Journal of Advances in Medicine and Medical Research

23(3): 1-8, 2017; Article no.JAMMR.35222
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, ISSN: 2231-0614, NLM ID: 101570965)

A Complicated Case of Dyspnea

Dafne T. Moretta[1*], Christopher Gasho[1], Laura Denham[1] and Laren A. Tan[1]

[1]Loma Linda University Medical Center, 11234 Anderson St, Loma Linda, CA 92354, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Author DTM wrote the first draft of the manuscript. Author CG focused on the pathology discussion and in collaboration with author DTM managed the overall literature searches and the patient's chart review. Author LD supplied the analysis of the pathology slides and provided the microscope pictures. Author LAT imparted scholar mentorship. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2017/35222
Editor(s):
(1) Andrea S. Melani, Antismoking Centre, Azienda Ospedaliera Senese, Italy.
Reviewers:
(1) Serdar Özkan, Medova Hospital, Turkey.
(2) Coquart Jeremy, University of Rouen, France.
Complete Peer review History: http://www.sciencedomain.org/review-history/20441

Case Study

Received 1st July 2017
Accepted 12th July 2017
Published 9th August 2017

ABSTRACT

This is the case of a patient initially presenting with productive cough, pleuritic chest pain, and hypoxemia. After a complicated clinical course the patient was eventually diagnosed with mucinous adenocarcinoma of the lung and associated pleural amyloidosis.
The relation between cancer and amyloidosis is still unclear; however it is a very well- known fact that amyloid deposits are linked to malignancy. Gene mutations in cancer can trigger the expression of proteins which can aggregate into amyloid like fibrils.

Keywords: Adenocarcinoma of the lung; pleural amyloid; mucinous adenocarcinoma; pulmonary cavitations; multifocal lung cancer; amyloidosis.

1. CASE PRESENTATION

A 70 year-old male was referred to our institution for breathlessness, chest pain, and cavitary lung lesions.

The patient complained of persistent dyspnea on exertion, a six-month history of productive cough, and pleuritic chest pain. His vital signs were normal; his oxygen saturation level (SpO2) was 91% on 2 lpm of oxygen supplementation. He was obese, without distress at rest but with visible breathlessness on 10-15 feet ambulation. He had 1+ lower extremity pitting edema, bilateral expiratory wheezes, and decreased breath sounds on auscultation.

**Corresponding author: E-mail: dtmoretta@gmail.com*

The patient had a remote smoking history, a questionable asbestos exposure, and had worked as a sheet metal worker. He had recently traveled to Arizona and Oregon and denied any exposure, and/or personal/familial history of tuberculosis. Spirometry revealed a forced vital capacity (FVC) of 47%, a forced expiratory volume in one second (FEV1) of 57%, and a ratio (FEV1/FVC) of 120% of predicted. *Histoplasma*, *Coccidiodes*, and *Aspergillus* titers were all negative. Sputum cultures for acid fast bacillus (AFB), bacterial, and fungal infections were also negative.

Initial chest x-ray (CXR) showed multiple patchy opacities bilaterally. Original chest CT, revealed irregular peripheral areas of consolidation with internal lucency scattered throughout both lungs with associated patchy ground glass opacities surrounding the consolidations, and micro-honeycombing. Repeat chest CT one year later, redemonstrated wide spread of peripheral consolidations and ground glass opacifications. Bilateral lucent foci, likely representing cavitations, and foci of consolidation with increased solid component were also observed. There was ground glass with scattered centrilobular nodules in both lungs and fibrotic changes with associated traction bronchiectasis in lung bases.

Bronchoscopy with fluoroscopy guided right upper lobe biopsy and bronchoalveolar lavage (BAL) of the left upper lobe were performed. No malignancy was identified on pathology report. BAL revealed atypical cells with cytoplasmic clearing and <1,000 *Streptococcus viridans.*

The patient was subsequently hospitalized for acute on chronic hypoxemic respiratory failure. He was empirically treated with Voricanozole and Micafungin for suspected invasive fungal infection. Patient eventually underwent video-assisted thoracoscopic surgery (VATS) of his left upper lobe with wedge lingular resection and pleural biopsy.

Pathology results revealed fibro-membranous soft tissue with dense fibrous plaque and focal amyloid deposits in the left parietal pleural tissue. Sulfated Alcian Blue stain was positive. Congo red stain showed characteristic apple green birefringence with polarized light and pinkish staining without polarization. Tissue findings of the left upper lobe wedge resection also revealed fibro-vascular cores lined by mucinous tumor cells replacing the alveolar lining, as well as complex papillary structures also lined by mucinous cells. No lymph-vascular or pleural invasions were identified. All tissue microbiologic studies were negative.

2. DIAGNOSIS

Adenocarcinoma of the Lung and associated pleural Amyloidosis. The potential relation between both entities is discussed below.

3. CLINICAL DISCUSSION

The incidence of amyloidosis is low [1] and that of only lung involvement is extremely rare [2]. There are only few case reports describing isolated pleural amyloidosis [3,4]. Furthermore, pleural amyloid deposits related to lung malignancy have not been described before to our knowledge. Therefore, clinical manifestations of this particular entity are hard to define.

Amyloidosis results from the extracellular deposition of fibrillar amyloid protein [1]. This infiltrative process can trigger dyspnea with heart or lung involvement. However, the clinical presentation of pleural disease can be inconsistent. On a previous case report of isolated pleural amyloidosis initially mimicking mesothelioma, Nakano et al. [4] discussed a completely asymptomatic patient with an incidental finding of pleural thickening eventually found to have pleural amyloid deposits. Published cases of concomitant pleural amyloidosis and effusion usually present with dyspnea [5].

In lung malignancy, on the other hand, fatigue, cough, and dyspnea are the most common clinical presentations. In a longitudinal analysis of 2293 non-small cell lung cancer (NSCLC) patients, dyspnea occurred in 45% of patients. The most common symptom however was cough (55%) [6]. Dyspnea may be due to extrinsic or intraluminal airway obstruction, obstructive pneumonitis or atelectasis (most likely present in our patient), lymphangitic tumor spread, tumor emboli, pneumothorax, or pleural effusion [7].

4. RADIOLOGIC DISCUSSION

Although an infectious etiology was not originally excluded, our patient's radiographic findings were thought to be initially consistent with organizing pneumonia given their peripheral (subpleural) distribution, ground glass coexistence, multiplicity of opacities or consolidations that eventually cavitated, and lack of resolution after antibiotic management.

However, pathologic result of the radiographic abnormality revealed an unusual cavitating Adenocarcinoma.

Malignant processes may cavitate given internal desquamation of tumor cells with subsequent liquefaction or rapid tumor growth that exceeds the available blood supply with resultant central necrosis [8,9]. Onn et al. showed that 81% of tumors with cavitation had an associated over-expression of epidermal growth factor receptor (EGFR), which is associated with rapid growth, central necrosis, and formation of cavitation [10].

Numerous studies have demonstrated that cavity wall thickness is useful in predicting malignancy. In a recent retrospective study, Nin et al. showed that maximum wall thicknesses thresholds of ≤7 or ≥24 mm were the most accurate in suggesting non-malignant and malignant etiologies respectively [11]. Finally, cavitations are more frequently found among cases of squamous cell carcinomas than other histological types [12] and tumor-related cavitations have worse prognosis [13].

Complicating the diagnostic evaluation of cavitary lung lesions is the not infrequent coexistence of pulmonary infection and malignancy like in our patient. Multiple cases of combined infectious and malignant cavitary pulmonary lesions have been reported [14]. The causal pathway for this association can go both ways: chronic inflammation and scarring may contribute to malignancy, or cancer-associated immunosuppression may result in infections.

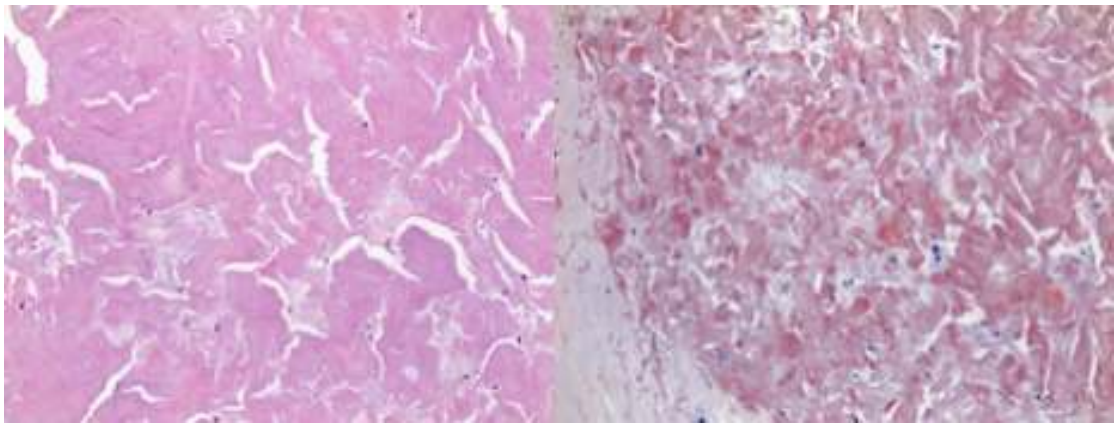
Pleural thickening though non-specific, is the main radiographic finding of pleural amyloidosis. Given his severe hypoxemic respiratory failure, our patient was unable to complete a fluorodeoxyglucose positron emission tomography (FDG-PET) as a mode to survey for malignant extent and to further characterize his pleural disease. However, false-positive findings of PET-CT make it difficult to diagnose pleural amyloidosis in distinguishing malignancy, especially because FDG is not a tumor-specific tracer and numerous nonmalignant processes can result in FDG accumulation. The uptake of FDG in pulmonary amyloid lesions is thought to be related to the abnormal production and metabolism of immunoglobulins by plasma cells [15].

In short, the diagnosis of any type of amyloid deposits involving the lung or pleura, needs a multidisciplinary approach, given the non-specific and variable imaging findings.

5. PATHOLOGIC DISCUSSION

It is a well-known fact that amyloid deposits are linked to malignancy [4,6]. Localized amyloid deposition is believed to arise from a small number of plasma cell tumors or infiltrates [16,17]. Histologically, these lesions are usually characterized by the presence of an amorphous eosinophilic material with focal collections of a lymphoplasmacytic infiltrate and associated focal clusters of giant cells. Histochemical stain Congo red shows strong positive apple-green birefringency, and immunohistochemical studies using kappa and lambda light chains reveal polyclonality [6].

Our patient had a rare presentation of pulmonary adenocarcinoma with concurrent pleural amyloid deposition without evidence of systemic amyloidosis. Our literature review search for “pleural amyloid” and “pleural amyloidosis” returned 91 and 184 publications respectively. From our investigation, this would be the first report of isolated pleural amyloid deposition related to malignancy (see Table 1).



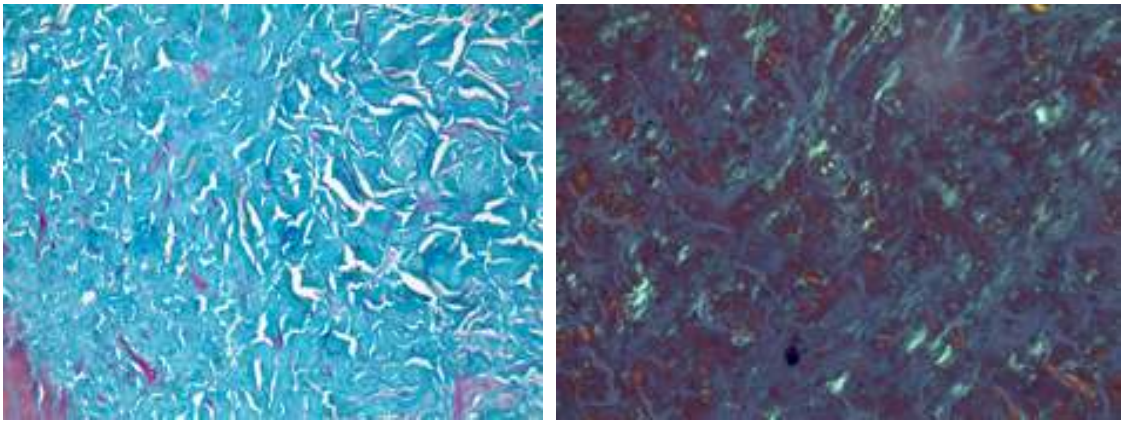


Fig. 1. Top Left: Amorphous, eosinophilic waxy material within pleural fibrous tissue, Amyloid deposit (H&E, 100x) Top Right: Non-polarized Congo Red staining amyloid a pinkish color (100x). Bottom Left: Sulfated Alcian Blue demonstrating bright aqua staining of amyloid (100x). Bottom Right: Congo Red showing characteristic birefringence (200x)

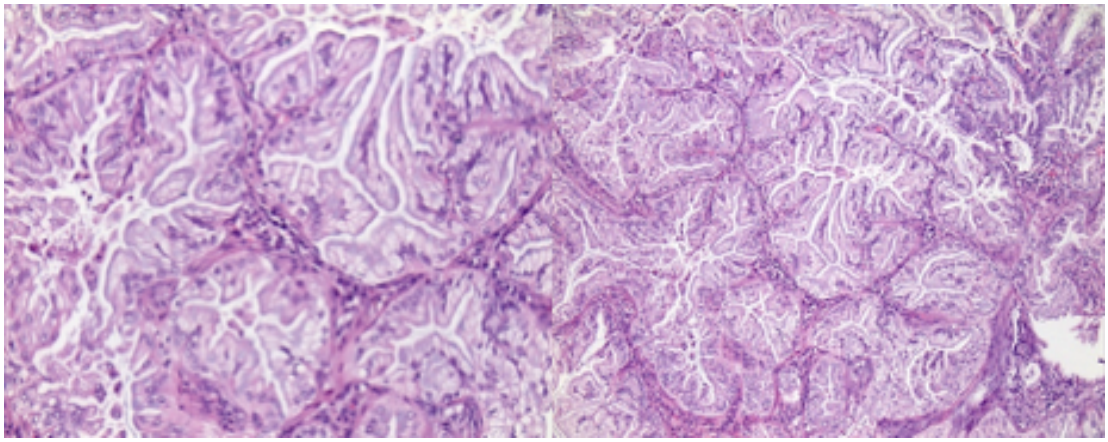


Fig. 2. Left: Scanning power demonstrates cuboidal to columnar mucinous cells completely replacing the normal pneumocytes (H&E, 200x) Right: Low power shows the complex papillary pattern, with fibrovascular cores lined by micropapillae (H&E, 100x)

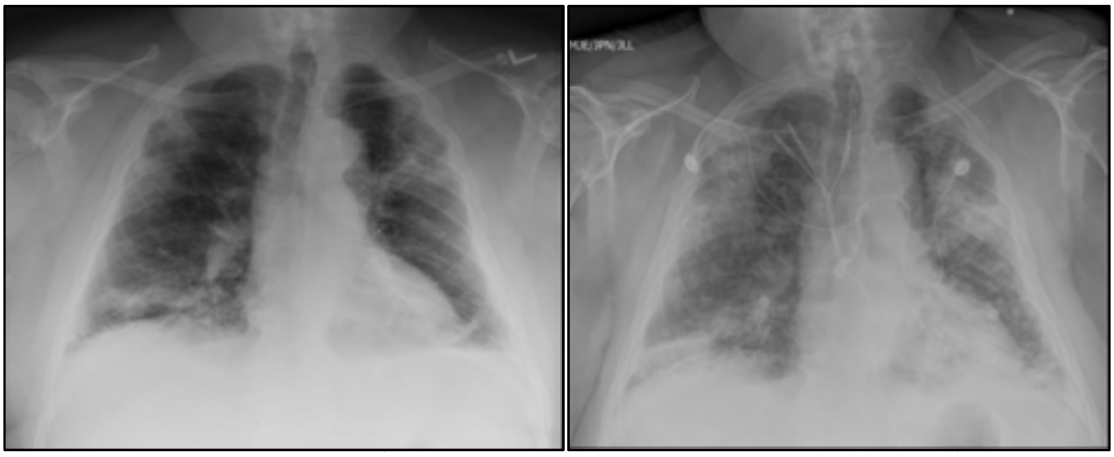


Fig. 3. Evolution of CXR from initial presentation to ICU management

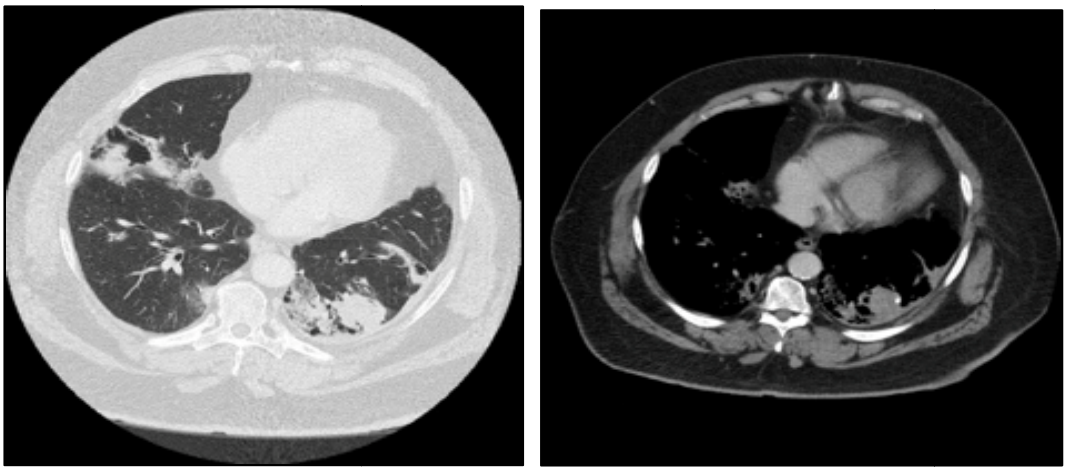


Fig. 4. Initial chest CT revealing peripheral-predominant areas of consolidation

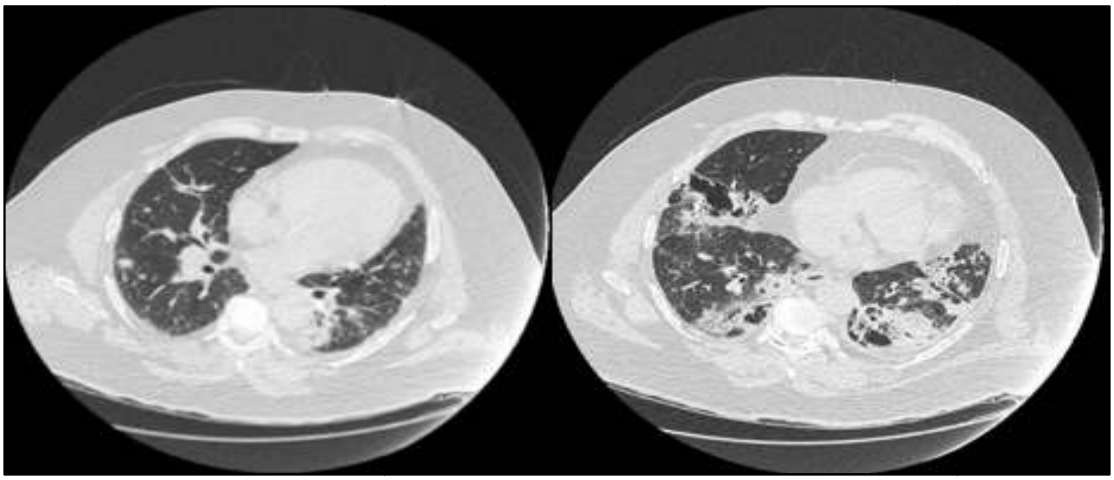


Fig. 5. With time, peripheral predominant consolidations persisted, however central area of lucency and surrounding ground-glass changes developed

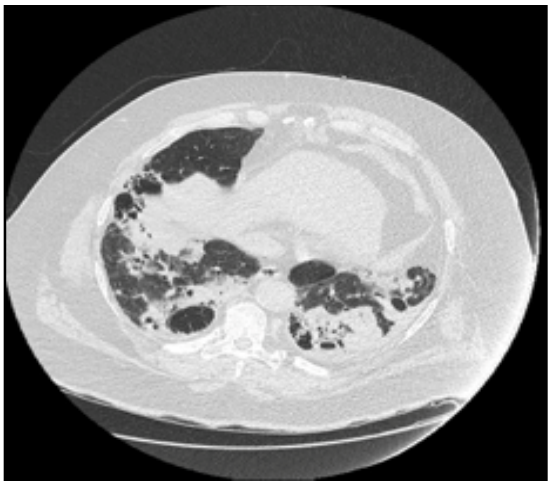


Fig. 6. Last Chest CT showing again areas of peripheral consolidation, with central lucency and pleural thickening

Table 1. Summary of case reports, case series, and review

Date	Author	Journal	Study type	Number of patients	Systemic amyloid	Pleural effusion	Pleural deposition	Adeno-carcinoma	Parenchymal findings
2013	Harvey- Taylor	J Thoracic Disease	CR	1	Y	Y	Y	N	N
2011	Marsalis, KA.	Amyloid	CR	1	Y	Y	Y	N	N
2010	Aichoaouia	Rev Pneumol Clin	CR	1	Y	Y	Y	N	Y
2009	Rodrigues	Int J Rheum	CR	1	N	N	N	N	Y
2005	Roux	Clin Rheum	CR	1	Y	Y	Y	N	N
2005	Suzuki	Internal Medicine	CR	2	N	Y	Y	N	N
2003	Leleu	Rev Mal Respir	CR	1	Y	Y	Y	N	N
2003	Berk, JL.	Chest	Retros-pective	636 amyloid, 35 persistent effusions, 6 biopsies	Y	Y	Y	N	N/A
2001	Adams, AL.	Ann Diagnostic Pathol	CR	2	N	N	Y	NO, but mesothe- lioma	N
1999	Looi	Malays J Pathology	CS	15/2	13	-	-	NO, but tumor like amyloid	2 cases with tumor
1996	Quinwuenek (French)	Rev Pneumol Clin	R	-	-	-	-	-	-
1995	Aprile, C.	Eur J Nuc Med	Prospec tive	24	Y	N/A	9 patients	N	9 patients
1995	Bontemps	Eur Resp J	CR	1	Y	Y	Y	N	N
1993	Smith FB	Ann J Clin Pathology	CR	1	N	Y	Y	N	N
1990	Kavuru	Chest	CS	5	Y	Y	Y	N	N
1988	Graham	Eur Resp J	CR	1	Y	Y	N/A	N	N

Legend: CR: Case Report; CS: Case Series; R: Review; N: no; Y: yes;

Although there is no well-defined link between adenocarcinoma and pleural deposition of amyloid there has been recent investigation which supports the biologic plausibility of such a link. Ishimaru et al. [18] showed that some proteins which are not associated with amyloid disease can aggregate into amyloid like fibrils in specimens with Tp53 core mutations under special conditions. A follow up study was completed by De Lima and colleagues [19] evaluating patients with NSCLC. Specimens were evaluated for the p53 mutation which had a prevalence of 57% however they were unable to detect amyloid on Congo stain with birefringence.

More recently Dowling et al. [20] evaluated the use of serum amyloid A (SAA) and other acute phase proteins as a biomarker for detecting both small cell lung cancer (SCLC) and NSCLC. This is further confirmed by Ma and collaborers who this year identified SAA as a acute phase protein which analyzed through multivariate models for diagnosis and therapeutic monitoring of lung cancer, was found to have an area under the curve (AUC) near 0.83 [21].

Shiels et al. [22] showed an odd ratio of 1.8 for overall lung cancer risk in those patients with elevated SAA. These markers are not specific to lung cancer and have been investigated in a myriad of other malignancies and inflammatory entities.

6. CONCLUSION

Our patient's immediate postoperative course was uncomplicated. However, after 48 hours in the Intensive Care Unit (ICU), he became increasingly hypoxemic and hypotensive, experienced increased work of breathing requiring high flow nasal cannula and eventually Bilevel Positive Airway Pressure (BPAP) therapy. In light of his diagnosis and prognosis, patient refused intubation and decided to switch goals to comfort care only. Patient expired soon after.

The relationship between cancer and amyloidosis is still unknown. Amyloid fibril deposition has been described in patients with malignant diseases, mostly hematological neoplasms but also solid tumors [23,24]. The circulating precursors of amyloid fibrils in cancer patients are not always, however, followed by amyloid deposition. Lung cancer may contribute to amyloid deposits through paraneoplastic mechanisms in systemic amyloidosis. Nevertheless, in our case, the process by which the malignancy precipitated amyloid infiltration selectively to the neighboring pleura is unclear. Speculatively, local inflammation and/or invasion of malignant cells byproducts can be associated to biochemical or genetic changes which will eventually trigger the fibrils to burden the pleura. Other mechanisms such as precursor of the amyloid protein originating from tumor or a tumor-derived enzyme cleaving a serum precursor of amyloid protein may also be considered. Hundreds of mutations and polymorphisms driven by autoin- flammatory diseases have been associated with heritable and acquired forms of amyloidosis [25]. A similar oncogenic effect could be possible. In either case, the mechanisms of amyloid formation and selective deposition in association with lung cancer are unknown and further research in this field is warranted.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

Postmortem informed consent was obtained from patient's guardian to confirm permission for publication of patient information. Protection of privacy was ensured during the entire writing process.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gertz MA, Lacy MQ, et al. Amyloidosis Review Best Practice and Research ClinicalHaematology. 2005;18(4):709-27.
2. Berk JL, O'Regan A, et al. Pulmonary and tracheobronchial amyloidosis. Seminary of Respiratory and Critical Care Medicine. 2002;23(2):155-65.
3. Bontemps F, Tillie-Leblond I, et al. Pleural Amyloidosis: thoracoscopic aspects. European Respiratory Journal. 1995;8(6): 1025-7.
4. Nakano T, Endo S, et al. Asymptomatic localized pleural amyloidosis mimicking

mali-gnant pleural mesothelioma: Report of a case. Journal of Thoracic Disease. 2016; 8(1):E157-E160
5. Adams AL, Castro CY, et al. Pleural amyloidosis mimicking mesothelioma: A clinicopa- thologic study of two cases. Annals of Diagnostic Pathology. 2001;5: 229-32.
6. Kocher F, Hilbe W, et al. Longitudinal analysis of 2293 NSCLC patients: A comprehensi- ve study from the TYROL registry. Lung Cancer. 2015;87(2):193.
7. Midthun D. Overview of the risk factors, pathology, and clinical manifestations of lung cancer. UpToDate®. Feb 23; 2015.
8. Miura H, Taira O, et al. Cavitating adenocarcinoma of the lung. Annals of Thoracic and Cardiovascular Surgery. 1998;4:154–158.
9. Sasaki T, Kinoshita Y, et al. Aggressive cystic and cavitary appearances in lung Ade-nocarcinoma. Internal Medicine. 2017; 56(1):119-120.
10. Onn A, Choe DH, Herbst RS, et al. Tumor cavitation in stage I non-small cell lung can- cer: epidermal growth factor receptor expression and prediction of poor outcome. Radiology. 2005;237:342-347.
11. Nin CS, de Souza VV, et al. Solitary lung cavities: CT findings in malignant and non-malignant disease. Clinical Radiology. 2016;71(11):1132-6.
12. Chiu FT. Cavitation in lung cancers. Australian and New Zealand Journal of Medicine. 1975;5:523–530.
13. Kolodziejski LS, Dyczek S, et al. Cavitated tumor as a clinical sub-entity in squamous cell lung cancer patients. Neoplasma. 200350:66–73.
14. Liao WY, Liaw Y, et al. Bacteriology of infected cavitating lung tumor. American Journal of Respiratory and Critical Care Medicine. 2000;161:1750–1753.
15. Kung J, Zhuang H, et al. Intense fluorodeoxyglucose activity in pulmonary amyloid le- sions on positron emission tomography. Clinical and Nuclear Medicine. 2003;28:975-6.
16. Berk JL, O' Regan A, Skinner M. Pulmonary and tracheobronchial amyloidosis. Semin Respir Crit Care Med. 2002;23:155-65.
17. Glenner GG. Amyloid deposits and amyloidosis: The B-fibrilloses. N Engl J Med.1980;302:1283-1292,1333-1343.
18. Ishimaru D, Ano Bom AP, et al. Cognate DNA stabilizes the tumor suppressor p53 and prevents misfolding and aggregation. Biochemistry. 2009;48(26):6126-35.
19. De Lima Araujo LH, Pinto LW, at al. Amyloid-like fibrils are not detected in non-small cell lung cancer tissue samples. Medical Oncology. 2012;29(6):614-7.
20. Dowling P, Clarke C, et al. Analysis of acute-phase proteins, AHSG, C3, CLI, HP, and SSA, reveals distinctive expression patterns associated with breast, colorectal, and lung can- cer. International Journal of Cancer. 2012;131(4):911-23.
21. Ma R, Xu H, et al. Identification of serum proteins and multivariate models for diag- nosis and therapeutic monitoring of lung cancer. Oncotarget. 2017;(5): 1-12.
22. Shiels MS, Katki HA, et al. Circulating inflammation markers, risk of lung cancer, and utility for risk stratification. Journal of the National Cancer Institute. 2015; 107(10):199.
23. Muller A, et al. Primary amyloidosis in plasma cell disorders. The Oncologist. 2006;11(7):824-830.
24. Chan DC, Chen CJ, et al. Evaluation of Serum amyloid a as a biomarker for gastric cancer. Annals of Surgical Oncology. 2007;14:84–93.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20441