT:** Amyloidosis is a disorder characterised by the extracellular deposition of amyloid, a fibrillary protein, in various organs such as the lungs. Pulmonary nodular amyloidosis can mimic other lung conditions that present with pulmonary nodules, such as metastasis, sarcoidosis and hyalinising granuloma. We report a 60-year-old man who presented to the Royal Hospital, Muscat, Oman, in 2017 with a history of shortness of breath upon exertion, orthopnoea and bilateral lower limb swelling. A chest X-ray showed bilateral nodular opacities. Enhanced chest computed tomography revealed bilateral pulmonary nodules with a predominantly perilymphatic and subpleural distribution, giving the impression of a neoplastic nodule. A histopathological examination of biopsied lung tissue confirmed a diagnosis of nodular pulmonary amyloidosis.

**Keywords:** Multiple Pulmonary Nodules; Amyloidosis; Computed Tomography; Case Report; Oman.

**المخلص:** داء النشواني (الأميلويد) هو حالة مرضية تتصف بترسب مادة شبيهة النشا (الأميلويد، بروتين ليفي) خارج جسم الخلية في أعضاء مختلفة من جسم الإنسان بما في ذلك الرئتين، داء النشواني العقيدي الرئوي قد يشابه أمراضا وحالات رئوية أخرى تتصف بظهور عقيدات رئوية، ومن هذه الحالات العقيدات السرطانية الخبيثة المنتقلة من عضو آخر، وتضخم الساركويد والورم الحبيبي الشفاف، نعرض هنا حالة لرجل يبلغ من العمر 60 عاما تم معاينته في المستشفى السلطاني في مسقط بسلطنة عمان في عام 2017، وكان يعاني من ضيق في التنفس عند بذل مجهود وعند الاضطجاع وكذلك من انتفاخ في القدمين، وقد أظهرت الأشعة السينية للصدر وجود عقيدات في كلتا الرئتين، لمعرفة المزيد عن طبيعة هذه العقيدات الرئوية تم إجراء إشعة مقطعية مع استخدام صبغة عن طريق الوريد والتي أوضحت وجود عقيدات رئوية تتوزع بشكل ملحوظ في محيط الأوعية اللمفاوية وتحت الجنبية، أعطت هذه العقيدات اشتباها بأنها تمثل أوراما سرطانية، إلا أن الفحص المجهرى النسيجي لعينة أخذت من الرئة أكدت تشخيص داء النشواني (الأميلويد) الرئوي العقيدي.

**الكلمات المفتاحية:** عقيدات رئوية متعددة؛ داء النشواني (الأميلويد)؛ أشعة مقطعية؛ تقرير حالة؛ عمان.

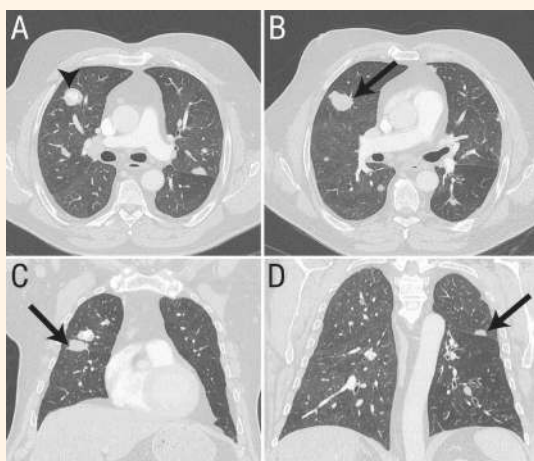
AMYLOIDOSIS IS A DISORDER RESULTING FROM the abnormal extracellular accumulation of amyloid in various tissues and organs.<sup>1</sup> Amyloidosis can be primary (i.e. idiopathic) or, more commonly, secondary to a variety of pathological conditions, including neoplastic, infectious and inflammatory aetiologies.<sup>2–4</sup> Pulmonary amyloidosis may be part of a systemic process or confined only to the lung, at which point it is classified as tracheobronchial, parenchymal nodular or diffuse alveolar septal pulmonary amyloidosis.<sup>5,6</sup> Although rare, nodular pulmonary amyloidosis can mimic other, more common, pulmonary disorders that manifest as multiple pulmonary masses or nodules, such as neoplastic and granulomatous conditions.<sup>2,7,8</sup> Therefore, pulmonary amyloidosis should be included in the differential diagnosis of single or multiple pulmonary nodules.

## Case Report

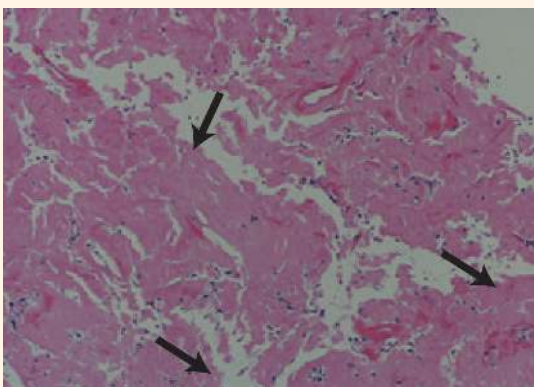
A 60-year-old man presented to the Emergency Department of the Royal Hospital, Muscat, Oman, in 2017 with a recent history of shortness of breath upon exertion, orthopnoea and bilateral lower limb swelling. He was an ex-smoker, diabetic and was currently taking insulin. There was no history of fever or chest pain, although he had dilated cardiomyopathy with a left ventricle ejection fraction of 35%. Upon physical examination, there were bilateral chest crepitations and bilateral lower limb oedema. All vital signs and other systemic examinations were unremarkable. A complete blood count, erythrocyte sedimentation rate, C-reactive protein level and renal and liver function tests were within normal limits.



**Figure 1:** Chest X-ray of a 60-year-old man with shortness of breath upon exertion, orthopnoea and bilateral lower limb oedema showing several nodular opacities (arrows), predominantly in the right lung.



**Figure 2:** High-resolution chest computed tomography scans in the (A & B) axial and (C & D) coronal views of a 60-year-old man with shortness of breath upon exertion, orthopnoea and bilateral lower limb oedema showing bilateral pulmonary nodules (arrows) with central calcification of the right upper nodule (arrowhead).



**Figure 3:** Haematoxylin and eosin stain at x10 magnification showing eosinophilic and amorphous material deposits (arrows).

The patient subsequently underwent a chest X-ray which showed bilateral nodular opacities [Figure 1]. Further evaluation using enhanced computed tomography (CT) revealed bilateral pulmonary nodules with a predominantly perilymphatic and subpleural distribution. The largest nodule arose in the right upper lobe, abutting the fissure, and measured  $2.3 \times 2.9$  cm. There was no evidence of pleural effusion or enlargement of the lymph nodes, although some of the nodules showed central calcification [Figure 2]. The preliminary diagnosis was of a neoplastic nodule that required further investigation. Accordingly, CT scans of the abdomen and pelvis were performed; however, the findings were unremarkable.

A tissue biopsy from the lung nodules was obtained under CT guidance. A microscopic examination of the tissue sample showed cores of hyalinised tissue with foci of haemorrhage. A haematoxylin and eosin stain showed deposits of eosinophilic amorphous material [Figure 3]. A special stain with Congo red and thioflavin T dyes revealed deposition of amyloid fibrils, consistent with a histological diagnosis of amyloidosis. As the patient was asymptomatic and there were no features suggestive of systemic amyloidosis, the decision was made to keep the patient under regular follow-up and observation.

## Discussion

Amyloidosis has an estimated global incidence of approximately 10 cases per million patients each year.<sup>9</sup> To the best of the authors' knowledge, the present case is the first to be reported from Oman. According to the site of deposition, amyloidosis can be categorised as systemic or localised. The four subtypes of systemic amyloidosis are primary light-chain amyloidosis, secondary amyloid A amyloidosis, familial amyloidosis and  $\beta 2$ -microglobulin-related amyloidosis.<sup>10</sup> The most common is secondary amyloid A amyloidosis, resulting from deposited amyloid P component. It mainly occurs in patients with chronic infections and those with rheumatic or autoimmune diseases.<sup>1,2</sup> In contrast, primary light-chain amyloidosis is due to deposited kappa and lambda light chains and can be associated with multiple myeloma, Waldenström's macroglobulinaemia and asymptomatic monoclonal gammopathy.<sup>1</sup>

Isolated pulmonary amyloidosis is rare and can be categorised into tracheobronchial, parenchymal nodular and diffuse alveolar septal amyloidosis.<sup>5,6</sup> Hui *et al.* reported 48 patients with localised respiratory amyloidosis, of which 14 had tracheobronchial amyloidosis, 28 showed either solitary or multiple pulmonary nodules and six had a diffuse interstitial parenchymal pattern.<sup>11</sup> Most of the

patients with nodular amyloidosis were asymptomatic, while those with tracheobronchial or diffuse interstitial amyloidosis had respiratory symptoms.<sup>11</sup> In a 13-year study of 55 patients with biopsy-proven pulmonary amyloidosis, Utz *et al.* reported that 35 had primary systemic amyloidosis, 17 had amyloidosis localised to the respiratory system and three had secondary or familial amyloidosis.<sup>6</sup> Of the patients with localised amyloidosis, seven had nodular amyloidosis and four had tracheobronchial amyloidosis. Nodular amyloidosis was not associated with systemic amyloidosis and had a predominantly benign prognosis.<sup>6</sup>

Tracheobronchial amyloidosis usually presents with symptoms related to airway obstruction such as dyspnoea, coughing, recurrent pneumonia and haemoptysis.<sup>7,9</sup> The classic radiological features of tracheobronchial amyloidosis are tracheal *lumen* irregularities, bronchial wall thickening and calcified amyloid deposition, which can be mural or endobronchial, resulting in subsegmental collapse.<sup>5,7,12</sup> Diffuse interstitial parenchymal amyloidosis is the rarest type of pulmonary amyloidosis and usually occurs among patients with systemic amyloidosis.<sup>9</sup> The deposited amyloid results in alveolar wall and capillary damage, leading to impaired gas exchange. As with tracheobronchial amyloidosis, patients usually present with a cough, dyspnoea and haemoptysis, or a combination of these symptoms. Classic radiological findings include non-specific interstitial and alveolar opacities, predominantly basal and peripheral, well-defined nodules and confluent subpleural opacities.<sup>5,13</sup>

Nodular amyloidosis is usually localised to the respiratory system.<sup>6</sup> Affected patients are generally asymptomatic and the amyloid nodules detected incidentally.<sup>14</sup> On CT imaging, nodular amyloidosis can present as multiple lesions or, less commonly, as a single lesion with lower lobe and subpleural predominance.<sup>14–16</sup> The amyloid nodules are usually well-defined with lobulated contours; they can vary in size from 0.5–15 cm and may gradually grow over time without regression. Approximately half of all amyloid nodules calcify, although they rarely cavitate.<sup>14,15</sup> In the current case, the patient had localised amyloidosis with no evidence of systemic involvement. A chest CT scan showed bilateral pulmonary nodules with a perilymphatic and subpleural predilection and occasional central calcification.

Nodular pulmonary amyloidosis can mimic other nodular pulmonary disorders, such as neoplastic and granulomatous processes.<sup>7,8,17</sup> Therefore, a biopsy is required for diagnosis and to differentiate it from other nodular pulmonary disorders. Immunohistochemistry remains the gold standard for the detection of amyloid material which appears inert, proteinaceous, homogeneous, acellular and eosinophilic; with Congo

red staining, the amyloid proteins display green birefringence under polarised light.<sup>2,3,9,12</sup>

Due to the rarity of the condition, no randomised controlled trials have yet been conducted regarding nodular pulmonary amyloidosis management. However, the general consensus is that treatment depends on the severity of the symptoms. For example, for asymptomatic patients, regular follow-up and careful monitoring may be sufficient.<sup>2</sup> In contrast, different treatment options may be necessary for symptomatic patients, including conservative excision, carbon dioxide laser ablation and low-dose external beam radiation.<sup>9,18</sup>

## Conclusion

Nodular pulmonary amyloidosis is a rare and usually localised disease that can mimic other nodular pulmonary disorders, such as neoplastic and granulomatous processes. As such, this condition should be included in the differential diagnosis of pulmonary nodules or masses.

## References

1. Baker KR, Rice L. The amyloidoses: Clinical features, diagnosis and treatment. *Methodist Debakey Cardiovasc J* 2012; 8:3–7.
2. Lee SH, Ko YC, Jeong JB, Park CW, Seo SH, Kim JT, et al. Single nodular pulmonary amyloidosis: Case report. *Tuberc Respir Dis (Seoul)* 2015; 78:385–9. doi: 10.4046/trd.2015.78.4.385.
3. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, et al. Amyloid fibril protein nomenclature: 2012 recommendations from the Nomenclature Committee of the International Society of Amyloidosis. *Amyloid* 2012; 19:167–70. doi: 10.3109/13506129.2012.734345.
4. Gernay C, Médart L. Multiple calcified nodules in pulmonary amyloidosis. *JBR-BTR* 2014; 97:370. doi: 10.5334/jbr-btr.133.
5. Czeyda-Pommersheim F, Hwang M, Chen SS, Strollo D, Fuhrman C, Bhalla S. Amyloidosis: Modern cross-sectional imaging. *Radiographics* 2015; 35:1381–92. doi: 10.1148/rg.2015140179.
6. Utz JP, Swensen SJ, Gertz MA. Pulmonary amyloidosis. The Mayo Clinic experience from 1980 to 1993. *Ann Intern Med* 1996; 124:407–13. doi: 10.7326/0003-4819-124-4-199602150-00004.
7. Gaurav K, Panda M. An uncommon cause of bilateral pulmonary nodules in a long-term smoker. *J Gen Intern Med*. 2007; 22:1617–20. doi: 10.1007/s11606-007-0324-z.
8. Morisaki K, Shoji F, Kawano D, Yano T, Maehara Y. [Primary nodular pulmonary amyloidosis]. *Kyobu Geka* 2009; 62:1006–9.
9. Milani P, Basset M, Russo F, Folli A, Palladini G, Merlini G. The lung in amyloidosis. *Eur Resp Rev* 2017; 26:1740046. doi: 10.1183/16000617.0046-2017.
10. Real de Asúa D, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: Epidemiology, diagnosis, and management. *Clin Epidemiol* 2014; 6:369–77. doi: 10.2147/CLEP.S39981.
11. Hui AN, Koss MN, Hochholzer L, Wehunt WD. Amyloidosis presenting in the lower respiratory tract: Clinicopathologic, radiologic, immunohistochemical, and histochemical studies on 48 cases. *Arch Pathol Lab Med* 1986; 110:212–18.

12. Chatkin G, Pipkin M, Pinto JA, Silva VD, Chatkin JM. [Primary tracheobronchial amyloidosis]. *J Bras Pneumol* 2008; 34:528–31. doi: 10.1590/S1806-37132008000700013.
13. Graham CM, Stern EJ, Finkbeiner WE, Webb WR. High-resolution CT appearance of diffuse alveolar septal amyloidosis. *AJR Am J Roentgenol* 1992; 158:265–7. doi: 10.2214/ajr.158.2.1729778.
14. Suzuki H, Matsui K, Hirashima T, Kobayashi M, Sasada S, Okamoto N, et al. Three cases of the nodular pulmonary amyloidosis with a longterm observation. *Intern Med* 2006; 45:283–6. doi: 10.2169/internalmedicine.45.1487.
15. Vieira IG, Marchiori E, Zanetti G, Cabral RF, Takayassu TC, Spilberg G, et al. Pulmonary amyloidosis with calcified nodules and masses: A six-year computed tomography follow-up - A case report. *Cases J* 2009; 2:6540. doi: 10.4076/1757-1626-2-6540.
16. Feng J, Li J, Ling C, Liu Q. A rare case of multinodular pulmonary amyloidosis. *Clin Respir J* 2016; 10:389–92. doi: 10.1111/crj.12220.
17. Shin B, Ko J, Lee SS, Lim KS, Han JH, Chung MP, et al. [A case of pulmonary amyloidosis mimicking lymphangitic lung carcinomatosis]. *Korean J Med* 2014; 86:339–42. doi: 10.3904/kjm.2014.86.3.339.
18. Nugent AM, Elliott H, McGuigan JA, Varghese G. Pulmonary amyloidosis: Treatment with laser therapy and systemic steroids. *Respir Med* 1996; 90:433–5. doi: 10.1016/S0954-6111(96)90119-5.