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IN-DEPTH REVIEW ARTICLE

Pulmonary amyloidosis: clinical, radiological, and pathological correlations

Jorge A. Carrillo-Bayona[1], Paula A. Navarrete-Sosa[2], Javier L. Galindo-Pedraza[2], Fernando Polo-Nieto[3], and Santiago Martinez-Jimenez[4]*

[1]Radiology Unit, Hospital Universitario Mayor, Mederi, Rosario University, Bogota, Colombia; [2]Pneumology Unit, Hospital Universitario Mayor, Mederi, Rosario University, Bogota, Colombia; [3]Pathology Unit, Hospital Universitario Mayor, Mederi, Rosario University, Bogota, Colombia; [4]Department of Radiology, New York University Langone Health. New York, New York, United States of America

ABSTRACT

Amyloidosis is a heterogeneous group of disorders associated with extracellular amyloid deposits. Pulmonary amyloidosis can occur as a localized or systemic disease with amyloid deposits in various lung structures, including the alveolar septum, blood vessel wall, airways, and lymph nodes. The spectrum of amyloidosis-associated lung disease includes nodular amyloidosis (NA), cystic amyloidosis (CA), diffuse alveolar–septal amyloidosis (DASA), and tracheobronchial amyloidosis (TBA). TBA and NA are the most common. Other manifestations in the thorax, including cardiac, mediastinal, and chest wall amyloidosis, are beyond the scope of this review. Various findings on affected lung structures are seen in imaging examinations, especially computed tomography (CT). NA presents as bilateral pulmonary nodules with a peripheral predominance toward the lung bases with smooth, lobulated, or spiculated contours. CA presents bilateral and predominantly peribronchovascular or subpleural multiple cysts of varying size. DASA presents reticulation, thickening of the interlobular septa and the peribronchovascular interstitium, micronodules, ground-glass appearance, and consolidation. TBA presents concentric thickening of the tracheal wall, a long segment with secondary stenosis, nodular thickening of the tracheal wall, calcification, and airway obstruction. Pleural amyloidosis can present diffuse or localized pleural thickening with pleural plaques and/or pleural effusion.

Keywords: *Amyloidosis. Amyloid. Amyloidoma. Solitary pulmonary nodule. Interstitial lung disease. Tracheal disease.*

INTRODUCTION

Amyloidosis is a large group of multisystemic disorders with heterogeneous clinical presentations characterized by pathological deposition of amyloid fibrils in the extracellular matrix of organs[1]. In 1854, the pathologist Rudolf Ludwig Karl Virchow named this deposition material amyloid, which means “starch-like”[2,3]. The first case of amyloidosis of the lower respiratory tract was described by Lesser[4] in 1877 in an autopsy. Congo red staining of amyloid was discovered incidentally in 1922 by Hans Hermann Benhold[2] while measuring blood volume. It was in the late 1960s when the usefulness of the histopathologic diagnosis of amyloidosis was described. In the second half of the 20th century, with the advent of electron microscopy, it was found that amyloid consists of protein fibrils with wide biochemical heterogeneity[3]. Amyloid fibrils are formed by

***Corresponding author:**
Jorge A. Carrillo-Bayona
E-mail: jorcarbay@hotmail.com

Received for publication: 12-06-2024
Accepted for publication: 23-06-2024
DOI: 10.24875/JMEXFRI.M24000078

Available online: 03-10-2024
J Mex Fed Radiol Imaging. 2024;3(3):138-149
www.JMeXFRI.com

a conformational and metabolic change of proteins (amyloidogenic), which causes their deposition as insoluble aggregates in tissues[1,3].

The most representative proteins associated with amyloidosis lung disease are immunoglobulin light-chain-derived amyloid (AL) formerly called *primary amyloidosis*, wild-type transthyretin amyloid (ATTRwt) and its variants (ATTRv), formerly called age-related or senile systemic amyloidosis, and serum apolipoprotein A (AA) amyloidosis, formerly called *secondary amyloidosis*, which is associated with chronic inflammatory diseases that increase this acute phase reactant (e.g., autoimmune diseases, tuberculosis, bronchiectasis, or neoplasms)[5,6].

The distinction between localized and systemic amyloidosis depends on the production site of the fibril precursor protein and its deposition[5]. It is considered systemic when the site of synthesis is anatomically distant from the site of deposition[5]. Mortality associated with systemic amyloidosis is commonly attributed to infiltration of the heart, followed by complications arising from pulmonary infiltration[7]. However, pulmonary amyloidosis is not usually diagnosed in the early stages of the disease.

EPIDEMIOLOGY

The number of amyloidosis cases has increased in the United Kingdom, with systemic AL amyloidosis being the most common (55%)[8]. This finding contrasts with a decrease in systemic AA amyloidosis (13% before 2010 to 3% in 2016-2019) and an increase in ATTRwt amyloidosis (less than 3% before 2010 to 25% in 2016-2019)[8]. AL amyloidosis is a rare disease with an incidence of 6-14.3 per million person-years and a prevalence of 8-65 per million person-years in Western countries[9,10]. In the United States, the incidence of AL amyloidosis has increased[11,12]. Each year, 3852 new cases are diagnosed, with an incidence of approximately 1.2-1.4% per 100,000 person-years and a mean age of 63 years[11,12]. ATTR amyloidosis has been found in 15-25% of autopsies in adults over 85 years. The estimated incidence of ATTRwt and ATTRv amyloidosis is 155-191 cases and 5.2 cases per million people/year, respectively[13,14].

The prognosis of the entity varies according to the type of amyloidosis and the organ affected. It is estimated that 25% of patients with AL amyloidosis die within 6 months of diagnosis, and 25% of patients with ATTR amyloidosis die within 24 months[13,14]. The heart and kidneys are the most commonly affected organs in systemic AL amyloidosis. These presentations have a survival rate of less than 50% five years after diagnosis, a significantly impaired quality of life, and a high financial burden on healthcare systems[9,10]. In ATTR amyloidosis, the heart is the most affected organ, followed by the peripheral nervous system[13,14]. The kidney, spleen, adrenal glands, liver, or intestine are organs affected by AA amyloidosis[15,16]. The prognosis and mortality in these patients correlate with serum amyloid A protein concentration, advanced age, and impaired renal function[15,16].

Localized amyloidosis occurs mainly in the mucosa[17]. The predominant amyloid type is AL (91%), while a lower percentage of cases are associated with AA (6%) or ATTR amyloidosis (2%)[17]. In general, the disease occurs more frequently between the fifth and sixth decades of life and without gender predominance[17,18]. Localized AL amyloidosis has a better 10-year survival rate (80.3-96.0%) than systemic AL amyloidosis (26.0-51.9%)[18,19]. Localized amyloidosis rarely progresses to systemic disease, so the clinical manifestations relate to the affected organ. The larynx, trachea, bronchi, and lung parenchyma are commonly affected structures, followed by the skin, the gastrointestinal tract, and the urinary tract[17,18].

PHYSIOPATHOLOGY

The International Society of Amyloidosis (ISA) recommends that the term “amyloid” be used for any β-sheet fibril (natural or synthetic, functional or non-functional), and the term “amyloidosis” corresponds to amyloid fibrils in a living organism[5]. Currently, 42 human amyloid fibril proteins are known, of which 14 occur as systemic deposits, 24 as local amyloids, and 4 as systemic or local deposits[5].

The basic structure of amyloid is the fibril, defined as an aggregate structure of insoluble proteins consisting of protofilaments in a configuration of folded β-sheets that are superimposed and resistant to proteolysis[5,13]. Approximately 95% of amyloid consists of fibrillar proteins. The remaining 5% is the P component of serum amyloid and other glycoproteins[20]. Increased synthesis, point mutations, or proteolytic cleavages can induce structural changes in the precursor proteins that predispose to an aggregation state[1]. Exposure to denaturing stimuli, such as low pH, elevated temperatures, proteolysis, and ions, causes an unfolding of the polypeptide chains of amyloidogenic proteins, which may be exposed to hydrophobic residues during

refolding that promote the protein's susceptibility to misfolding and self-aggregation[1,20]. Amyloid fibrils are stabilized by polar hydrogen bonds between parallel chains, and their intermediate aggregates are stabilized by hydrophobic and electrostatic interactions[1].

Amyloid fibril deposition causes cell toxicity, tissue damage, and organ dysfunction through a direct cytotoxic effect, leading to mitochondrial dysfunction, oxidative stress, and apoptosis[1]. However, the precise mechanisms of tissue damage are not fully understood. Lysosomal dysfunction appears to be the main cause of impaired autophagy and amyloid-induced proteotoxicity[21].

DIAGNOSIS

The gold standard for diagnosing amyloidosis is histopathologic confirmation of amyloid fibrils with identification of their crystallographic diffraction patterns using stains such as thioflavin T and Congo red[5,20]. Amyloid is birefringent with Congo red under polarized light microscopy and produces a mixture of blue-green, yellow-green, or typical "green birefringence," depending on the optical configuration of the filters[2]. Amyloid can also be stained with metachromatic dyes such as crystal violet[20].

A biopsy of an organ infiltrated by amyloid carries a high risk of bleeding. An organ biopsy is not considered necessary to confirm AL amyloidosis in the presence of a compatible syndrome and monoclonal gammopathy[13]. If systemic disease is suspected, a biopsy can be performed at various anatomical sites: subcutaneous abdominal fat (sensitivity 78-100%), labial salivary glands (sensitivity 61%), rectal mucosa (sensitivity 75-85%), and bone marrow (sensitivity 57%). A lower diagnostic yield has been described in patients with ATTR amyloidosis[13,22,23]. Another diagnostic alternative is immunoelectron microscopy, which combines immunohistochemistry and electron microscopy with gold-labeled antibodies[24,25]. Congo red-based light microscopy and immunoelectron microscopy are equally sensitive for systemic forms (79% and 76.1%, respectively), with the latter being more specific in abdominal fat samples (100% vs. 79.7%, $p < 0.001$)[24]. The sensitivity for both techniques decreases in AL κ amyloidosis (sensitivity 71%) or ATTR amyloidosis (sensitivity 43%)[24].

The amyloid molecule involved in the disease can be identified by immunohistochemistry (AA amyloid and immunoglobulin λ and κ light chains) or mass spectrometry, a technique with a good diagnostic yield, but complex and expensive[22,24,25]. Immunohistochemistry using immunofluorescence or immunoperoxidase can be performed on frozen or paraffin-embedded samples. However, interpretation can be affected by the background staining of the tissue[20,25].

Once the diagnosis of amyloidosis is established, the systemic disease should be assessed with a blood count, renal and liver function tests, proteinuria, serum protein electrophoresis, immunofixation, an electrocardiogram, and an echocardiogram[22]. Scintigraphy with a radiolabeled serum amyloid P component is a sensitive and highly specific method for detecting AA deposits or visceral AL amyloid[22,26].

Table 1. Types of pulmonary amyloidosis

Description
Nodular amyloidosis (NA)
Cystic amyloidosis (CA)
Diffuse alveolar–septal amyloidosis (DASA)
Tracheobronchial amyloidosis (TBA)

PULMONARY AMYLOIDOSIS

Amyloid deposits are located in various lung structures, including the alveolar septum, blood vessel wall, airways, and lymph nodes. The spectrum of clinical manifestations and imaging findings includes nodular amyloidosis (NA), cystic amyloidosis (CA), diffuse alveolar–septal amyloidosis (DASA), and tracheobronchial amyloidosis (TBA) (Table 1). TBA and NA are the most common[27-29]. NA is commonly associated with localized forms of the entity[27,29]. DASA is rare and usually associated with systemic amyloidosis[27,29]. The mean survival after diagnosis is longer in patients with localized disease[27].

In general, the prevalence of pulmonary alterations in systemic AL amyloidosis in histopathologic studies is 36-90%[7]. In a Mayo Clinic study of 76 autopsies between 1997 and 2014, AL amyloidosis was described in many patients with amyloidosis and pulmonary disease (76%), with a lower percentage of cases associated with ATTR amyloidosis (22%)[7]. The pattern of pulmonary vascular involvement (97%) and DASA (78%) was more frequent than TBA (29%), mainly in AL amyloidosis and less frequently in ATTRwt amyloidosis.

The Kiel Amyloid Registry of Heidelberg, Germany, in a study of 207 lung samples between 2006 and 2017, reported that AL amyloidosis was the most common type (AL λ in 141 cases and AL κ in 27 cases). Localized amyloidosis was the most common (90.1%) with a predominant NA pattern[19]. The mean age was 67 years

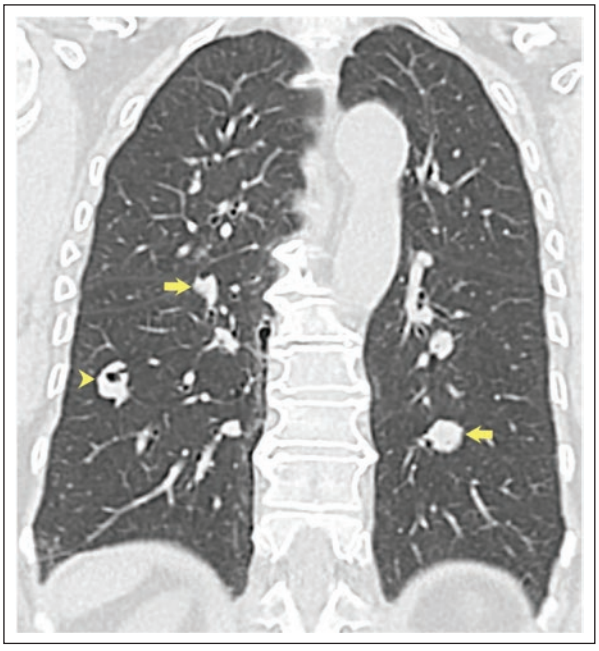

Figure 1. Nodular amyloidosis. A chest CT coronal reconstruction shows solid pulmonary nodules in the lower lobes (arrows) with nodule cavitation in the right lower lobe (arrowhead).

CT: computed tomography.

(range 24-88). Patients with ATTR amyloidosis had a higher mean age (79 years) and it was observed more commonly in men (80%) than those with AL amyloidosis (54.7%).

The type of presentation also varied with age. In a Heidelberg University Hospital cohort study, 67 patients were examined between 2002 and 2018, AL amyloidosis was diagnosed in 61 cases (NA n = 41 and TBA n = 20)[28]. The mean age for NA, TBA, and systemic pulmonary parenchymal amyloidosis was 67 (range 37-81), 56 (range 39-77), and 58 (range 44-75) years, respectively. In a retrospective review of 55 cases of pulmonary amyloidosis from the Mayo Clinic between 1980 and 1993, imaging findings of a reticulonodular interstitial pattern were found in 35 patients with systemic amyloidosis (mean age 64; range 41-90)[27]. Localized pulmonary amyloid was found in 11 patients, and 7 (mean age 67 years; range 43-78 years) had amyloidomas. Four TBA cases were reported (mean age 62; range 35-85).

The clinical manifestations of systemic amyloidosis are nonspecific and include fatigue, edema, weight loss, dyspnea, and orthostatic hypotension[13]. Some signs, such as macroglossia and periorbital purpura, may be

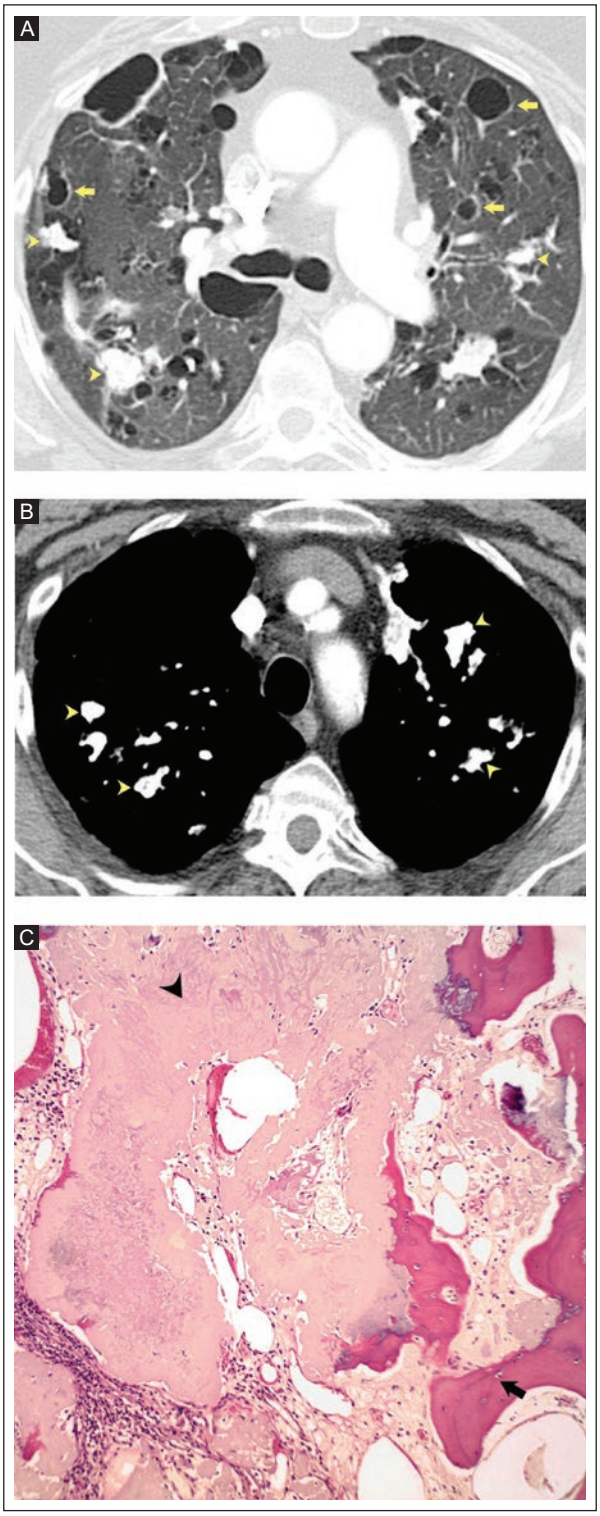

Figure 2. Nodular–cystic calcified amyloidosis. Chest CT axial view. **A:** the lung window shows thin-walled cysts (arrows) in the upper lobes with associated nodules (arrowheads). **B:** the mediastinal window shows calcification of the pulmonary nodules (arrowheads). **C:** the histopathologic findings show amorphous amyloid deposits (arrow) between ossification areas (arrowhead).

CT: computed tomography.

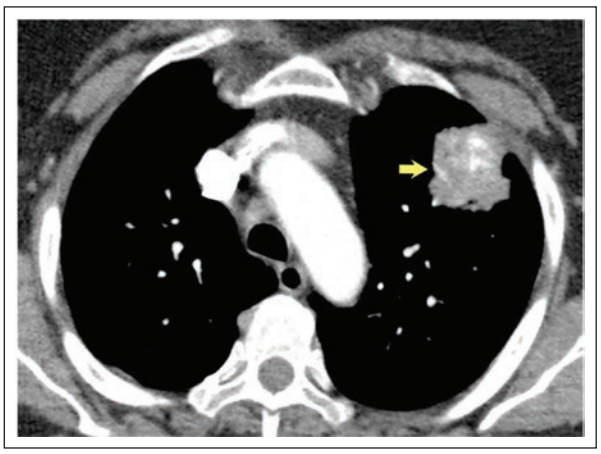

Figure 3. Amyloidoma. Chest CT, axial view, showing subpleural mass in the left upper lobe, solid, irregular contour, with calcifications (arrow).

CT: computed tomography.

specific for AL amyloidosis but occur in only 15% of patients[13,24]. Non-cardiac signs in ATTR amyloidosis include carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, small fiber neuropathy, and autonomic dysfunction[13]. Pulmonary disease can be associated with nonspecific respiratory symptoms, particularly cough, which is more common in patients with TBA than in patients with pulmonary parenchymal amyloidosis (90% vs. 46%)[28].

NODULAR AMYLOIDOSIS

NA is characterized by localized (single or multiple) tumor-like amyloid deposits in the lung parenchyma[20]. NA has been described more frequently in patients with localized AL or AL/AH (mixed immunoglobulin light-chain/heavy-chain) amyloidosis and is three times more common in κ-type light-chain immunoglobulins than λ-type light-chain immunoglobulins[20]. NA is less frequently described in patients with systemic AL or specific types of localized amyloidosis such as AA, ATTRwt, and AB2M/AL (light-chain/mixed immunoglobulin light-chain β2)[20]. In a significant percentage of cases, NA is associated with lymphoproliferative disorders, particularly extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)[30-32]. An association between NA and systemic autoimmune diseases has been demonstrated, most commonly in Sjögren's syndrome[30-32]. These diseases are thought to promote the synthesis and local accumulation of light chains[30-32].

NA most commonly manifests in the seventh decade of life, with a mean age of 65.5 years (range 36-80 years)[18]. The natural history of NA is relatively benign, asymptomatic with slow progression, has no impact on survival, and is often discovered incidentally on imaging examination[4,18,29]. The behavior of the nodules is variable. They can remain stable, progressively increase in number and size, or sometimes decrease in size[33]. NA is the most common form of pulmonary amyloidosis in patients with Sjögren's syndrome. However, it is a rare cause of pulmonary opacities in this population (0-2% of symptomatic patients)[34]. It occurs almost exclusively in women (96.5%) in the sixth decade of life after the diagnosis of Sjögren's syndrome (median 7 years) and mostly the AL type[31,34]. Cases with concomitant lymphoma or lymphoid interstitial pneumonia have been described in patients with Sjögren's syndrome and NA[34].

Imaging findings

Imaging examination, especially computed tomography (CT), shows bilateral pulmonary nodules (83%) with peripheral predominance toward the lung bases with smooth, lobulated, or spiculated contours[28,29]. The nodules may have central or punctate calcification (41%) or cavitation (15%)[28] (Figure 1). In most cases, lesions are less than 10 mm in diameter, but masses up to 15 cm in diameter have been described[27]. The nodules are usually numerous, and more than 10 lesions are described in 59% of patients[33]. Most nodules are solid, but in multiple nodules, at least one calcified nodule can be found in 82% of cases[33] (Figure 2A-C). Zamora et al.[33] described partially solid or ground-glass nodules in 65% of patients.

The term amyloidoma refers to pseudotumoral amyloid deposits (single or multiple) without systemic amyloidosis. Patients are generally asymptomatic, and deposits are usually incidental findings on imaging[35] (Figure 3). Larger amyloidomas may invade adjacent anatomical structures causing secondary clinical manifestations suggesting alternative diagnoses (primary or metastatic neoplasms)[35]. On magnetic resonance imaging, amyloidomas are isointense to muscle on T1 images and slightly hypointense on T2 images and may show heterogeneous enhancement[35]. Positron emission tomography (PET) with fluorodeoxyglucose lacks sensitivity and specificity for diagnosing amyloidosis and does not differentiate between amyloidosis and primary or secondary neoplasia[35,36].

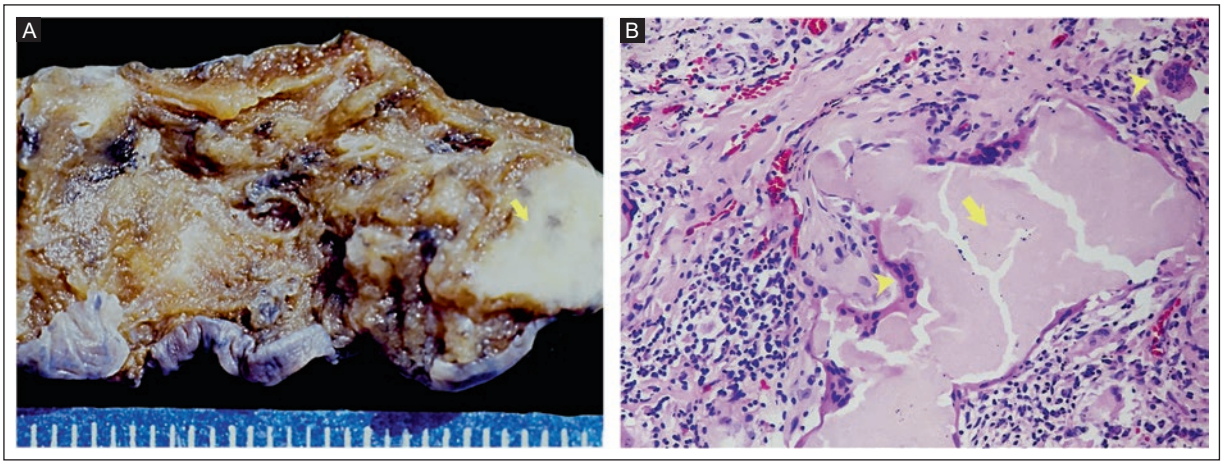

Figure 4. Nodular amyloidosis. **A:** segmentectomy showing lung parenchyma with subpleural nodule 7 mm in diameter, solid, white with irregular borders (arrow). **B:** histopathologic findings (HE 40×): eosinophilic acellular amorphous material (arrow) with multinucleated giant cells (arrowheads) and lymphoplasmacytic inflammation.

HE: hematoxylin and eosin.

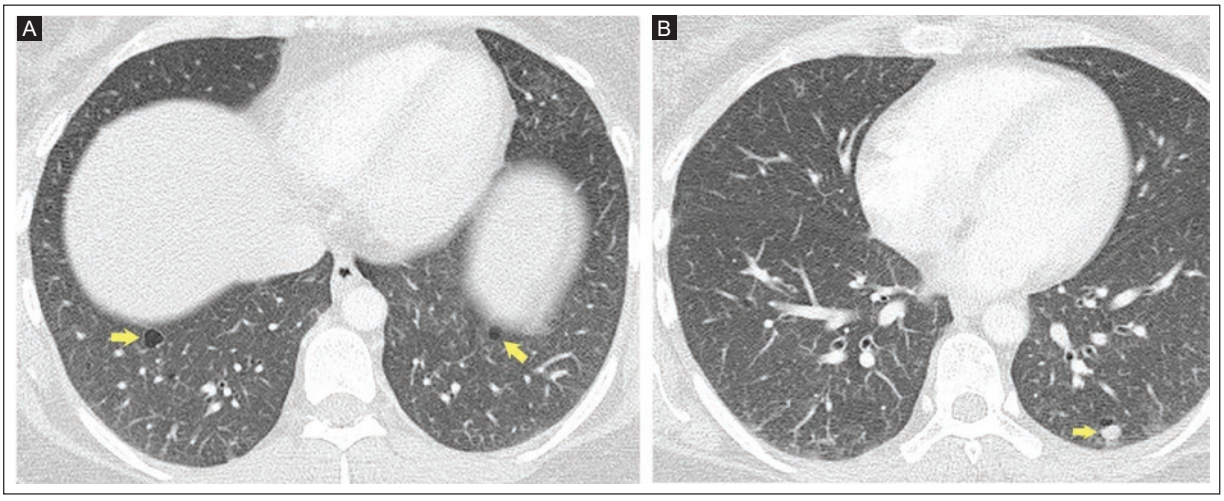

Figure 5. Cystic amyloidosis. Chest CT, axial view. **A:** thin-walled cysts in the lower lobes (arrows). **B:** same patient with a solid nodule in the left lower lobe (arrow).

CT: computed tomography.

The differential diagnosis of NA is broad and includes metastatic disease, multicentric primary lung neoplasms, lymphoproliferative disorders, and granulomatous diseases (tuberculosis and histoplasmosis), among others[37].

Histopathologic findings

Macroscopic examination of the lung shows nodules ranging in size from 0.4 to 15 cm (Figure 4A). Histologically, the nodules are well demarcated and consist of homogeneous, acellular, densely eosinophilic material that may be associated with small clusters of lymphocytes, plasma cells, multinucleated giant cells, calcifications, and bone metaplasia[20] (Figure 4B).

CYSTIC AMYLOIDOSIS

CA is rare. In many patients, the cysts are associated with solid nodules (Figures 5A, B and 6). Patients may be asymptomatic, and symptomatic cases present a wide spectrum of clinical manifestations, including cough, dyspnea, and hemoptysis in severe cystic lung disease[33].

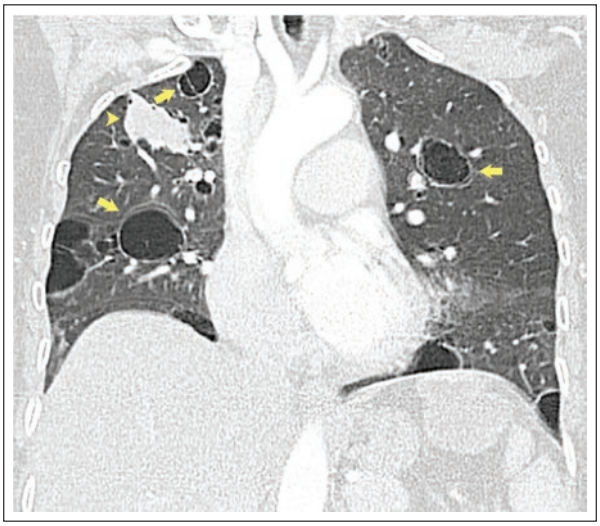

Figure 6. Cystic amyloidosis and amyloidoma. Chest CT coronal reconstruction showing multilobar, bilateral, spherical, thin-walled pulmonary cysts (arrows). Septa in the right apical cyst (arrows). Solid mass in the right upper lobe with lobulated contours corresponding to an amyloidoma (arrowhead).

CT: computed tomography.

Most amyloidosis cases with lung cysts correspond to patients with localized AL amyloidosis and are associated with systemic autoimmune diseases, most commonly Sjögren's syndrome and MALT pulmonary lymphoma[28,33]. CA and lymphocytic interstitial pneumonia, characteristically also associated with pulmonary cysts, have been described simultaneously in some patients with Sjögren's syndrome[28,33]. In patients with Sjögren's syndrome and pulmonary cysts, the presence of solid nodules or calcifications is suggestive of CA, and the simultaneous presence of centrilobular ground-glass nodules and cysts is suggestive of lymphocytic interstitial pneumonia[33].

In a cohort of 187 patients with pulmonary amyloidosis from the Mayo Clinic (1997-2010), 11.2% of patients had CA. In the group of patients with cysts, 62% were women with a median age of 61 years (range 26-91) and 57% had associated autoimmune disease, particularly Sjögren's syndrome (83%)[33].

The pathophysiology of pulmonary cysts in amyloidosis is not clear. Some authors postulate that the cysts are formed by a valve mechanism secondary to partial obstruction of the distal airways by amyloid deposits and inflammatory cells, particularly mature lymphocytes and plasma cells[32]. It has been suggested that amyloid deposition in the pulmonary capillaries may lead to ischemia and destruction of the alveolar wall[38]. It is also proposed that, similar to light-chain deposition disease, the recruitment of macrophages induces the production of metalloproteinases that degrade elastic fibers and collagen, leading to the formation of cysts[39,40]. However, cysts and nodules may have imaging manifestations similar to those of light-chain deposition disease; in the latter, the structure of amyloid fibrils is not recognized on histopathologic examination[40].

Imaging findings

A report on cystic lung disease associated with amyloidosis (22 patients) describes multiple cysts (more than 10) in 67% of patients, bilateral (100%), predominantly basal (43%), peribronchovascular (90%) or subpleural (90%), spherical (100%) or lobular (95%), with a wall thickness of less than 2 mm (81%), and varying size, <1 cm (100%) and between 1 and 2 cm in 81% of cases[33] (Figure 7A). Solid or calcified nodules related to the cyst wall are described[33]. On follow-up, cysts tend to increase in size and number less frequently than nodules[33].

Histopathologic findings

Respiratory epithelium and lymphoid infiltrates line the cysts, and amyloid deposits are found in the wall[31]. The bronchiole wall is dilatated and thickened with eosinophilic material, lymphoid hyperplasia, or follicular bronchiolitis[31,33] (Figure 7B).

DIFFUSE ALVEOLAR–SEPTAL AMYLOIDOSIS

DASA is related to amyloid deposits in the alveolar septa and blood vessel wall[20,41]. Most cases are associated with systemic AL amyloidosis and in a much smaller proportion to systemic AA, systemic ATTRwt, and systemic hereditary ATTR amyloidosis[20,37]. DASA is described in 12% of patients with Sjögren's syndrome in association with different amyloid types (AA and AL)[34]. The prognosis of patients with DASA is poor, with a median survival of 13 months in untreated patients, and may worsen in patients with heart failure (less than 4 months)[41].

Most patients with DASA have generalized symptoms that reflect the systemic nature of the underlying disease[41]. Dyspnea is the most common clinical manifestation. The frequency of respiratory symptoms is lower than expected, as a high percentage of pulmonary infiltration has been described in autopsies of patients with systemic amyloidosis[41]. Isolated cases of pulmonary arterial hypertension associated with

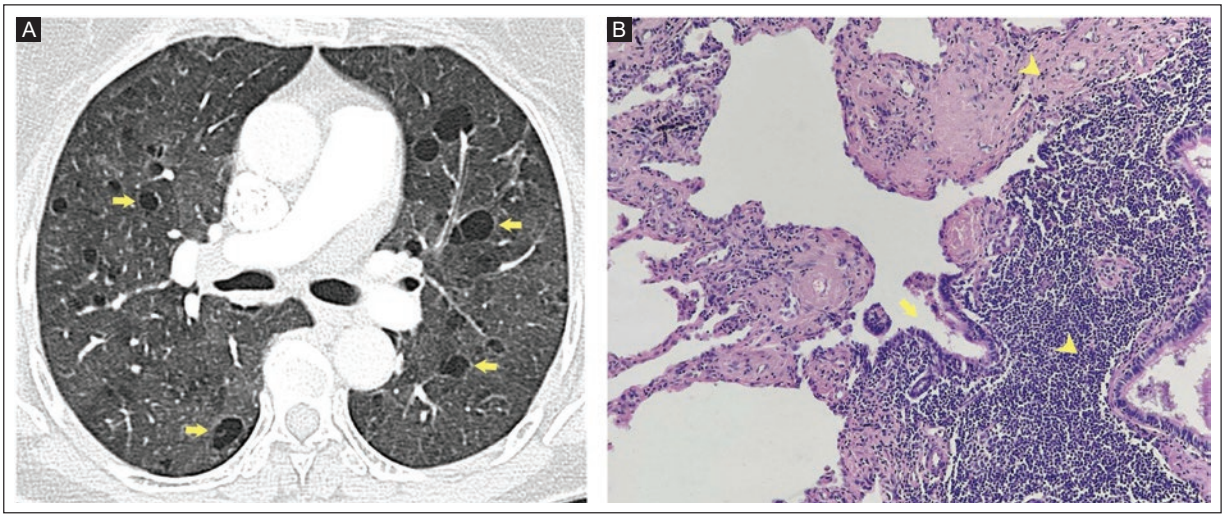

Figure 7. Cystic amyloidosis. Chest CT, axial view. **A:** spherical, smooth-contour, thin-walled lung cysts in the upper lobes (arrows). **B:** histopathologic findings (HE 20×). Dilated bronchiole (arrow) with submucosal thickening (arrowheads), lymphoid hyperplasia, and eosinophilic amorphous material.
CT: computed tomography; HE: hematoxylin and eosin.

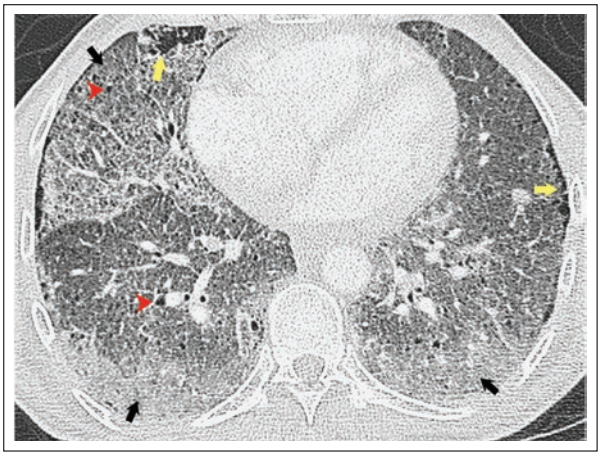

Figure 8. Alveolar hemorrhage associated with amyloidosis. Chest CT axial view showing multilobar ground glass (black arrows), bilateral pulmonary cysts (red arrowheads), and paraseptal emphysema (yellow arrows).
CT: computed tomography.

amyloidosis and related to amyloid deposition in the blood vessels causing vasoconstriction and proliferation of smooth muscle and endothelium have been reported[42]. On the contrary, diffuse alveolar hemorrhage has been described in patients with systemic amyloidosis due to alterations in the alveolar wall caused by amyloid deposition[37,43] (Figure 8).

Imaging findings

The CT chest findings are extensive and include reticulation, interlobular septa thickening, peribronchovascular interstitium thickening, micronodules, ground glass, and consolidation[41]. Micronodularity may be distributed perilymphatically, similar to that described in patients with lymphangitic carcinomatosis[29,44] (Figure 9A). Less commonly, cysts, calcifications, pleural effusion, and mediastinal adenomegaly are described in these patients[41,45]. The associated basal emphysematous changes are explained by damage to the alveolar walls[46].

The differential diagnosis by imaging is related to radiologic markers such as silicosis, sarcoidosis, lymphangitic carcinomatosis, and entities belonging to the group of interstitial lung disease in patients with reticulation as the most evident abnormality on a CT chest scan[41].

Histopathologic findings

On gross examination, the lung is uniformly rubbery with a sponge-like appearance[20]. Histology shows eosinophilic amyloid deposits in the alveolar septa[20,41]. The vessel walls are frequently affected, where small nodules may be formed[20,41]. Few plasma cells may be present, and multinucleated giant cells are rare[20,41] (Figure 9B).

TRACHEOBRONCHIAL AMYLOIDOSIS

This form of amyloidosis is characterized by focal, multifocal, or diffuse submucosal deposits of amyloid in the trachea, the main bronchi, and, in exceptional cases, the segmental bronchi[47,48]. It occurs more frequently

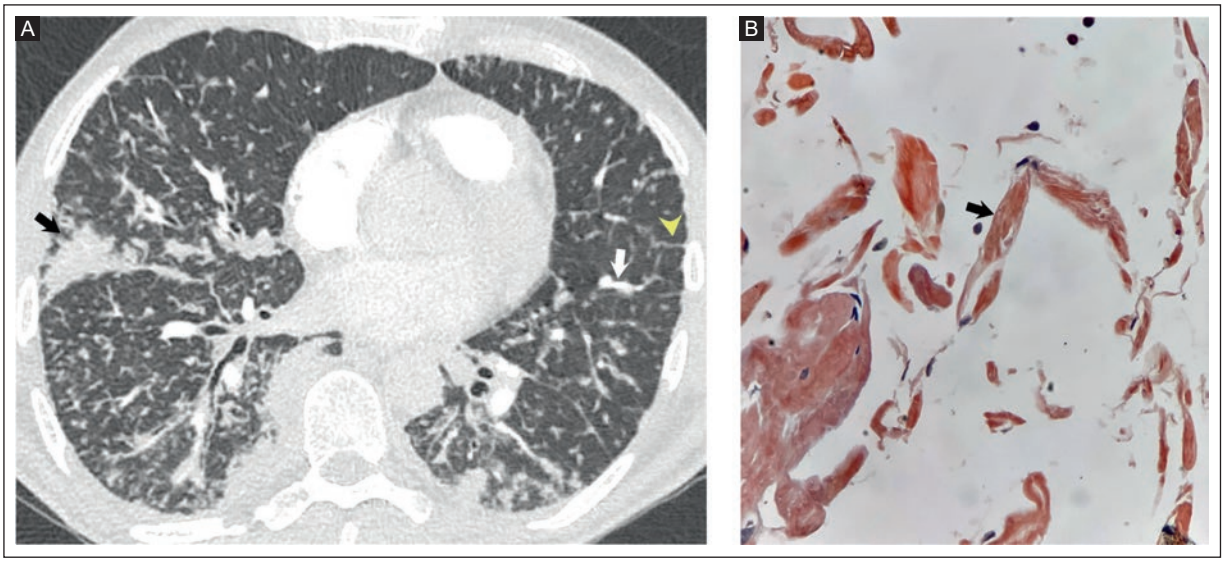

Figure 9. DASA. **A:** chest CT axial view showing periarteriolar micronodularity (white arrow), thickening of the peribronchovascular interstitium, nodular thickening of the interlobular septa (arrowhead), and subpleural consolidation (black arrow) in the lateral segment of the middle lobe and the posterior segment of the left lower lobe. **B:** DASA with Congo Red staining (40×) shows septal thickening with salmon-colored amorphous material (black arrow).

CT: computed tomography. DASA: diffuse alveolar–septal amyloidosis.

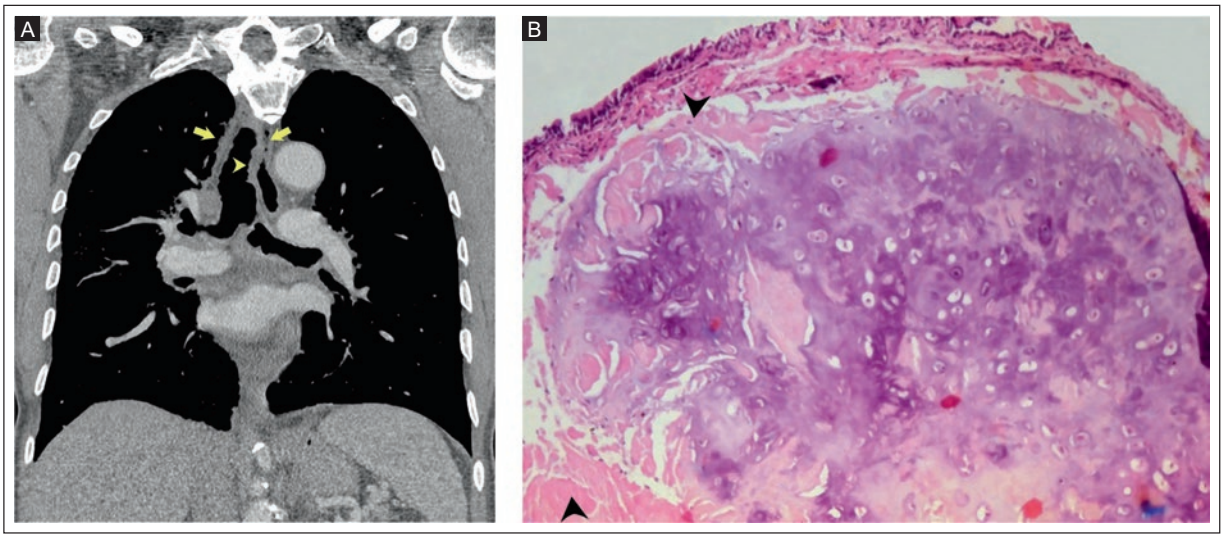

Figure 10. Tracheobronchial amyloidosis. **A:** chest CT coronal reconstruction showing trachea wall (arrows) and large bronchi thickening with nodularity in the tracheal mucosa (arrowhead). **B:** histopathologic findings (HE 4×). Tracheal wall with predominantly submucosal amyloid deposits surrounding the cartilage (arrowheads).

CT: computed tomography; HE: hematoxylin and eosin.

in men than women (1.6:1) between the fifth and sixth decades of life[47-51]. Most cases correspond to localized AL amyloidosis and are less commonly associated with systemic AL amyloidosis or AA[20,48]. The course of TBA is indolent, and the development of systemic amyloidosis in the natural history of the entity has not been described[52]. As in other patients with localized AL amyloidosis, clonal proliferation of a small number of B cells has been noted adjacent to light-chain amyloid deposits[53].

The clinical manifestations are related to airway narrowing and inflammation, including cough, dyspnea,

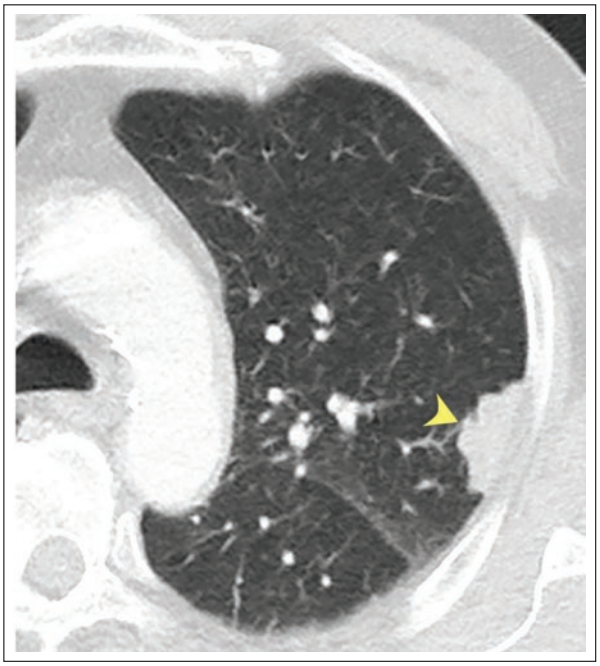

Figure 11. Pleural amyloidosis. Chest CT, axial view showing left apical focal pleural thickening (plaque) with lobulated contours (arrowhead). CT: computed tomography.

hemoptysis, wheezing, chest pain, and stridor[47,49-51]. Patients are often treated for years with a diagnosis of chronic bronchitis or asthma[47,52]. Patients with severe proximal disease have airway obstruction requiring dilatation or surgical treatment, and patients with the middle and distal third tracheal or main bronchus have atelectasis or recurrent infections of the lung parenchyma or airways[47,49-52].

Bronchoscopy can identify circumscribed yellow plaques, generally multifocal, nodules, or diffuse infiltration[47]. The lesions are predominantly proximal and associated with friable, inflamed, and irregular mucosa[47,50,52]. A biopsy by bronchoscopy confirms the diagnosis of TBA and is useful in treating stenotic lesions[47,50,51].

Laryngeal amyloidosis may coexist in patients with TBA[51]. The larynx is the most common site of amyloidosis in the head and neck region. The anatomical structures infiltrated by amyloid include the laryngeal ventricles, vestibule, vocal cords, epiglottis, and arytenoepiglottic folds[54]. Larynx amyloidosis is more common in men, with a mean age of 46 years (range 9-84). It presents with clinical dysphonia (96%) and dyspnea (27%)[54,55].

Imaging findings

The main TBA findings on CT examination are concentric thickening of the tracheal wall (>3 mm) and a long segment with secondary stenosis[28,48,52]. It is possible to detect nodular thickening of the tracheal wall (60%), calcification (53%), and airway obstruction (47%)[28,48,52]. Other less common findings on CT are solid pulmonary nodules, mediastinal adenomegaly, atelectasis, and bronchiectasis[28,48,52] (Figure 10A).

The differential diagnosis of TBA on CT includes granulomatosis with polyangiitis, granulomatous diseases (tuberculosis or sarcoidosis), and inflammatory bowel disease. The alteration of the posterior membrane of the trachea in patients with TBA allows differentiation of this entity from others with similar tomographic findings, such as relapsing polychondritis and osteochondroplastic tracheobronchopathy[54].

Histopathologic findings

Irregular wall thickening with yellow, gray, or white lesions can be observed macroscopically[20]. Histologically, the deposits consist of predominantly submucosal eosinophilic material surrounding seromucous glands and cartilage plates, plasma cells, multinucleated giant cells, calcifications, and ossification[20] (Figure 10B).

PLEURAL AMYLOIDOSIS

Pleural disease due to amyloidosis is underreported in most series. However, in the work by Brandelik et al.[28], pleural plaques are described in 25% of patients, most without pleural effusion. Pleural amyloidosis is rare in localized forms and is generally associated with systemic amyloidosis[56]. The most common forms of amyloidosis with pleural disease include AL amyloidosis (70.4%), ATTR amyloidosis (16.3%), and AA amyloidosis (8.2%)[21]. The mean age at presentation was 63 years (range 16-92 years), with older patients being more frequently affected (91.9% older than 50 years)[57]. The majority of patients were men (61.2%), with dyspnea, chest pain, and cough as symptoms[57].

The pleural fluid detected in patients with amyloidosis may be explained by increased pulmonary venous pressure associated with restrictive cardiomyopathy or nephrotic syndrome or by altered fluid reabsorption in the parietal pleura due to amyloid deposition on the surface of the pleura and in lymphatic and blood vessels[58,59]. In a Boston University study between 1994 and 2001 with 636 patients with AL amyloidosis, 6% had persistent pleural effusion due to pleural amyloid deposits demonstrated in pleural biopsies[58]. The pleural fluid may have characteristics of a transudate (43.4%) or an exudate (42.6%), with a predominance of

lymphocytes[57]. Although rare, pleural effusion may be hemorrhagic or chylous[60,61].

The diagnostic yield of closed pleural biopsy and thoracoscopy is 75% and 96.7%, respectively, with a better performance described in patients with unilateral or exudate-like effusion[57]. On thoracoscopy, diffuse inflammation was associated with disseminated light brown nodules in the parietal and visceral pleural sheets and the diaphragmatic surface of the pleura[59].

Imaging findings

CT findings include pleural fluid characteristically occupying less than one-third of the hemithorax (50%), bilateral (55%) or predominantly right (34%), and diffuse or localized thickening with pleural plaques that may calcify[56] (Figure 11).

The differential diagnosis of pleural plaques associated with amyloidosis is asbestos-associated pleural disease, and in cases of diffuse pleural thickening, infection (smooth thickening), or primary (mesothelioma) or secondary neoplasia in the case of nodular diffuse thickening[62,63]. As with NA, PET is of limited use in distinguishing pleural amyloidosis from primary or metastatic pleural neoplasia[56].

CONCLUSION

Pulmonary and pleural amyloidosis are rare. The nodular form of pulmonary amyloidosis is associated with localized amyloidosis, characteristically has a good prognosis, and should be considered for diagnosing single or multiple pulmonary nodules, especially when calcifications are present and the patient is asymptomatic. CA is rare and usually associated with pulmonary nodules and systemic autoimmune diseases, especially Sjögren's syndrome and MALT-type lymphoma. DASA is a manifestation of systemic amyloidosis with a poor prognosis and nonspecific manifestations on imaging examination, requiring histopathologic confirmation for diagnosis in a significant percentage of patients. Pleural plaques associated with systemic amyloidosis may be more common than traditionally thought, and their differential diagnosis with secondary neoplasms and pleural plaques associated with asbestos exposure represents a diagnostic challenge.

Funding

The authors declare that they received no funding or support for this article.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of individuals. The author declares that no experiments were performed on humans or animals.

Confidentiality of data. The author declares that no patient data are included in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence. The authors state that they did not use generative artificial intelligence to prepare this manuscript and/or create tables, figures, or figure legends.

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