Nodular pulmonary amyloidosis – rare cause of calcified pulmonary nodules

Anca Macri[1], Radu Matache[2], Diana Leonte[3], Radu Stoica[4]

"Marius Nasta" Pneumology Institute of Bucharest

1. Pneumology Ward III

2. Thoracic Surgery Ward

3. Anatomical Pathology Unit

4. Anesthesia and Intensive Care Unit

Correspondence:
Anca Macri,
"Marius Nasta" Pneumology Institute of Bucharest, Ward III,
90 Sos. Viilor, district 5
e-mail: ancamacri@yahoo.com

Abstract

The article presents the case of a 60-year-old asymptomatic woman whose chest X-ray screening showed bilateral pulmonary nodules of uncertain etiology. Initially, the main suspicion concerned multiple pulmonary metastases, but the anatomical pathology examination of two of the surgically removed lung nodules revealed a benign pattern – foreign body granulomatous reaction to cholesterol crystals. Patient follow-up with a repeat computed tomography one year later showed that some pulmonary nodules had slightly increased in number and size, so the diagnosis required re-evaluation. Congo red staining revealed a positive reaction in the amorphous material, pointing to a nodular form of pulmonary amyloidosis. This case attests to the wide range of investigations needed to examine multiple pulmonary nodules and to the great variety of possible diagnoses. Surgical biopsy, alongside histopathological examination and immunohistochemical tests of the lung are critical in establishing a positive diagnosis. Pulmonary amyloidosis requires additional investigations and long-term follow-up of the patient, as this condition is frequently associated with MALT (mucosa-associated lymphoid tissue) lymphoma or multiple myeloma.

Keywords: *calcified pulmonary nodules, nodular pulmonary amyloidosis, foreign body granuloma, MALT lymphoma, multiple myeloma*

Rezumat

Amiloidoza pulmonară nodulară – cauză rară de noduli pulmonari calcificați

Se prezintă cazul unei paciente de 60 de ani, asimptomatică respirator, la care radiografia toracică efectuată ocazional a evidențiat prezența de noduli pulmonari bilaterali de etiologie incertă. Suspiciunea inițială principală a fost cea de metastaze pulmonare multiple, însă examenul anatomopatologic a doi din nodulii pulmonari extirpați chirurgical a evidențiat aspecte benigne – reacție granulomatoasă de corp străin la cristale de colesterol. Urmărirea pacientei prin repetarea examenului de tomografie computerizată peste 1 an a arătat o discretă creștere numerică și dimensională a unora dintre nodulii pulmonari, ceea ce a impus reevaluarea diagnosticului. Utilizarea colorației cu roșu de Congo a evidențiat reacție pozitivă în materialul amorf, orientând diagnosticul către amiloidoză pulmonară, formă nodulară. Cazul prezentat ilustrează amploarea investigațiilor care trebuie efectuate în situația nodulilor pulmonari multipli, ca și varietatea mare de diagnostice posibile. Biopsia chirurgicală a nodulilor, alături de examenul histopatologic și testele imunohistochimice joacă un rol esențial în stabilirea diagnosticului pozitiv. Evidențierea amiloidozei pulmonare impune investigații suplimentare și supraveghere îndelungată a pacientului pentru asocierea frecventă a acestei entități cu limfoame MALT (mucosa-asssociated lymphoid tissue) sau cu mielomul multiplu.

Cuvinte-cheie: *noduli pulmonari calcificați, amiloidoză pulmonară nodulară, granuloame de corp străin, limfom MALT, mielom multiplu*

Introduction

Amyloidosis is a systemic disease caused by extracellular accumulation of amyloid. It can be idiopathic (primary form) or associated with various inflammatory, hereditary or neoplastic diseases (secondary form). Pulmonary amyloidosis may be part of a widespread process that involves many organs, or it may be localized to the airways and lung parenchyma. Unlike systemic sarcoidosis, localized pulmonary amyloidosis usually follows a benign course[1]. The respiratory system is involved in approximately 50% of patients diagnosed with amyloidosis. Three patterns of involvement have been described: tracheobronchial, diffuse parenchymal and nodular[1,2].

Nodular pulmonary amyloidosis is considered a limited form of disease characterized by one or more intrapulmonary nodules or masses (amyloidomas). The incidence has a peak in the 6th decade of life. Patients are usually asymptomatic; some may rarely present with cough or shortness of breath[6].

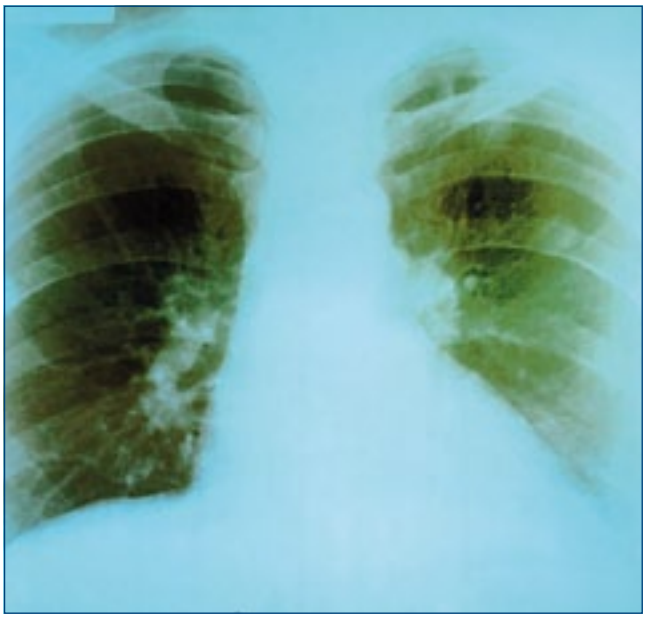
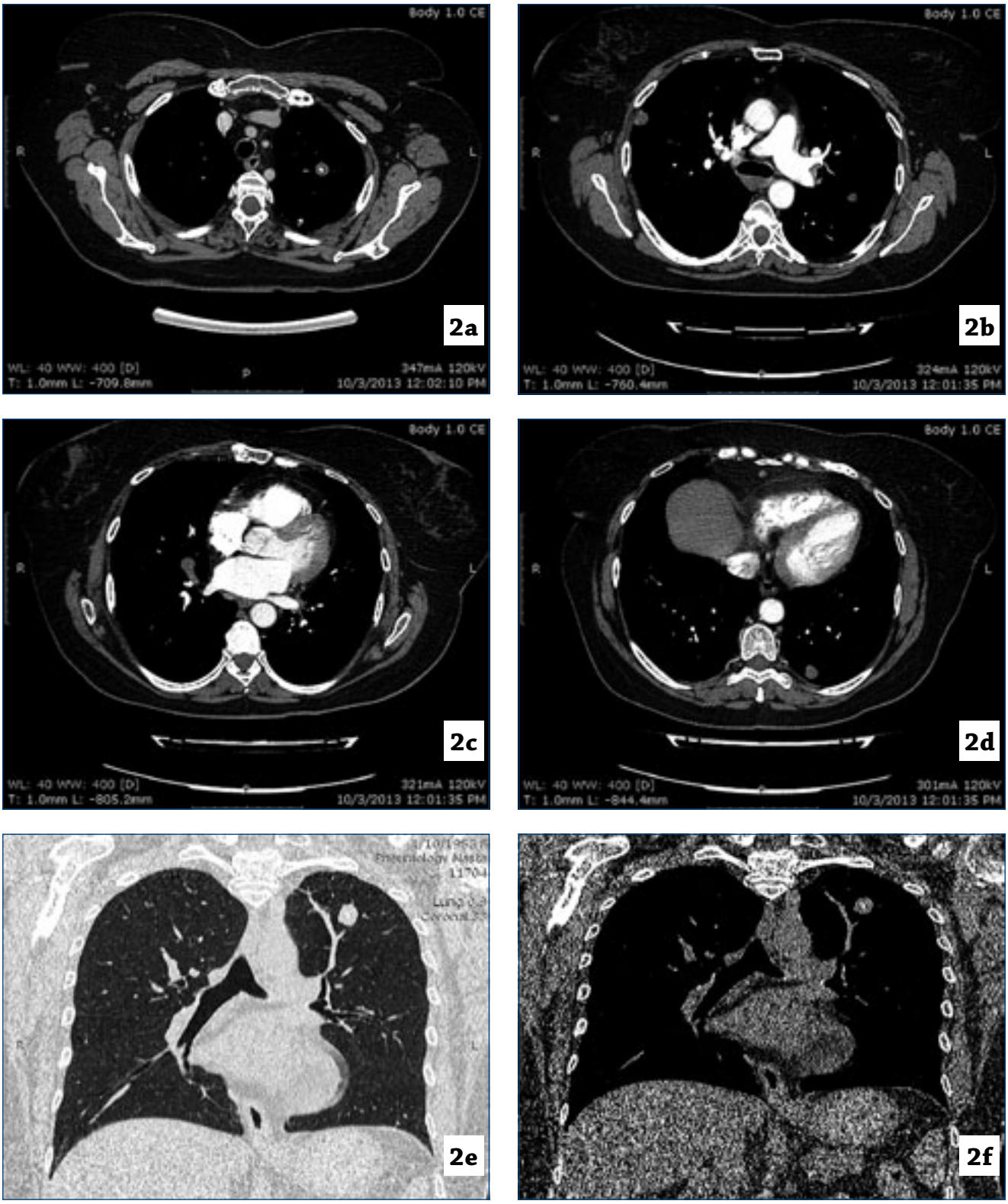


Figure 1. *Chest X-ray, 2013*



Figures 2a→2f. *Cross and coronal sections of a thoracic CT scan – multiple bilateral nodules, some calcified*

History

D.D., a 60-year-old non-smoking female patient with no occupational exposure to respiratory hazards was referred to the pneumology unit in 2013 in order to establish the etiology of bilateral pulmonary nodules identified in a chest X-ray performed upon admission to a cardiology ward.

The patient's medical history indicated she had pulmonary TB forty years ago - correctly treated and cured, dyslipidemia with hypercholesterolemia, as well as recent repetitive fainting episodes.

The patient was asymptomatic and the pulmonary **clinical examination** turned out normal, with a SaO_2 of 96% in room air. Heart sounds were regular, VR 80/min,

BP 120/60 mmHg, no murmurs in the auscultation sites or on carotids, no leg edemas or signs of deep vein thrombosis.

The cardiological examination (EKG, EKG Holter monitoring, echocardiogram) and the neurological examination (brain CT) showed no pathological changes, therefore the recent episodes of loss of consciousness were identified as vagal syncopes (since they would also occur in conditions of heat, stress or in crowded places).

Biology: Hb=13.56 g/dl, Ht=37.95%, WBC=5230/mm^3 (with normal WBC count), ESR=3 mm/h, urea=41 mg/dl, serum creatinine=1 mg/dl, glycemia=104 mg/dl, GOT=16 UI/l, GPT=14 UI/l, LDH=310 U/l, CK=76 U/l, CK-MB=17 U/l, fibrinogen=444 mg/dl, INR=1.08, total cholesterol=208 mg/dl, LDL cholesterol=144 mg/dl, HDL cholesterol=34 mg/dl, Na^+=144 mEq/l, K^+=4,1 mEq/l.

Chest X-ray (figure 1) revealed multiple homogenous, distinct opacities of variable sizes (Ø 5-15 mm) in both lungs; enlarged right hilum of enhanced intensity.

Chest-abdomen CT scan with contrast agent (fig. 2a→2f) revealed "multiple iodophile nodular parenchymal lesions in both lungs, variable in size, located in peripheral, subpleural and central sites; some lesions exhibit micro-calcifications inside, others are not calcified...". Conclusion of the imaging specialist: "the findings might suggest the presence of multiple secondary lesions in the lungs. A differential diagnosis should also consider the probability of a primary lesion, most likely in the right perihilar area".

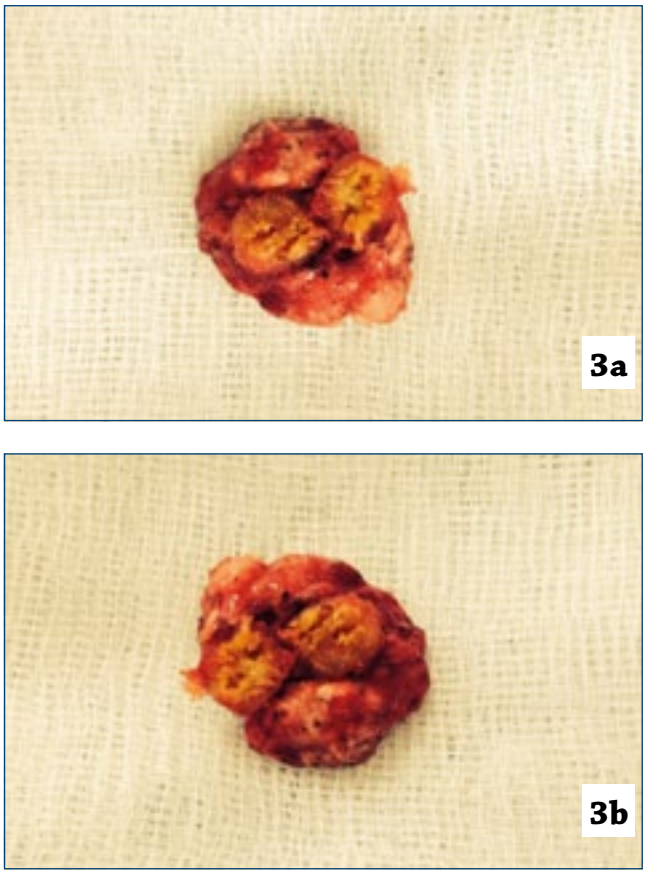
Fibrobronchoscopy found normal laryngeal dynamics, diffuse bilateral bronchitis aspect, no apparent proliferative elements or active lesions of the mucous tissue in the examined areas. The **bronchoalveolar lavage** performed in the upper left lobe area revealed no tumor cytology or other pathological elements.

Ziehl-Neelsen staining from the lavage liquid revealed no acid-fast bacilli.

The main imagistic suspicion suggested metastatic pulmonary nodules of unidentified origin, thus requiring additional investigations to locate a potential source of tumor dissemination: upper digestive endoscopy, colonoscopy, abdomen-pelvic ultrasound, gynecological exam with Babes-Papanicolau smear, bilateral mammography, endocrinology exam with thyroid ultrasound. Everything came out normal, revealing no extra-thoracic tumor that could have been the source of the pulmonary metastatic dissemination.

Based on these findings, two of the pulmonary nodules (one from the lower left lobe and another one from the upper left lobe) were subject to a **surgical biopsy** through minimum left thoracotomy, with simple post-op evolution and release of the patient five days after the intervention.

Macroscopic appearance of removed nodules (figures 3a, 3b): two nodules, one 1.1 cm, another one 0.4 cm, hard, light-brown, with yellow areas in the middle.



Figures 3 a,b. *Macroscopic appearance of removed nodules*

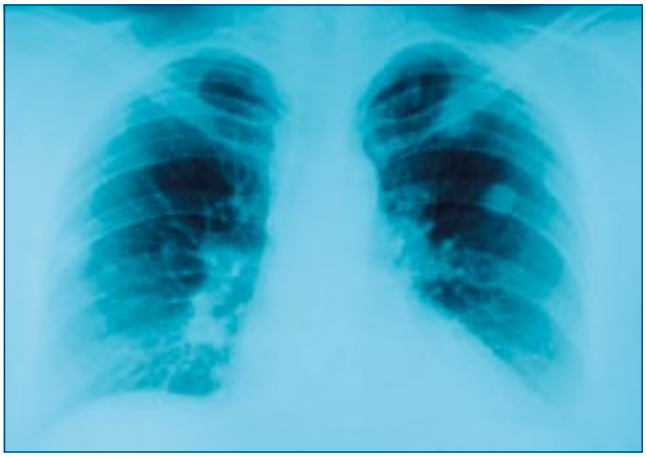
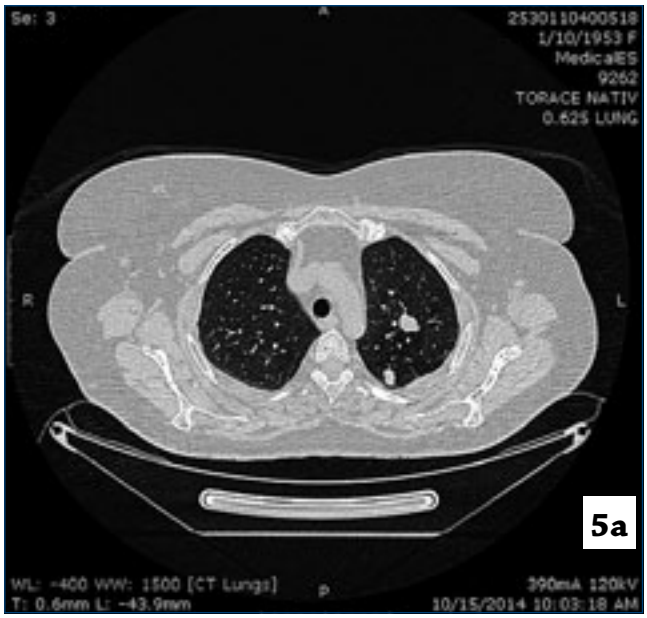
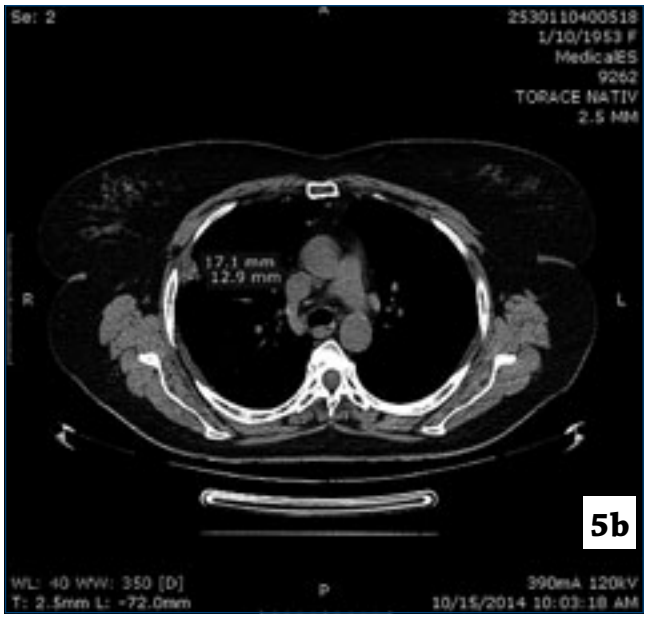


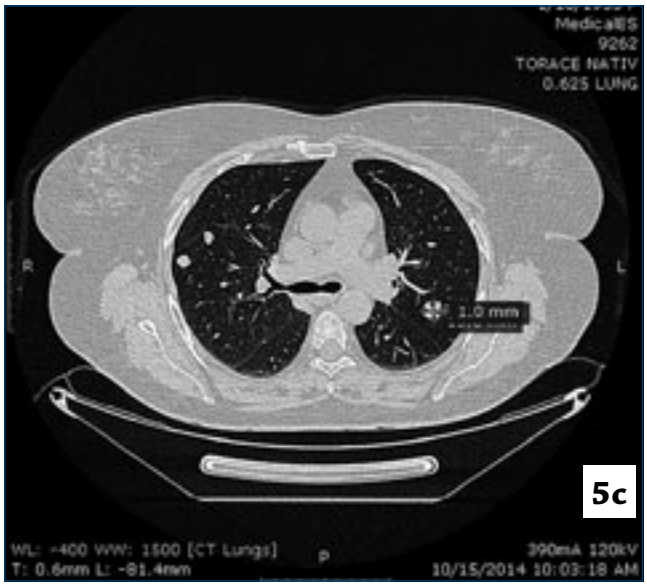
Figure 4. *Chest X-ray 2014*

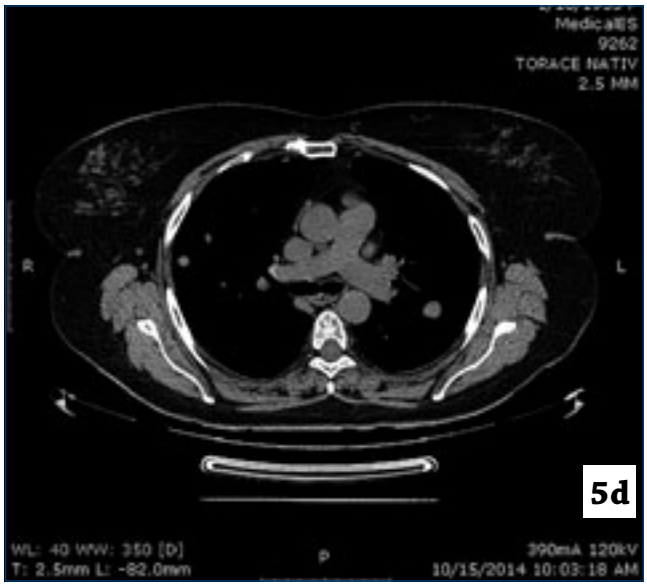
Histopathological examination of the removed parts revealed "fragments of pulmonary parenchyma and two pulmonary nodules with overlap histology including amorphous, acellular, eosinophilic masses with a distinct structure, bordered by foreign body granulomas, made of histiocytic cellularity and foreign-body multinucleate giant cells, associating clusters of many lymphocytes and isolated cholesterol crystals. *Conclusion: foreign body granulomatous reaction in the lungs*".

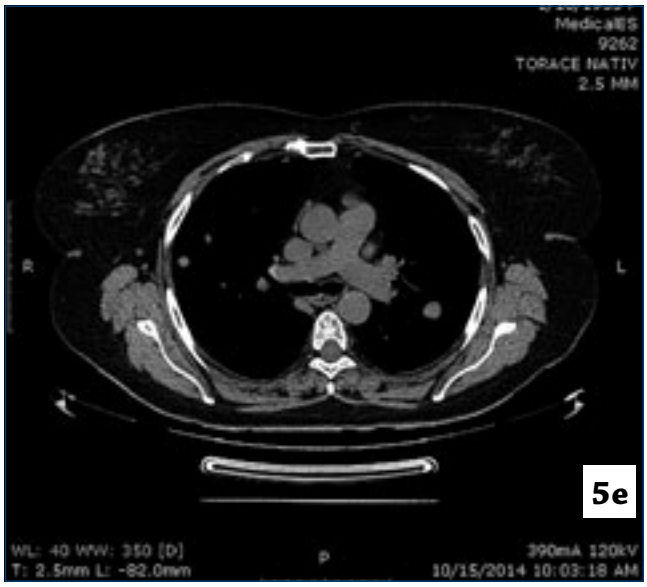
The patient was discharged without indications of treatment at home and with the recommendation of imagistic monitoring in 12 months.











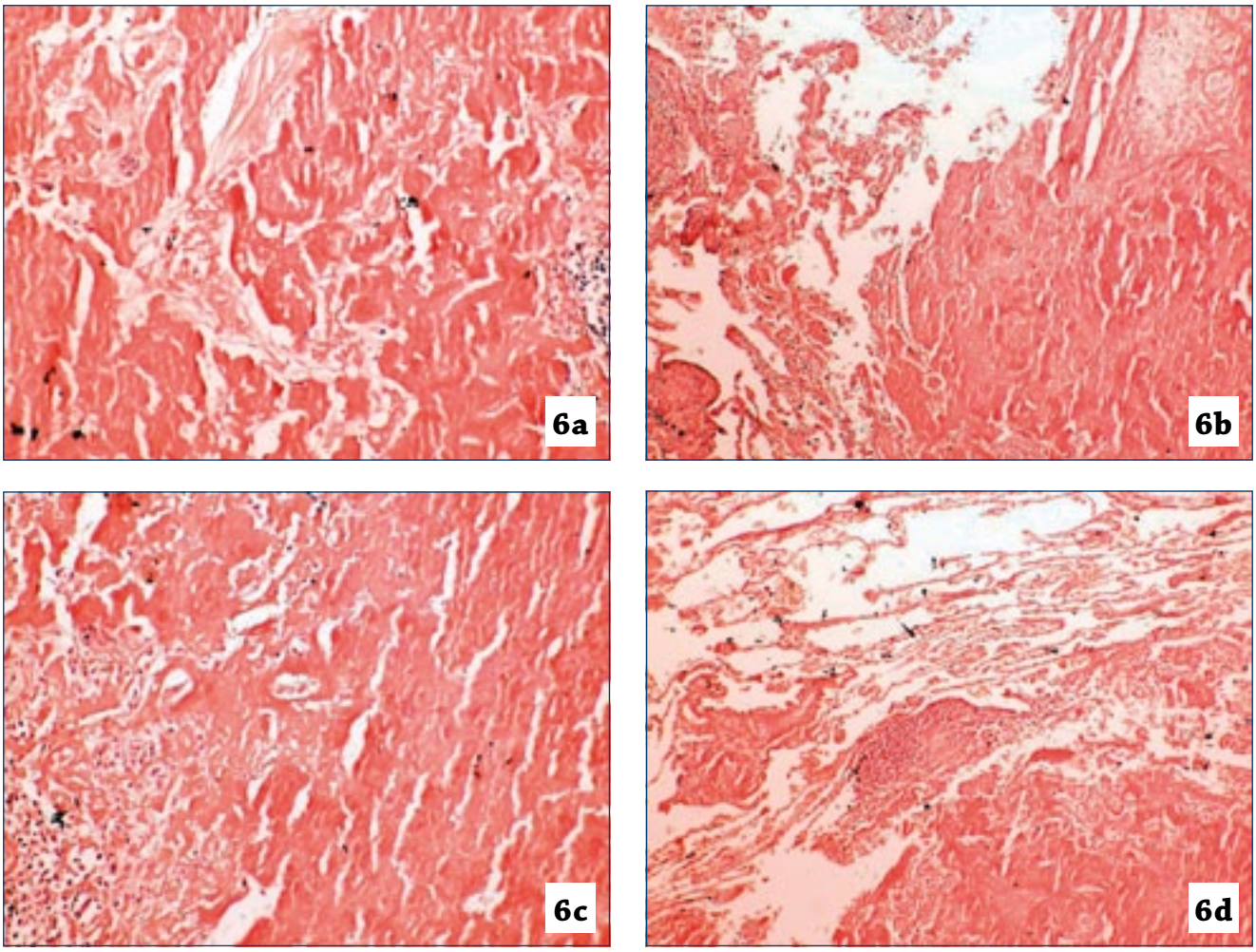
Figures 5a→5e. *Thoracic CT images 2014 – multiple bilateral nodules, some calcified*

The 2014 evaluation revealed the same clinical, biological and functional aspects as in 2013, except for a **mild inflammatory syndrome** (ESR=19 mm/h, fibrinogen=446 mg/dl). **Chest X-ray** (fig. 4) demonstrated the presence of the same bilateral pulmonary nodules, seemingly slightly larger.

Native thoracic CT scan revealed a minor increase in size and number of certain pulmonary nodules (note that the CT scan technique was different in the two exams) (fig. 5a→5e).

Under the circumstances, a **re-assessment of the histopathological examination slides** from 2013 was requested and the additional **Congo red staining** demonstrated positive staining in the amorphous material. *Final conclusion: "nodular pulmonary amyloidosis"* (fig. 6a→6d).

As a result of these findings, the nodules removed by biopsy were subject to **immunohistochemical tests (IHC)** that showed positive lambda chains in frequent plasma cells, positive kappa, a λ/k ratio >1:4. Conclusions: the IHC tests indicate a monoclonal proliferation in the context of amyloidosis.



(source of images: anatomical pathology unit, courtesy of Dr. Diana Leonte)

Figures 6a→6d. *– Sections of lung parenchyma with amyloid nodule (positive Congo red staining); 6c – foreign-body multinucleate giant cell (10 o'clock); 6d – pulmonary parenchyma is also visible in the upper quadrant*

Serum protein electrophoresis: albumin 54.4%, alpha-1 globulins 2.6%, alpha-2 globulins 14.1% (normal 6.6-13.5%), beta globulins 14.9%, gamma globulins 14%, A/G ratio 1.19.

Serum protein electrophoresis with immunofixation did not reveal monoclonal bands (IgG, IgA, IgM, k or λ chains).

24-hour urine protein test: proteinuria 176 mg/2,200 ml (normal 0-149).

Abdomen ultrasound: liver – right lobe 140 mm, left lobe 61 mm, discreetly hyperechogenic, homogenous. Spleen 98/42 mm, homogenous. CBD 3 mm, PV 10 mm. No retroperitoneal adenopathies.

The patient was subsequently referred to a hematology clinic for further investigations in this matter (osteomedullar biopsy, abdominal fat biopsy, bone X-ray etc).

Discussions

The initial imagistic appearance – of multiple bilateral pulmonary nodules of various sizes, some partially calcified – raised the major suspicion of bilateral pulmonary metastases of unknown origin. Cancers that most often result in secondary pulmonary involvement are found in lungs, breast, ovary, uterus, digestive tube, kidneys, thyroid and bones. The investigations conducted in this case failed to reveal any primary intra- or extra-thoracic neoplasm.

Another assumption would have been that of a fungal infection or benign nodules (sequelae from the previous TB, benign tumors: hamartoma, hamartochondroma, nodular sarcoidosis, pulmonary hyalinising granuloma). However, these benign nodules are rarely multiple, grow very slowly and the patient's previous X-rays showed no changes.

The decision to conduct a surgical biopsy on two of the pulmonary nodules in the left lung was therefore perfectly justified and the histopathological result was surprising – foreign body granuloma, probably in cholesterol crystals.

The patient's clinical follow-up with a repeat CT scan showing a slight expansion of the lesion led to the reassessment of the smears and a Congo red staining, which confirmed the diagnosis of nodular pulmonary amyloidosis.

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of insoluble fibrillar proteins. The birefringence at Congo red staining is the diagnostic standard.

Amyloid proteins can infiltrate virtually all organ systems. Pulmonary involvement is most commonly observed in the localized (primary) form of amyloidosis.

Three histopathologic types of pulmonary amyloidosis have been described: tracheobronchial deposition, diffuse parenchymal or alveolar septal involvement and parenchymal nodules[1,2].

- The *tracheobronchial type* is characterized by submucosal deposition of amyloid in the trachea and segmental airways, with bronchial wall thickening and luminal narrowing[3,4] which can lead to obstruction with consolidation, atelectasis, hyperinflation and bronchiectasis.
- The *diffuse parenchymal or alveolar septal type* is most commonly associated with systemic amyloidosis, but occasionally it is localized to the lungs; CT findings include reticulation, interlobular septal thickening, micronodules (2-4 mm)[5].
- *Nodular amyloidosis* is almost always localized to the lungs. The nodules are typically subpleural or peripheral, concentrated in the lower lobes[6] ; they vary in shape and size (0.5-15 cm), have usually a slow growth with no regression; calcification is seen in up to 50% of cases[1,7,8]. Associated cavitation and/or cyst occurrence have been described but are very rare.

Immunohistochemical analysis of the pathologic specimen can enable fibril type determination[6], in our case amyloid light chains. These light chains can also be found in patients with monoclonal plasma cell dyscrasias, such as multiple myeloma.

Histologically, polyclonal plasma cells, lymphocytes, giant cells or localized mucosa-associated lymphoid tissue (MALT) lymphoma may surround the amyloid nodules[9].

A recent study[10] demonstrated that nodular pulmonary amyloidosis is associated with immunoglobulin light chains (AL type) and variably with low-grade lymphoma. 18 cases were investigated: 5 out of 14 had autoimmune disease; all 18 cases showed a peptide profile with an abundance of immunoglobulin light chains (12k, 4λ and 2 mixed k and λ). Out of 14 patients with follow-up, 3 developed recurrent pulmonary amyloidoma, 2 had pulmonary recurrence plus cutaneous extranodal marginal zone lymphoma of MALT type and 1 had a history of parotid gland MALT lymphoma. The association of nodular pulmonary amyloidoma with autoimmune disease and lymphoma indicate the majority of these lesions relate to an underlying lymphoplasmocytic neoplasm in the spectrum of MALT lymphoma.

Parenchymal amyloid nodules generally grow slowly and remain asymptomatic[11]. In such cases, treatment is generally not needed. Surgical resection may be considered; however, there is a possibility of relapse[12].

Conclusions

Although nodular pulmonary amyloidosis is a rare disease, it should be considered in the differential diagnosis of calcified pulmonary nodules and masses, mainly with primary or metastatic neoplasms and granulomatous diseases.

Tissue biopsy is essential for a definitive diagnosis, showing deposition of an extracellular, homogenous, acellular, eosinophilic proteinaceous material[6].

The birefringence at Congo red staining is the diagnostic standard, but the immunohistochemistry method remains the gold standard of diagnosis.

Even though the short-term prognosis is good and complications are rare, investigations to rule out malignant hematological diseases such as MALT lymphoma and multiple myeloma should be carried out, as well as long-term follow-up of the patients. ■

References

1. Urban BA, Fishman EK, Goldman SM et al. CT evaluation of amyloidosis: spectrum of disease. *RadioGraphics* 1993; 13(6):1295-1308.
2. Slanetz PJ, Whitman GJ, Shepard JA, Chew FS. Nodular pulmonary amyloidosis. *AJR* 1994; 163(2):296.
3. Aylwin AC, Gishen P, Copley SJ. Imaging appearance of thoracic amyloidosis. *J Thoracic Imaging* 2005; 20(1):41-46.
4. Kim HY, Im JG, Song KS et al. Localized amyloidosis of the respiratory system: CT features. *J Comput Assist Tomogr* 1999; 23(4):627-631.
5. Graham CM, Stern EJ, Finkbeiner WE, Webb WR. High-resolution CT appearance of diffuse alveolar septal amyloidosis. *AJR* 1992;158(2):265-267.
6. Gillmore JD, Hawkins PN. Amyloidosis and the respiratory tract. Thorax 1999; 54(5):444-451.
7. Lee AY, Godwin JD, Pipavath SN. Case 182: Pulmonary Amyloidosis. *Radiology* 2012;263(3):929-932.
8. Pitz MW, Gibson IW, Johnston JB. Isolated Pulmonary Amyloidosis: case report and review of the literature. *American Journal of hematology* 2006;81:212-213.
9. Lim JK, Lacy MQ, Kurtin PJ, Kyle RA, Gertz MA. Pulmonary marginal zone lymphoma of MALT type as a cause of localized pulmonary amyloidosis. *J Clin Pathol* 2001; 54:642-646.
10. Grogg KL, Aubry MC, Vrana JA, Theis JD, Dogan A. Nodular Pulmonary Amyloidosis is characterized by localized immunoglobulin deposition and is frequently associated with an indolent B-cell lymphoproliferative disorder. *American Journal of Surgical Pathology* 2013; 37:406-412.
11. Vieira IG, Marchiori E, Zanetti G, Cabral RF, Takayassu TC, Spilberg G, Batista RR. Pulmonary amyloidosis with calcified nodules and masses – a six-year computed tomography follow-up: a case report. *Cases Journal* 2009;2:6540.
12. Gaurav K, Panda M. An uncommon cause of bilateral pulmonary nodules in a long-term smoker. *J Gen Intern Med* 2007;22:1617-1620.