Case Report

Amyloidosis involving the respiratory system: 5-year's experience of a multi-disciplinary group's activity

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Submitted: 20-10-2014
Accepted: 19-12-2014

Abstract:

Amyloidosis may involve the respiratory system with different clinical-radiological-functional patterns which are not always easy to be recognized. A good level of knowledge of the disease, an active integration of the pulmonologist within a multidisciplinary setting and a high level of clinical suspicion are necessary for an early diagnosis of respiratory amyloidosis. The aim of this retrospective study was to evaluate the number and the patterns of amyloidosis involving the respiratory system. We searched the cases of amyloidosis among patients attending the multidisciplinary rare and diffuse lung disease outpatients' clinic of Pulmonology Unit of the Hospital of Arezzo from 2007 to 2012. Among the 298 patients evaluated during the study period, we identified three cases of amyloidosis with involvement of the respiratory system, associated or not with other extra-thoracic localizations, whose diagnosis was histo-pathologically confirmed after the pulmonologist, the radiologist, and the pathologist evaluation. Our experience of a multidisciplinary team confirms that intra-thoracic amyloidosis is an uncommon disorder, representing 1.0% of the cases of rare and diffuse lung diseases referred to our center. The diagnosis of the disease is not always easy and quick as the amyloidosis may involve different parts of the respiratory system (airways, pleura, parenchyma). It is therefore recommended to remind this orphan disease in the differential diagnosis of the wide clinical scenarios the pulmonologist may intercept in clinical practice.

Key words:

Amyloidosis, lung amyloidosis, pleural amyloidosis, pulmonary amyloidosis, respiratory system

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.157290

Amyloidosis is a group of diseases characterized by the progressive deposition of abnormal proteic, eosinophilic, and insoluble material (amyloid) in the extracellular space of body tissues.

The recent international classification of amyloidosis[1] recognizes 30 types of human amyloid and its precursors, defined by an abbreviations of the main protein involved in the deposits, prefixed with the letter A.[1] The most important proteins in the human disease are amyloid L (AL) and amyloid A (AA). According to this classification amyloid is defined by the type of amyloid, the diffusion (local or systemic), the nature of the disease (acquired or inherited), and the organs involved. [Table 1] shows some of the most important clinical forms of amyloidosis:

1. Immunoglobulin light chain amyloidosis (AL) which can be found in myeloma;
2. Amyloid A amyloidosis (AA) due to chronic inflammatory diseases like: Tuberculosis, rheumatoid arthritis, and cancer;
3. Transthyretin amyloidosis (ATTR) which includes two forms: The inherited form due to a mutation of ATTR and associated with poly-neuropathy and familial cardiac disorders and the elderly adults form linked to "wild -type" ATTR and causing prevalent cardiac disease;
4. Beta-2 microglobulin amyloidosis (Aβ2M) usually linked to renal dialysis.

The incidence of amylodosis is estimated at 14 cases per million person-year.[2] The mean annual incidence of the AL form is 0.8/100.000 person-year[3,4] while the frequency of the AA form is decreasing, thanks to the improvement achieved in the treatment of infections and chronic inflammatory diseases.[5] The inherited form's prevalence is below 1 case per 100.000 person-year in the US clinical records.[2] The "wild-type" ATTR form has been found in autopsy reports in about the 25% of people older than 80 years but the clinical significance of this data remains unclear. The prevalence of "wild-type" protein TTR deposition that can cause a cardiac disorder as the main clinical manifestation of amyloidosis is still to be clarified, but this form is very rare and the extra-cardiac involvement is not a common event.[6-8]

In literature, there are not confirmed data about the real incidence of lung involvement in

amyloidosis. This is mainly due to the rarity of the disease, the different diagnostic criteria used, and the heterogeneity of the clinical records reported.

The involvement of the respiratory system is estimated at the 50% of patients affected by amyloidosis.[9] It can be either an isolated manifestation or a part of a systemic disease and is usually divided in three forms:

1. Tracheo-bronchial;
2. Parenchymal with nodular pattern; and
3. Parenchymal with diffuse, septal or interstitial pattern.

Amyloidosis can even affects pleura, pulmonary arteries, lymphonodes, and diaphragm.[9,10]

The current therapeutic approach to systemic amyloidosis is based on the observations that organ dysfunction improves and survival increases if the synthesis of the amyloidogenic protein precursor is halted. Decisions about specific treatment regimens for individual patients must take into consideration the balance between anticipated treatment efficacy and tolerability. High-dose melphalan (HDM) followed by autologous peripheral blood stem cell transplantation (SCT) presently is considered the most effective treatment for AL amyloidosis.

In many cases regardless to the lack of a specific treatment, the only possible therapeutic approach is supportive care to decrease the symptoms and improve organ function.[11]

The aim of this retrospective study is to define the incidence and describe the features of amyloidosis cases with respiratory tract involvement who referred to our center. In this paper, we did not aim to discuss therapeutic approaches to the disease.

Methods

Three patients affected by amyloidosis with respiratory tract involvement have been identified among 298 patients who referred to the "Interstitial lung diseases Multidisciplinary Group" (GIM) ambulatory of Arezzo's Pulmonology Unit during the period 2007-2012.

In these cases, the lung involvement was both isolated or associated with extra-thoracic lesions and the diagnosis was confirmed by the histopathological exam after the evaluation of the multidisciplinary group, composed by a pathologist, a pulmonologist, and a radiologist.

Table 1: Main forms of amyloidosis in the recent international classification

Main protein involved	Concomitant disease	Organs involved
*AL	Multiple myeloma, lymphoma Waldestrom syndrome	Heart, kidney, liver, gastro-intestinal tract, peripheral/autonomic nervous system, lung
*AA	Autoimmune inflammatory chronic diseases, infections, neoplasms, inherited chronic diseases (familial mediterranean fever)	Kidney, nervous system, heart, lung
*ATTR mutation variant		Heart, nervous system, lung-renal
*ATTR "Wild-type"		Heart
*Aβ2M	Dialisis linked	Autonomic nervous system, muscoloskeletal system

*AL = Light chain immunoglobulin, AA = Seric amyloid A, ATTR = Transthyretin, Aβ2M = β2-microglobuline

Case Reports

Case report 1

A 71-year-old non-smoker woman presented at our ambulatory with persistent dyspnea despite many months therapy with systemic steroids and inhaled bronchodilator plus steroids for a previous history of bronchial asthma. Lung function tests showed a plateau in the middle of the expiratory part of the flow-volume curve without significant improvement after short-acting beta2 agonist inhalation, suggesting the presence of intra-thoracic irreversible obstruction [Figure 1]. At the chest X-ray, a relevant latero-lateral stenosis of the distal trachea was evident. Chest computed tomography (CT) scan was then performed showing a diffuse thickening of lateral right tracheal wall until the carina with involvement of right upper lobe bronchus and apical segmental bronchus. Fibrobronchoscopy confirmed the presence of tracheal right deviation with a stenosis of about the 25% of the distal tracheal lumen extended to the right upper lobe bronchus caused by marked mucosal hypertrophy [Figure 2]. Bronchial biopsy was positive to the Congo red stain so the diagnosis of primary tracheo-bronchial amyloidosis (isolated AL) was performed. The presence of extra-pulmonary lesions was then excluded through radiological examination (total-body CT scan) and immunological and serological chemistry tests (immunoglobulins and pro-B-type natriuretic peptid -pro-BNP- measurement, Bence Jones protein lab test, routine blood tests). The patient was successfully treated with the placement of a metallic tracheal stent following a Nd-Yag laser-assisted disobstruction of central airways.

Case report 2

A 71-year-old male patient, former smoker, had a diagnosis of cardiac amyloidosis treated since few years with talidomide, melphalan, and disodic pamidronate. He presented at our ambulatory with worsening dyspnea. The chest X-ray showed bilateral pleural effusion despite of optimized diuretics

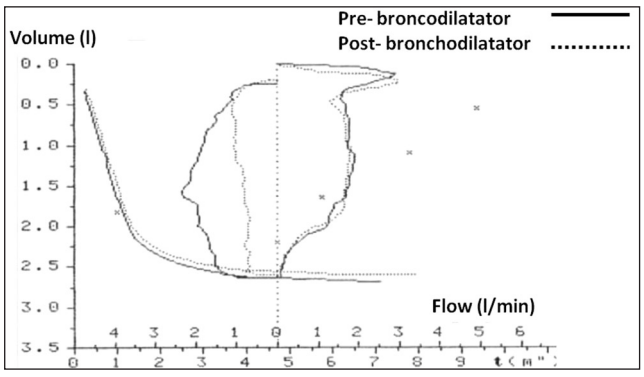

Figure 1: Curve-volume curve with evident plateau in the mid-expiratory phase (case 1)

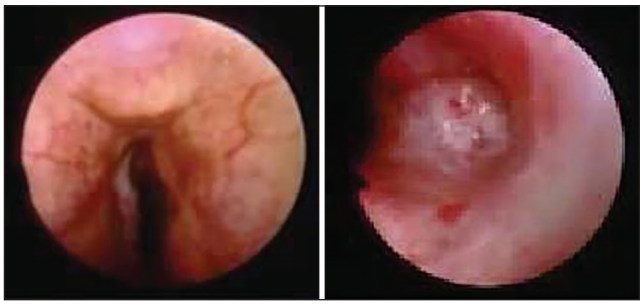

Figure 2: Fibrobroncoscopy showing reduction of the 25% of the tracheal lumen in its distal tract extended to the right upper lobe bronchus caused by important mucosal hypertrophy (case 1)

therapy. Serum pro-BNP was within normal values. Chest and abdomen CT-scan was performed showing moderate bilateral pleural effusion, pleural thickening with enhancement after contrast mean injection, and multiple micro-calcifications in the distal lung regions and in the spleen. Lung function tests resulted in severe restrictive impairment (vital capacity (VC), total lung capacity (TLC), residual volume (RV), and forced vital capacity (FVC): 40%, 43%, 42%, and 45% of the predicted values) and severe diffusing capacity of the lung for carbon monoxide (CO)(DLCO) reduction (38% of the predicted value). The chemical-physical analysis demonstrated the trasudative nature of the drained pleural fluid. The diagnosis of primary systemic AL amyloidosis with pleural involvement was then performed by means of tissue specimen examination obtained with the Cope needle pleural biopsy.

Case report 3

A 53-year-old, non-smoker, male patient came to our ambulatory and subsequently admitted in our Respiratory Intensive Care Unit for severe dyspnea associated with severe non-hypercapnic hypoxemia (PaO2/FiO2 ratio 120; PaCO2 28.5 mmHg, pH 7.485). He had a history of chronic kidney failure due to type I membrano-proliferative glomerulonephritis. As the hypoxemia was refractory to high-flow oxygen-therapy (Reservoir mask with O2 at 15 liters per minute), a trial of non invasive ventilation (NIV) delivered via a full-face mask was attempted (mode Pressure-support, PS = 20 cm H2O; PEEP 8 cm H2O; FiO2 0.80); then, after 20 hours, endotracheal intubation and invasive mechanical ventilation resulted mandatory due to NIV failure. Chest CT-scan showed a pattern of bilateral alveolar consolidations and ground glass areas suggesting three possible diagnostic hypotheses: Organizing pneumonia (OP), vasculitis, or Goodpasture syndrome [Figure 3].

A large battery of immunological and microbiological investigations resulted negative. Fibro-bronchoscopy with bronchoalveolar lavage fluid (BAL) and transbronchial lung biopsy (TBLB) were performed during NIV; the histological exam of the collected tissue showed a pathologic pattern of unspecific neutrophilic capillaritis. As the patient refused to underwent surgical biopsy, the empiric therapy with intravenous pulsed bolus of cyclophosphamide and steroids was given. He died after a worsening of his clinical conditions, radiological findings, and lung gas exchange. The autopsy reported systemic AL amyloidosis with prevalent lung and renal involvement.

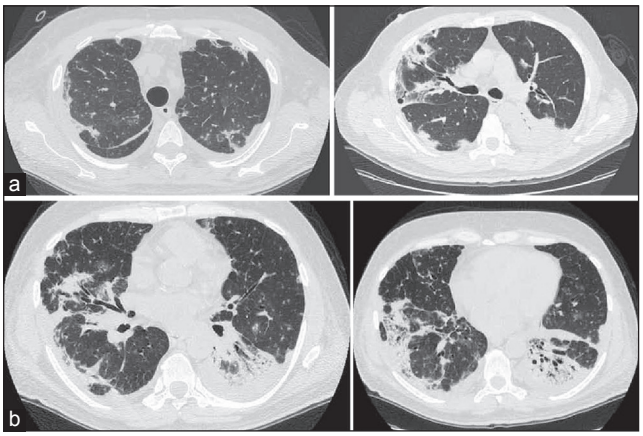

Figure 3: Chest high resolution computed tomography (HRCT) showing inter and intralobular bilateral reticulations, smooth, nodular and subpleural (a) and multiple parenchymal consolidations more evident in the lower lobes (b)

Discussion

Our multidisciplinary group work experience confirms:

1. The rarity of intra-thoracic amyloidosis having a frequency of about 1.0% among the large data set of diffuse interstitial lung diseases that referred to our center during the study time (3 cases out 298 subjects);
2. The difficult and often delayed identification of amyloidosis, which was misdiagnosed as different diseases in all the three reported cases, due to an initial wrong evaluation of the available clinical-radiological and endoscopic findings.

In our opinion, the description of our case series of amyloidosis with lung involvement deserves some considerations that could be of help for the pulmonologists who are likely to face similar challenging situations in their clinical practice.

In case report 1, the lack of clinical improvement after a prolonged inhaled combined treatment with steroids and bronchodilators given for a suspect of bronchial asthma together with the morphology of the flow-volume curve suggesting the presence of intrathoracic obstruction helped us to critically revise the initial incorrect diagnosis.

Tracheo-bronchial involvement is a rare manifestation of amyloidosis which is usually found as a localized AL form characterized by amyloid submucosal deposition. In the literature, it has been recently demonstrated that this type of amyloidosis could be the expression of a B cells monoclonal lymphoproliferative process[12] with two clinical-pathological subtypes:

a. Nodular and localized; and
b. Sub-mucosal and diffuse. The latter subtype, which may cause trachea, main and lobar bronchus stenosis[13,14], usually develops in the fourth or the fifth decade of life and have a slow evolution with a frequently delayed diagnosis.[15,16]

It can be mislead as a severe asthma refractory to conventional therapy, even though symptoms like inspiratory dyspnea, hemoptysis, and tirage should "drive" the pulmonologist to

think about other possible diseases. Differential diagnosis could be made also with cancer, granulomatous diseases, osteo-chondroplastic trachea-bronchopathy, and light chain deposition disease (LCDD) involving central airways.[17-19]

CT-scan and lung function tests are the most useful means to raise other than asthma hypotheses.[20] Fibro-bronchoscopy, either with rigid or flexible technique, is essential to obtain an accurate histological diagnosis, evaluate the extension of the disease, perform specific interventional procedures (mechanical resections, laser ablations, dilations and stents placement)[21,22], and monitor the disease's progression.

In case report 2, the presence of bilateral pleural non-infectious transudative effusion in a patient who was affected by a cardiac disorder but with a normal left ventricular ejection fraction and a lack of response to diuretic therapy led us to hypothesize other than an hemodynamic etiology. Moreover, pro-BNP serum level was normal. It is well-known that this bio-marker of ventricular diastolic dysfunction has a good diagnostic and prognostic value in cardiac amyloidosis, when no other causes of restrictive cardiomyophaty are found and when no renal failure or atrial fibrillation are present.[5,6] In the suspect of a primary pleural disease with a CT finding of sierosal thickening we decided to perform pleural biopsy. Cope needle biospy is a mini-invasive old technique applied to obtain pleural tissue samples for histological diagnosis when thoracoscopy, which is the golden standard interventional procedure, is not available.[23-25] Pleural involvement is usually found within the context of systemic amyloidosis (AL type) with a concomitant cardiac disorder. It can be mainly unilateral with lymphocytic or, seldom, chylous pleural effusion.

In case report 3, on the basis of blood chemistry, radiological, and bronchoscopic-derived (BAL and TBLB) findings, severe pulmonary infections, vasculitis, OP, and lung-renal syndrome were less likely to be considered as the cause of the diffuse lung disease. Despite the high risk of complications in a very sick patient under mechanical ventilation, open lung biopsy was proposed to obtain the diagnosis through the examination of a large tissue sample.

In systemic amyloidosis, fine needle aspiration of abdominal fat pad is a less-invasive diagnostic procedure that is usually preferred as compared to the biopsy of internal organs as it reduces the risk of bleeding. However, fine needle aspiration of abdominal fat pad may results often inconclusive.[26] In the case reported, the fine needle aspiration of abdominal fat pad was not performed because of the lack of clinical suspicion of amyloidosis in a patient with a rapid worsening of respiratory conditions.

Pathologically, in lung parenchimal amyloidosis, that can be either localized or, more frequently, systemic AL type, the amyloid deposition involves both the media tunica of the small vessels and the interstitial space. It could be found either in form of solitary nodules or, less common, as multiple nodules with a diameter of 0,5-5 cm, and a prevalent localization in the lower lobes and in the lung periphery. The CT pattern can be nodular or reticular-nodular, with possible honey-combing areas, interlobular septa thickening, calcifications, pleural thickening, or effusion.[27] The nodules, of different size, are distributed mainly peripherally and in the lower lobes and may have, in about one third of patients, calcifications, and bone tissue deposition inside with a slow growth and sometimes cavitation.[28] A cystic pattern could be found, due to the alveolar wall fragility caused by amyloid deposition or to a concomitant lymphocytic interstitial pneumonia (LIP).[29]

The prognosis is usually poor with a median survival of 12 months in case of cardiac involvement.[30] Death usually occur for: Refractory hypoxemia in acute respiratory distress syndrome (ARDS), massive hemoptysis due to the arterial rupture caused by amyloid deposition in the vessels' wall, massive lung embolism due to the thrombosis of the inferior cava vein. Less frequently death occurs for chylo-thorax due to the thoracic duct involvement or for gas embolism, as a complication of the biopsy.[31,32] Mortality is higher in case of misdiagnosis and consequent delayed treatment.

Conclusions

The take-home message that could be derived from our experience on respiratory amyloidosis consists on the importance of considering "rare diseases" among the complex differential diagnostic pathways of diffuse interstitial lung diseases; contextually, in the daily clinical activity, it has to be underlined the importance of working in multidisciplinary group, coordinated by the pulmonologist, to achieve the correct diagnosis as soon as possible.

References

1. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, *et al*. Nomenclature Committee of the International Society of Amyloidosis. Amyloid fibril protein nomenclature: 2012 recommendations from the Nomenclature Committee of the International Society of Amyloidosis. Amyloid 2012;19:167-70.
2. Magy-Bertrand N, Dupond JL, Mauny F, Dupond AS, Duchene F, Gil H, *et al.* Incidence of amyloidosis over 3 years: The AMYPRO study. Clin Exp Rheumatol 2008;26:1074-8.
3. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, *et al*. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992;79:1817-22.
4. Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: A study of 52 North American-born patients examined during a 30-year period. Mayo Clin Proc 1992;67:428-40.
5. Desport E, Bridoux F, Sirac C, Delbes S, Bender S, Fernandez B, *et al.* Al amyloidosis. Orphanet J Rare Dis 2012;7:54.
6. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: A review. J Am Heart Assoc 2012;1:e000364.
7. Smith RR, Hutchins GM, Moore GW, Humphrey RL. Type and distribution of pulmonary parenchymal and vascular amyloid. Correlation with cardiac amyloid. Am J Med 1979;66:96-104.
8. Westermark P, Sletten K, Johansson B, Cornwell GG 3rd. Fibril in senile systemic amyloidosis is derived from normal transthyretin. Proc Natl Acad Sci U S A 1990;87:2843-5.
9. Urban BA, Fishman EK, Goldman SM, Scott WW Jr, Jones B, Humphrey RL, *et al.* CT evaluation of amyloidosis: Spectrum of disease. Radiographics 1993;13:1295-308.
10. Falk RH, Comenzo RL, Skinner M. The systemic amyloidosis. N Engl J Med 1997;337:898-909.
11. Sanchorawala V. Light-chain (AL) amyloidosis: Diagnosis and treatment. Clin J Am Soc Nephrol 2006;1:1331-41.

12. Borie R, Danel C, Molinier-Frenkel V, Prevot G, Deslee G, Debray MP, *et al.* Tracheobronchial amyloidosis: Evidence for local B-cell clonal expansion. Eur Respir J 2012;39:1042-5.
13. Kim HY, Im JG, Song KS, Lee KS, Kim SJ, Kim JS, *et al*. Localized amyloidosis of the respiratory system: CT features. J Comput Assist Tomogr 1999;23:627-31.
14. Berk JL, O'Regan A, Skinner M. Pulmonary and tracheobronchial amyloidosis. Semin Respir Crit Care Med 2002;23:155-65.
15. Dahl KA, Kernstine KH, Vannatta TL, Karwal MW, Thomas KW, Schraith DF. Tracheobronchial amyloidosis: A surgical disease with long-term consequences. J Thorac Cardiovasc Surg 2004;128:789-92.
16. Prakash UB. Tracheobronchopathia osteochondroplastica. Semin Respir Crit Care Med 2002;23:167-75.
17. Pozes, Aline Serfaty. Traqueobroncopatia osteocondroplástica: Experiência de uma Unidade de Broncologia. Radiologia Brasileira, 2003;36:126.
18. O'Regan A, Fenlon HM, Beamis JF Jr, Steele MP, Skinner M, Berk JL. Tracheobronchial amyloidosis: The Boston University experience from 1984 to 1999. Medicine (Baltimore) 2000;79:69-79.
19. Colombat M, Gounant V, Mal H, Callard P, Milleron B. Light chain deposition disease involving the airways: Diagnosis by fibreoptic bronchoscopy. Eur Respir J 2007;29:1057-60.
20. Usta J, Kanj N. Primary tracheobronchial amyloidosis. J Bronchol 2005;12:43-5.
21. Capizzi SA, Betancourt E, Prakash UB. Tracheobronchial amyloidosis. Mayo Clin Proc 2000;75:1148-52.
22. Pickford HA, Swensen SJ, Utz JP. Thoracic cross-sectional imaging of amyloidosis. Am J Roentgenol 1997;168:351-5.
23. Maskell NA, Butland RJ. Pleural disease group, Standards of care committee, British Thoracic Society. BTS guidelines for the investigation of a unilateral pleural effusion in adult. Thorax 2003;58:ii8-17.
24. Sokolowski JW Jr, Burgher LW, Jones FL Jr, Patterson JR, Selecky PA. Guidelines for thoracentesis and needle biopsy of the pleura. This position paper of the American Thoracic Society was adopted by the ATS Board of Directors, June 1988. Am Rev Respir Dis 1989;140:257-8.
25. Kavuru MS, Adamo JP, Ahmad M, Mehta AC, Gephardt GN. Amyloidosis and pleural disease. Chest 1990;98:20-3.
26. Ansari-Lari MA, Ali SZ. Fine-needle aspiration of abdominal fat pad for amyloid detection: A clinically useful test? Diagn Cytopathol 2004;30:178-81.
27. 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;110:212-8.
28. Kyle RA, Gertz MA. Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. Semin Hematol 1995;32:45-59.
29. Poletti V, Costabel U, Casoni GL, Bigliazzi C, Drent M, Olivieri D. Rare infiltrative lung diseases: A challenge for clinicians. Respiration 2004;71:431-43.
30. Liu YY, Lee YC, Chou TY, Perng RP. Pulmonary alveolar-septal amyloidosis presenting as heart failure with unilateral pleural effusion: A case report. Zhonghua Yi Xue Za Zhi (Taipei) 1999;62:838-43.
31. Road JD, Jacques J, Sparling JR. Diffuse alveolar septal amyloidosis presenting with recurrent hemoptysis and medial dissection of pulmonary arteries. Am Rev Resp Dis 1985;132:1368-70.
32. Strange C, Heffner JE, Collins BS, Brown FM, Sahn SA. Pulmonary hemorrhage and air embolism complicating transbronchial biopsy in pulmonary amyloidosis. Chest 1987;92:367-9.

How to cite this article: Scala R, Maccari U, Madioni C, Venezia D, La Magra LC. Amyloidosis involving the respiratory system: 5-year's experience of a multi-disciplinary group's activity. Ann Thorac Med 2015;10:212-6.

Source of Support: Nil, **Conflicts of interest:** None declared.