

Subsolid pulmonary nodules at multislice computed tomography. Characteristics and differential diagnosis with lung adenocarcinoma

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Resumen

En el último tiempo se ha incrementado la detección de nódulos pulmonares, debido al uso de la tomografía computada multicorte (TCMC) y a la implementación de métodos de cribado de cáncer de pulmón mediante el uso de la tomografía computada (TC) de baja dosis. Esto ha despertado especial interés en los nódulos de tipo subsólido por su probabilidad de tener una etiología maligna, en particular el adenocarcinoma (ADC).

Con el análisis minucioso de las imágenes adquiridas en la tomografía computada multicorte se pueden identificar las características morfológicas de cada nódulo y realizar una correlación en forma aproximada con su probable anatomía patológica. La evaluación, junto con el contexto clínico-epidemiológico del paciente, hace posible un diagnóstico presuntivo y un pronóstico aproximado, permitiendo determinar las conductas terapéuticas o los planes de seguimiento.

Palabras clave. Nódulo pulmonar subsólido. Adenocarcinoma de pulmón. Tomografía computada multicorte.

Abstract

Subsolid pulmonary nodules at multislice computed tomography. Characteristics and differential diagnosis with lung adenocarcinoma.

In recent years, detection of pulmonary nodules has increased as a result of the use of multislice computed tomography (MSCT) and the implementation of lung cancer screening programs with low-dose computed tomography (CT). This has raised special interest in the subsolid type of nodules because of their probable malignant etiology, especially adenocarcinoma (ADC).

With a thorough analysis of multislice computed tomography images, it is possible to identify certain morphological characteristics of each nodule and to make an approximate correlation with its probable histology considering the clinical and epidemiological context of the patient. This allows for a presumptive diagnosis and an approximate prognosis, on which we can base decisions on therapeutic management and follow-up procedures

Keywords. Subsolid pulmonary nodules. Lung adenocarcinoma. Multislice computed tomography.

OBJECTIVE

Emphasizing the usefulness of multislice computed tomography (MSCT) in the characterization of subsolid pulmonary nodules (SSPNs) and their differential diagnosis with adenocarcinoma (ACA) of the lung and other benign etiologies, such as focal fibrosis and focal inflammation or infections.

INTRODUCTION

ACA is the most common histologic type of lung cancer, accounting for approximately 45 % of primary lung tumors. It has been recently confirmed that lung cancer screening by using low-dose computed tomography (CT) has considerably reduced lung cancer mortality, as compared to chest radiographic (X-ray) screening in subjects at high risk for lung cancer,

current or former smokers aged 55-74 years⁽¹⁾. An immediate consequence of this confirmation is the increased number of patients studied by CT. Furthermore, the widespread use of MSCT has increased the detection of pulmonary nodules⁽²⁾.

The presence of pulmonary nodules in CT scans performed in lung cancer screening trials ranges between 10 % and 23 %, depending on the various series⁽³⁾.

Definitions

Pulmonary nodules are defined as round or oval areas of increased attenuation, not larger than 3 centimeters in diameter. Depending on their tomographic density, these nodules may be classified as solid or subsolid⁽⁴⁾.

Solid nodules are defined as areas of increased attenuation due to airspace collapse, which obscure

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Recibido: noviembre 2012; aceptado: abril 2013
Received: november 2012; accepted: april 2013
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doi: 10.7811/rarv77n2a02

underlying normal lung parenchymal structures (Fig. 1). In distinction, subsolid nodules include both pure ground-glass opacities (GGOs) and mixed nodules⁽⁴⁾. Pure GGOs (Fig. 2) are focal areas of increased attenuation through which underlying vessels can be defined⁽⁴⁾, while mixed nodules present both a ground-glass component and a variable solid component⁽⁴⁾ (Fig. 3).

This article focuses specially on subsolid pulmonary nodules (both mixed and pure GGOs). Even if this type of nodule may be of benign etiology (focal fibrosis, inflammation or hemorrhage), it is not rare that it may correspond to adenocarcinoma of the lung⁽²⁾.

Histopathologic classification

In 1995, Noguchi et al published a study based on the review of 236 peripheral ACAs measuring less than 2 cm and established 6 types (A-F) on the basis of the pattern of tumor growth^(5,6).

- Type A. Localized bronchioloalveolar carcinoma (BAC) with no pulmonary collapse or fibrosis (minimal septal thickening): 7%.
- Type B. Localized BAC with foci of pulmonary collapse (due to tumor cell degeneration): 7%.
- Type C. Localized BAC with foci of active fibroblastic proliferation (this is the most common type and it usually causes pleural retraction): 60%.
- Type D. Poorly differentiated adenocarcinoma: 18%.
- Type E. Tubular adenocarcinoma (originating from bronchial gland cells): 4%.
- Type F. Papillary adenocarcinoma with compressive and destructive growth: 4%.

In 1999 and then in 2004, the World Health Organization (WHO) classification determined that, to be classified as BAC, tumors must show pure lepidic growth (i.e., an exclusive growth pattern lining pre-

existing alveolar spaces). There should be no stromal, vascular or pleural invasion. In accordance with this definition, Noguchi types A and B strictly correspond to BAC and type C (which manifests as BAC but with an invasive component) is termed mixed subtype^(4,7).

The classification includes atypical adenomatous hyperplasia (AAH) as a premalignant lesion. AAH is defined as a proliferation of atypical epithelial cells along the alveoli and respiratory bronchioles less than 5 mm. On MSCT, it is seen as a well-defined oval or round focal pure GGO with no marginal spiculation or pleural retractions persistent in time. AAH most frequently occurs in patients with a current or past history of adenocarcinoma of the lung^(2,4,8).

In February 2011, a new ACA classification was published using a multidisciplinary approach, based on the joint work of the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society.

Both the 2004 and the 2011 classifications are summarized in Table 1⁽⁹⁾. As we can see ACA subtypes include bronchioloalveolar carcinoma / adenocarcinoma *in situ* (BAC / AIS), with distinguishing epidemiological, clinical, pathologic and radiological features. This tumor most frequently occurs in young women and it is the least frequently associated with smoking. It has peripheral location and an exclusive growth pattern lining pre-existing alveolar spaces. Furthermore, it has a slow growth and in most cases it is asymptomatic. It may be multifocal in up to 27% of cases^(4,10).

The new classification highlights the noninvasive nature of BAC, which is termed adenocarcinoma *in situ* and characterized as a pre-invasive lesion.

Within the lepidic growth pattern, we find Noguchi type A and B lesions, both encompassed under the term BAC in the 2004 WHO Classification. Currently, according to the new classification, BAC encompasses pre-invasive lesions, such as AAH and adenocarcinoma *in situ*. Noguchi type C has an invasi-

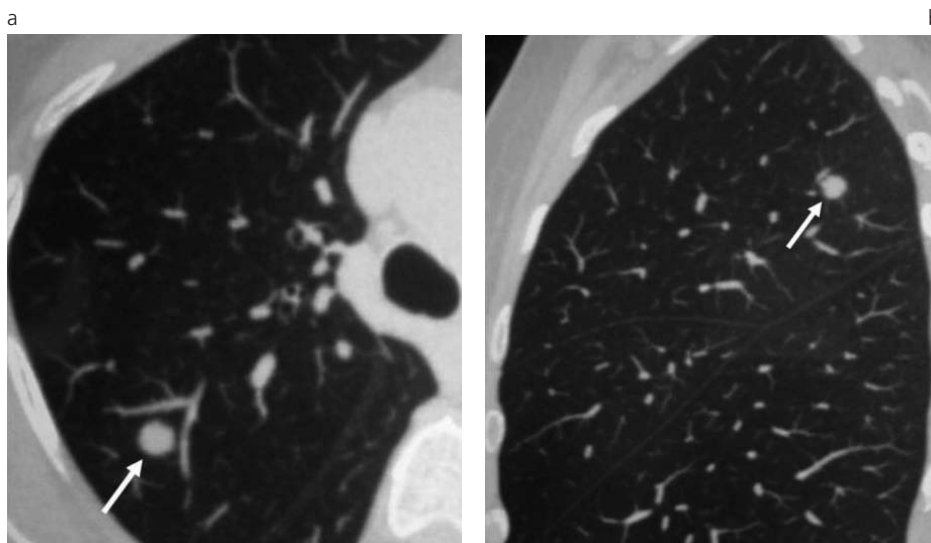


Fig. 1: Solid lung nodule (arrows). MSCT, axial (a) and sagittal (b) slices, in the posterior segment of the right upper lobe shows a 10-mm well-defined nodule without an internal air bronchogram.

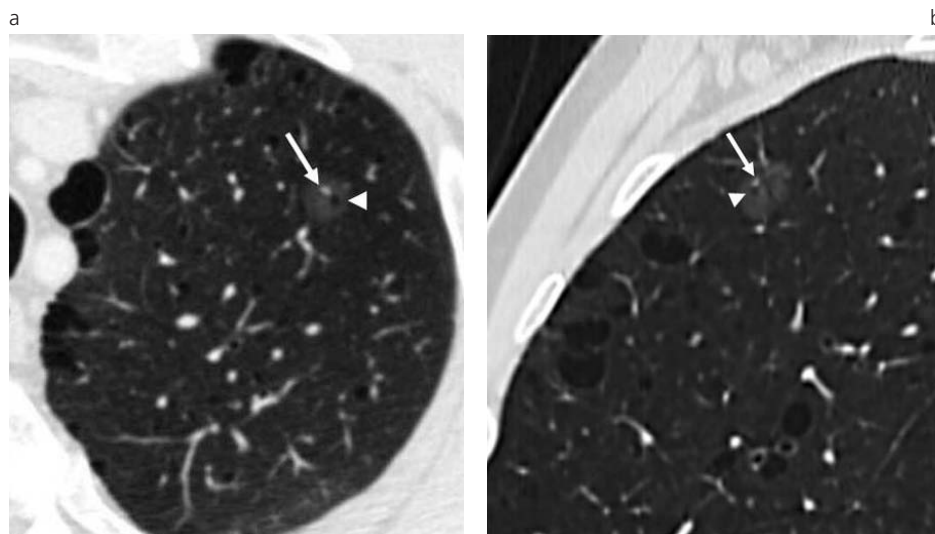


Fig. 2: Subsolid nodule with pure GGO. MSCT, axial (a) and sagittal (b) slices in the apical-posterior segment of the left upper lobe. A vascular structure (arrow) and a bronchial structure (arrowhead) are visible through the nodule. Presence of subpleural bulla.

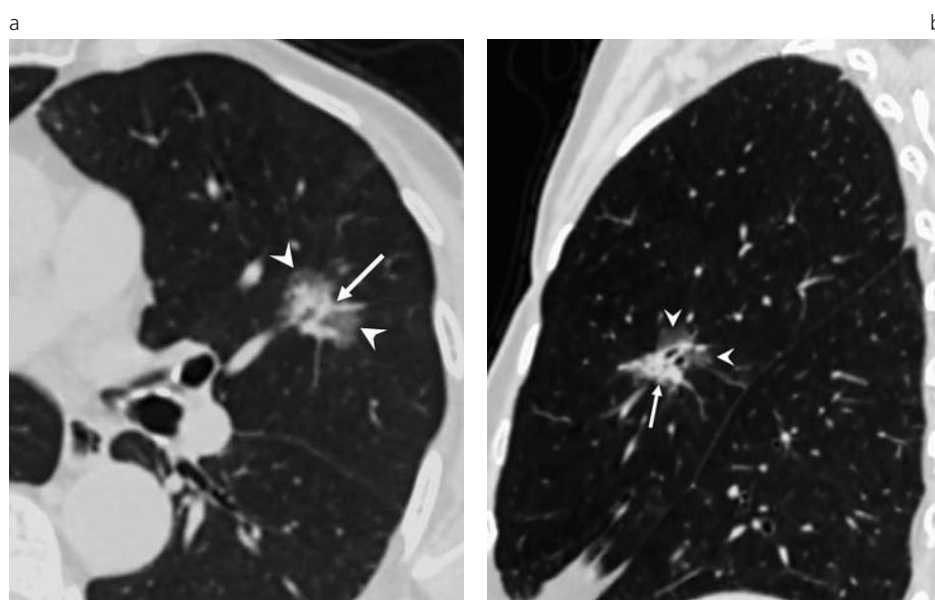


Fig. 3: Mixed nodule. MSCT, axial (a) and sagittal (b) slices at the level of the left lung. Solid central portion of spiculated margin (arrow) and a peripheral ground-glass component (arrowhead).

ve component of variable proportion, and was therefore considered in 2004 as a mixed subtype, and at present it somehow corresponds to the minimally invasive adenocarcinoma in the multidisciplinary classification ⁽⁴⁾. Furthermore, it should be added that these subtypes, both BAC *in situ* and minimally invasive BAC can only be applied to tumors less than 3 cm (studied as a whole). The importance of these categories lies in the fact that BAC *in situ* and minimally invasive BAC have a high survival rate (close to 100%) as compared to invasive BAC ⁽¹¹⁾.

Characteristics on MSCT

CT features are different depending on types. While Noguchi type A and B lesions usually have a

larger ground-glass opacity component and have rounded margins, type C lesions combine an appearance of ground-glass opacity with a solid component (the percentage of those components is variable and has prognostic significance) ⁽²⁾. Furthermore, type C lesions more frequently have lobulated and irregular margins, pleural thickening and spiculation. The presence of air bronchogram and/o bubble-like areas within the nodule is common mainly in Noguchi type C lesions and rare in non-lepidic lesions.

Non-lepidic nodules, Noguchi type D, E and F lesions, which currently correspond to invasive adenocarcinoma, have an expansive growth that compresses and destroys the adjacent lung parenchyma. They are clearly invasive, grow more rapidly and have a poorer prognosis than lepidic lesions. Lymph nodes metastases (as well as recurrences) occur more

Table 1: 2004 and 2011 classification of adenocarcinomas of the lung.

WHO 2004		MULTIDISCIPLINARY 2011	
Preinvasive lesions	AAH	Preinvasive Lesions	AAH Adenocarcinoma <i>in situ</i> (formerly BAC)
Bronchioloalveolar carcinoma	BAC Non mucinous, mucinous or mixed	Minimally invasive adenocarcinoma	Adenocarcinoma with predominantly lepidic growth pattern, with a small focus of invasion that is less than 5 mm.
Invasive Adenocarcinomas (non BAC)	Mixed adenocarcinoma	Invasive adenocarcinoma	Adenocarcinoma with predominantly lepidic growth pattern, with a focus of invasion that is greater than 5 mm.
	Acinar adenocarcinoma		Acinar predominant adenocarcinoma
	Papillary adenocarcinoma		Papillary predominant adenocarcinoma
			Micropapillary predominant adenocarcinoma
	Solid, mucin-producing adenocarcinoma		Solid predominant adenocarcinoma with mucin

frequently. In addition, pleural thickening and spiculation are common. Because of their invasive behavior, they frequently have a consolidation and solid appearance, where in general no air bronchogram or bubble-like areas are identified ^(4,12).

Correlation between MSCT and histologic findings

Based on several studies, a good correlation has been established among pathologic findings, MSCT findings and prognosis (Table 2) ⁽⁴⁾. While MSCT cannot confirm the benign or malignant origin of disease, it may provide an approximation based on some features of the nodules.

Size, margins and the presence of solid component have been the most decisive factors at the time of defining benignancy or malignancy. For pure GGOs, a size greater than 8 mm and the presence of lobulated borders are independent factors of malignancy, while pure GGOs measuring 4 mm or less are considered benign.

In mixed nodules, lobulation is associated with higher risk malignancy (although no cutoff point could be established for the size of the lesion, since small lesions proved to be malignant) ^(4,13). In these cases, the more extensive the solid portions of the lesion, the poorer the prognosis. When the ground-glass component predominates (over 50%) early-stage disease and better prognosis have been demonstrated ^(2,14).

A subsolid pulmonary nodule has a higher likeliho-

od for malignancy than a solid nodule (especially mixed types, which are at the highest risk) ^(13,15). GGO nodules are malignant in up to 20-40% of cases, while the rest corresponds to benign conditions, such as focal fibrosis, inflammatory, hemorrhagic or infectious foci ⁽²⁾.

The behavior of the nodule over time is a very important factor to predict its etiology. Most benign conditions resolve spontaneously or, after appropriate treatment over weeks or months, with clinical improvement. Malignant nodules may persist with no changes over lengthy periods (two or three years, and patients often have no clinical symptoms during that period) until they increase in size or density ⁽²⁾.

In an attempt to predict whether a SSPN will persist or regress over time, the morphologic features of nodules and the clinical characteristics of patients were evaluated. A nodule is defined as transient when at 3 months follow-up it has decreased in size by at least 20% (compared with the baseline CT image). If over such period a nodule has remained stable or increased in size, it is designated as persistent ⁽¹⁵⁾.

Transient nodules have been more frequently found in women and young adults with heavy smoking history (a pack per day for 30 years) and in subjects with peripheral blood eosinophilia ⁽¹²⁾. As regards morphologic features, this same study showed that multiple lesions with not spiculated margins and ill-defined borders had a tendency to be transient, while all nodules with spiculated margin, air bronchogram, bubbles or pleural retraction were persistent ⁽¹⁵⁾.

Table 2: Correlation with pathologic findings, MSCT and 5-year survival.

Histology (Noguchi 1995)	Multidisciplinary classification 2011	MSCT	5-year survival
Type A	AAH BAC <i>in situ</i>	Pure ground-glass Rounded borders	100%
Type B		Heterogeneous ground-glass	Close to 100%
Type C	Minimally invasive BAC	Mixed (pure GGO and solid component) Lobulated and irregular borders Pleural thickening Spiculation Air bronchogram/bubbles	Above 75%
Type D, E y F	Invasive BAC	Solid or predominantly solid Rounded borders Pleural thickening Spiculation NO air bronchogram/bubbles Lymph node metastases and frequent recurrence	Below 50%

Technical concepts about the evaluation of SSPN

In the initial evaluation and follow-up of SSPNs it is useful to determine first how the nodule will be studied in order to be able to perform reliable comparative tests. Two essential features should be considered at the time of the initial evaluation and subsequent follow-up: size and CT density.

Diameter measurement is not an accurate method because it is often subject to inter-observer variability and, besides, small variations in length do not truly reflect an increase in volume of the lesion studied. As a supplementary method to calculate whether a nodule has increased in size, the use of pulmonary volumetry is recommended (Fig. 4). This technique enables us to measure (in an automated manner by means of specific software) the volume doubling time of the nodule and, thus to know its biological behavior.

As we mentioned above, small changes in nodule measurement result in significant changes in volume. If we add to this the fact that many of the lung ACAs have a slow growth, probably the nodule will have doubled more than once by the time an increase in size becomes evident, and prognosis will be less favorable ⁽¹⁶⁾.

The other feature that should be evaluated during follow-up is CT density of SSPNs, as they may remain stable or increase in density (either in a diffuse or focal manner) and in solid component (which is associated with greater stromal invasion and a poorer prognosis).

For measuring the size of SSPNs, a lung window is usually used, while for measuring the solid portion in a mixed nodule, the longest diameter in the axial plane is usually taken, with the image being evaluated with mediastinal window setting ⁽¹²⁾.

The role of fluorodeoxyglucose (FDG) positron emission tomography

The role of positron emission tomography (PET / CT) in the characterization of SSPNs is not fully defined. In small lesions less than one centimeter in diameter and with pure ground-glass opacity appearance, as in the case of AAH and adenocarcinoma *in situ*, analysis by PET / CT is of limited usefulness. As these are noninvasive lesions with a low metabolism, in most cases the study yields negative results (false negatives close to 100%). The study would not be useful for the evaluation of distant metastatic disease, as the risk of spread is almost null ⁽¹²⁾.

Instead, in the case of suspected invasive or minimally invasive adenocarcinoma, the invasive component of these nodules increases the likelihood of demonstrating increased uptake by the lesion. Furthermore, these cases usually require surgical management, therefore a better characterization, as well as preoperative staging, warrants the use of PET / CT, especially considering the higher risk of metastasis in this group.

For solid lesions larger than one centimeter in diameter, PET / CT has a sensitivity and specificity of 96% and 88%, respectively ⁽⁴⁾.

Algorithm for the management of SSPNs proposed by the Fleischner Society

In 2005 the Fleischner Society published guidelines for the management of solid pulmonary nodules incidentally detected on CT. A new article has been

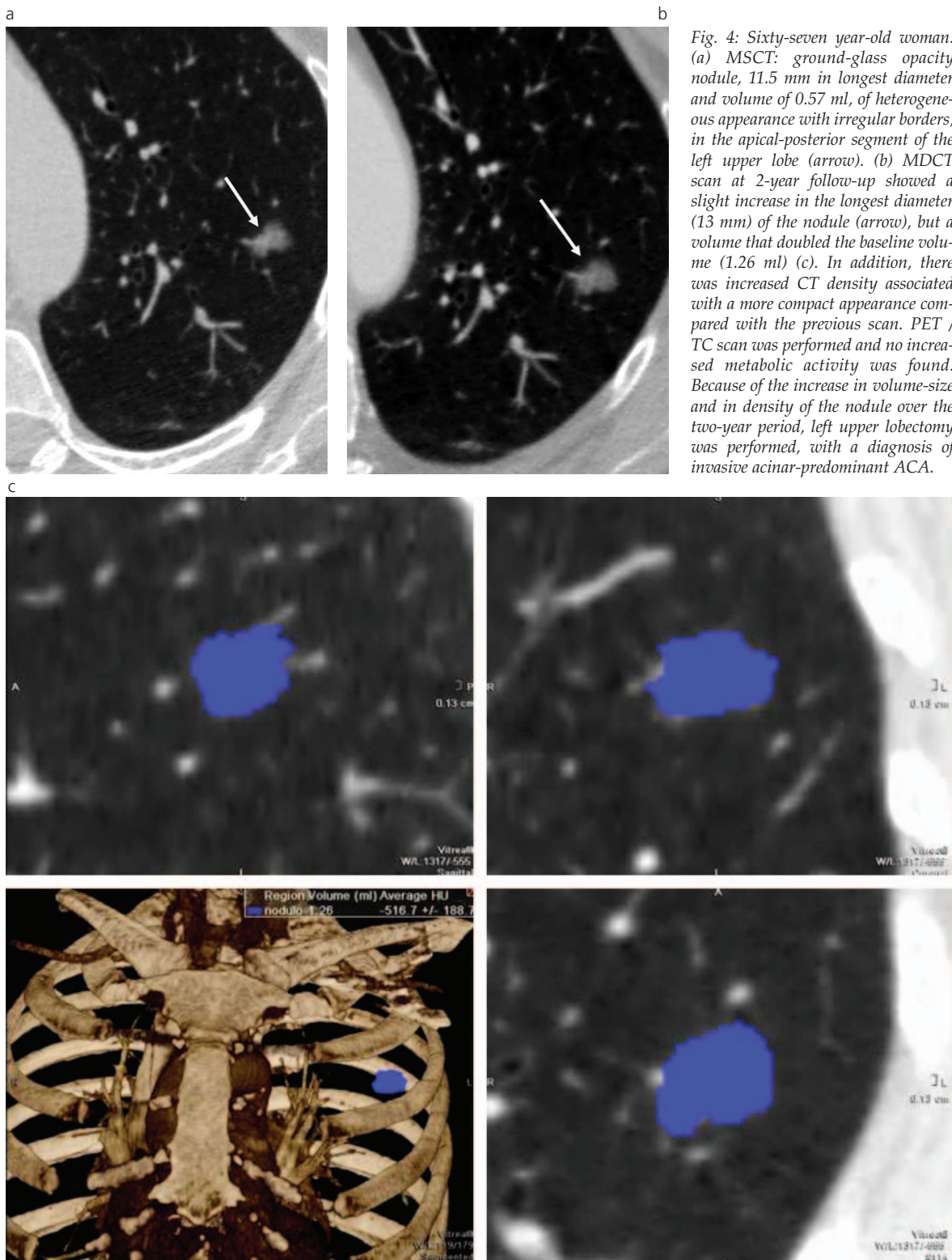


Fig. 4: Sixty-seven year-old woman. (a) MSCT: ground-glass opacity nodule, 11.5 mm in longest diameter and volume of 0.57 ml, of heterogeneous appearance with irregular borders, in the apical-posterior segment of the left upper lobe (arrow). (b) MDCT scan at 2-year follow-up showed a slight increase in the longest diameter (13 mm) of the nodule (arrow), but a volume that doubled the baseline volume (1.26 ml) (c). In addition, there was increased CT density associated with a more compact appearance compared with the previous scan. PET / TC scan was performed and no increased metabolic activity was found. Because of the increase in volume-size and in density of the nodule over the two-year period, left upper lobectomy was performed, with a diagnosis of invasive acinar-predominant ACA.

recently published by the Fleischner Society with recommendations for the management of subsolid pulmonary nodules ⁽¹¹⁾.

This new article includes guidelines for the management of solitary (algorithm 1) and multiple (algo-

rithm 2) SSPNs. Furthermore, it emphasizes that, despite the general guidelines for each type of nodule, each case should always be evaluated individually, considering the clinical and epidemiological history ⁽¹¹⁾.

CASE REPORTS

Focus of atypical adenomatous hyperplasia

A 31-year-old woman (Fig. 5) with a history of left lung adenocarcinoma resection underwent a follow-up CT scan.

Adenocarcinoma *in situ*

A 72-year-old man with a long smoking history underwent a screening CT scan (Fig. 6). Diagnosis was ACA *in situ* and there was complete correlation between MSCT imaging (showing a nodule of pure-

ground glass opacity appearance and lobulated borders) and pathologic findings (reporting a non-invasive lesion with lepidic growth pattern).

Minimally invasive adenocarcinoma

Incidental finding on a CT scan performed in a 68-year-old woman who presented with abdominal pain (Fig. 7).

Papillary-predominant invasive adenocarcinoma

A 35-year-old asymptomatic female smoker underwent a MSCT of the chest (Fig. 8).

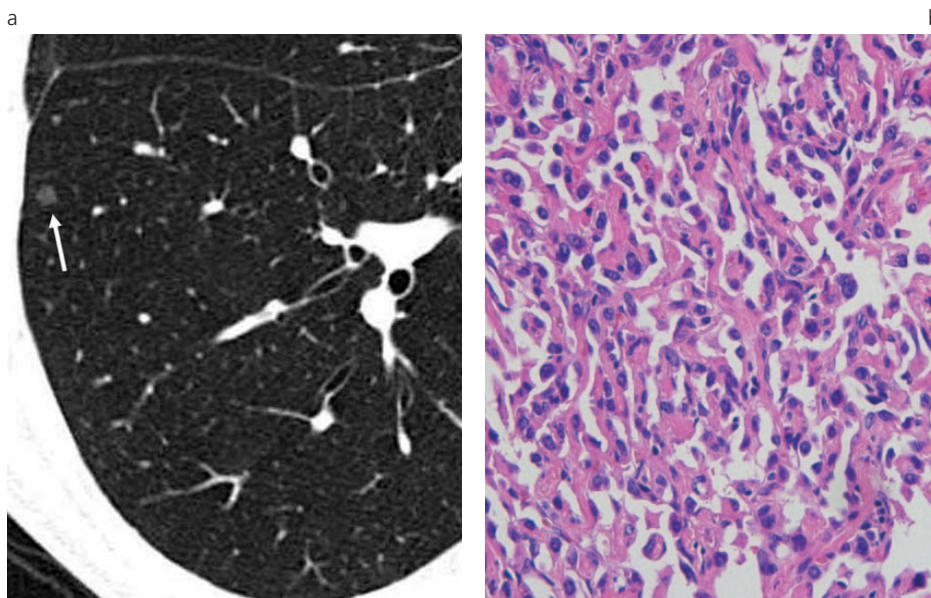
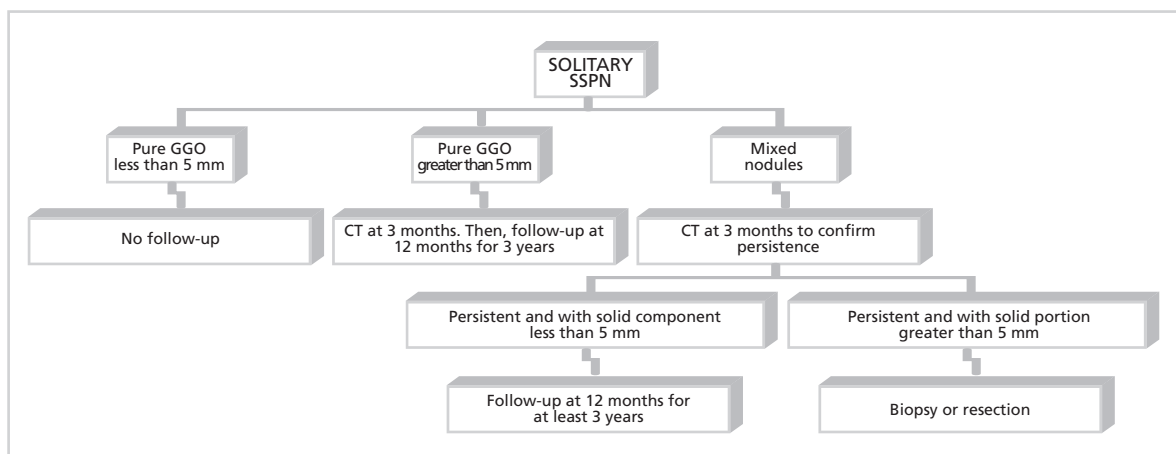


Fig. 5: (a) CT at the level of the right lower lobe shows a small SSPN of pure ground-glass opacity appearance and 4 mm in diameter (arrow). (b) Pathologic specimen (hematoxylin-eosin stain, 200x) shows slight thickening of the septa with fibrous tissue and alveolar lining epithelium with increased nuclear size without atypia.

It was diagnosed as a focus of atypical adenomatous hyperplasia (AAH). CT imaging is characteristic of this type of lesion (pure ground-glass opacity nodule less than 5 mm in diameter). It is consistent with a higher risk of AAH because of a previous history of ACA. What differentiates this lesion from ACA *in situ* is size (less than 5 mm in diameter), because the growth pattern is the same (lepidic).

Algorithm 1



Algorithm 2

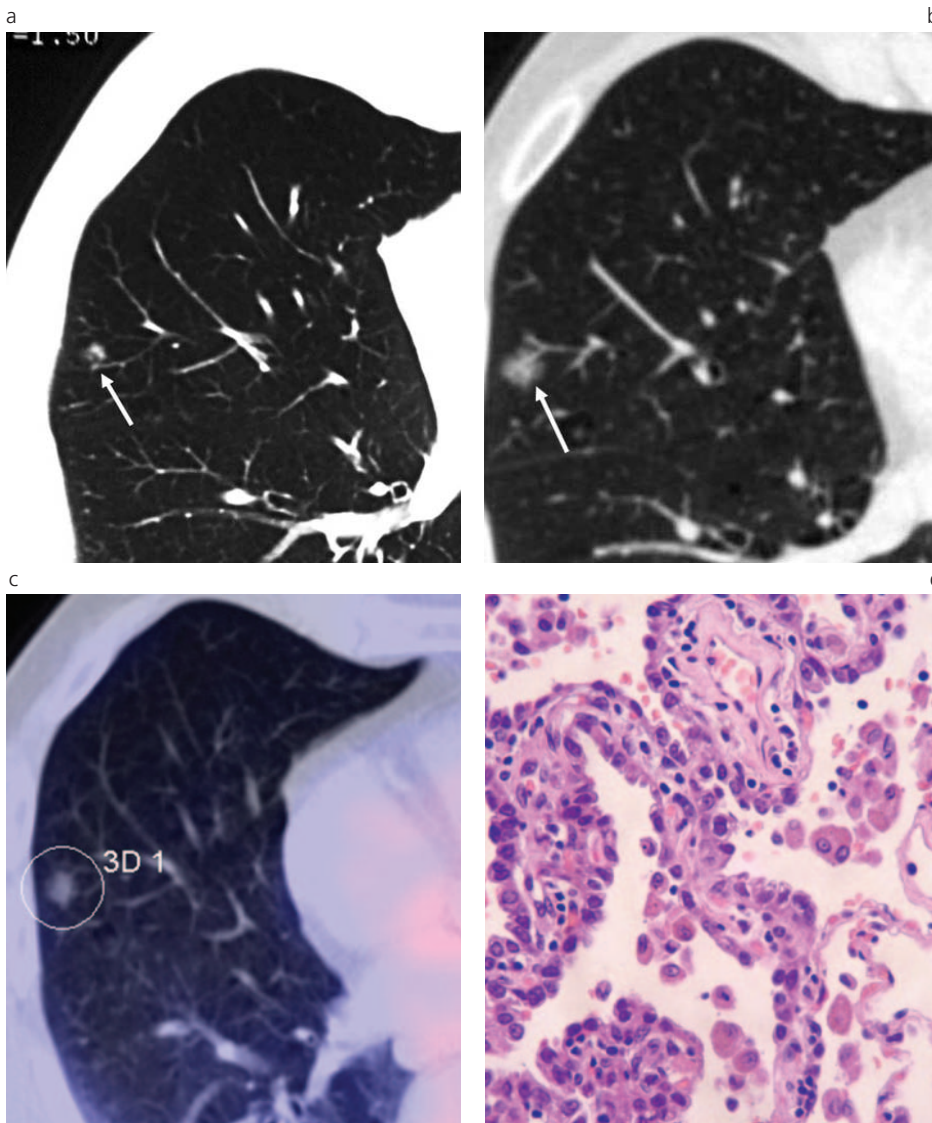
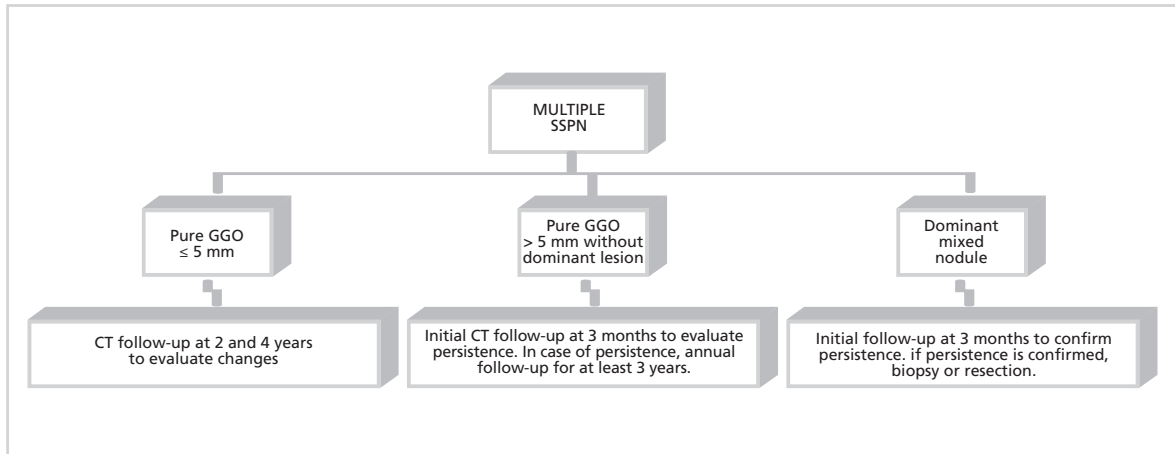


Fig. 6: (a) Screening CT showing an ill-defined SSPN (arrow), located in the lateral segment of the middle lobe of the right lung. Then (b) the follow-up CT analyzes the same nodule (arrow) of lobulated margins and pure ground-glass opacity appearance, showing an underlying vascular structure and an increase in size and density as compared to the scan performed two years earlier. (c) The lesion does not show increased FDG uptake in the PET / TC scan, indicating low metabolic activity. (d) Pathologic specimen (hematoxylin-eosin, 400x) shows tumor growth, lining irregular alveolar spaces and thickened septa in areas with mild mononuclear infiltrate. The tumor margin shows alveoli lined by tumor cells that continue with lining of flattened normal appearance.

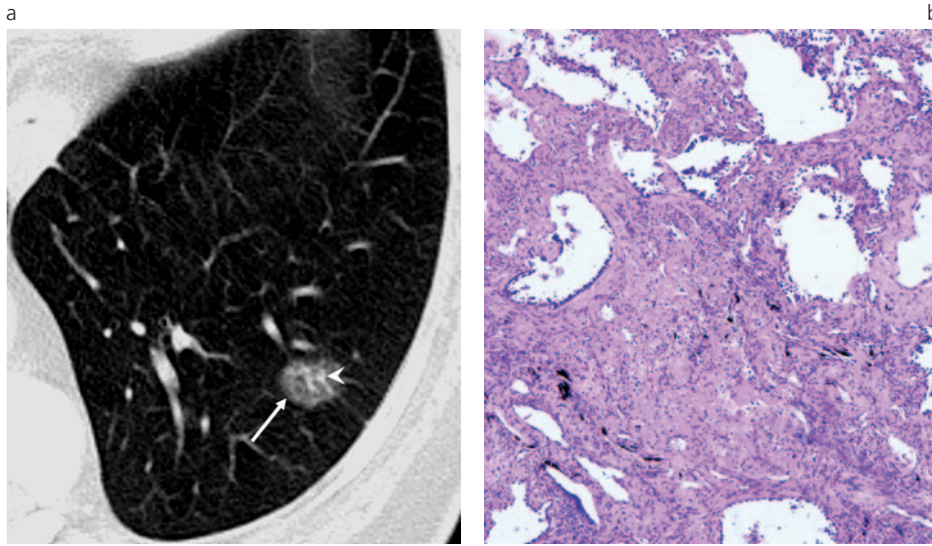


Fig. 7: (a) MSCT shows a SSPN in the left lower lobe, of ground-glass opacity appearance (arrow) with a minimum internal solid component (arrowhead). The lesion is 15 mm in diameter and has ill-defined borders. On PET /TC scan, the lesion did not show increased metabolic activity. Diagnosis was minimally invasive ACA. (b) Pathologic specimen (hematoxylin-eosin, 40x) shows the central area of the tumor with areas of fibrosis, alveolar collapse and greater cellular atypia as compared to the invasive component, represented on MSCT by more dense solid portions.

fibrosis, alveolar collapse and greater cellular atypia as compared to the invasive component, represented on MSCT by more dense solid portions.

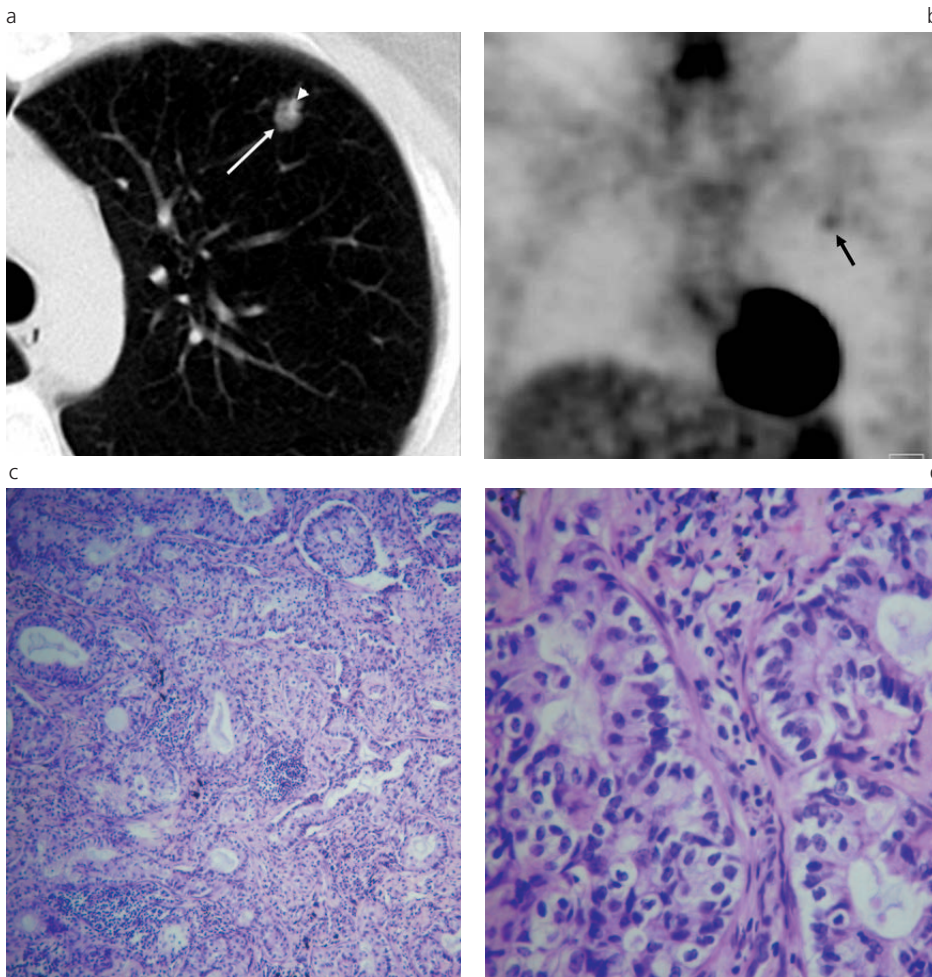


Fig. 8: (a) Chest MDCT showing a SSPN in the anterior segment of the left upper lobe. The lesion is 9 mm in diameter, with lobulated borders and ground-glass appearance (arrow) with a denser solid component, eccentrically located (arrowhead). (b) PET /CT imaging shows the increased uptake of the lesion (arrow). Pathologic specimens (c) (hematoxylin-eosin, 40 x) and (d) (hematoxylin-eosin, 100 x) show irregular tumoral glandular structures and papillae of variable size, lined by cells with hyperchromatic nuclei and clear cytoplasm. Final diagnosis was papillary-predominant invasive ACA.



Fig. 9: Invasive pulmonary aspergillosis. MSCT coronal slice at the level of the right upper lobe. Febrile patient with neutropenia has a focus of increased attenuation, of central solid appearance (arrow), surrounded by a ground-glass peripheral halo (arrowhead), showing the so-called "halo sign".

Differential diagnoses

The presence of a nodule with ground-glass opacity appearance, whether pure or with a solid component, forces us to perform a differential diagnosis with various entities. As we have mentioned, up to 40% of these nodules may represent some form of adenocarcinoma⁽¹⁴⁾, while others have their origin in benign conditions and rarely represent pulmonary metastasis⁽⁴⁾.

Focal interstitial fibrosis is one of the main benign entities that is manifested as persistent nodular ground-glass opacity, with little or no changes. Thus, differentiation from a malignant tumor is difficult. There may be or not a solid component, and the maximal diameter is often not longer than 2 cm. The absence of pleural indentation or spiculation is an indicator of benignancy⁽²⁾.

Infectious conditions include pulmonary aspergillosis, which, in immunocompromised patients is manifested invasively as a soft tissue-density nodular

lesion, with surrounding ground-glass opacity, called "halo sign" (Fig. 9). Even if this sign is not specific to aspergillosis, it is present at the onset of disease in over 90% of cases and represents alveolar hemorrhage related to infarction⁽²⁾.

Eosinophilic pneumonia is an idiopathic condition that presents with months of fever, cough and dyspnea. It may occur as a primary disease or in association with other conditions, including, but not limited to, sarcoidosis, parasitic infection and vasculitis. CT imaging shows ground-glass opacities that represent a predominantly eosinophilic intraalveolar inflammatory infiltration. The lesion occasionally has a central solid component corresponding to a small abscess^(2,17).

Bronchiolitis obliterans with or without organizing pneumonia (BOOP) may be primary (called cryptogenic organizing pneumonia, COP) or secondary to infections, autoimmune diseases or drugs. CT findings include the presence of bilateral ground-glass opacity or consolidation with a peripheral and peribronchial distribution. In some cases, there is central nodular ground-glass opacity surrounded by tissue with higher attenuation, known as "reverse halo sign". Even if this sign is an indicator of this disease, it may also be found in other conditions, such as fungal infection^(2,17).

CONCLUSION

Subsolid pulmonary nodules may correspond to adenocarcinoma of the lung, but they have a good prognosis in noninvasive or minimally invasive lesions. Their appropriate characterization by MSCT within the clinical and epidemiological context of the patient allows for a presumptive diagnosis, playing a significant role in decisions on therapeutic management and follow-up procedures for each individual case.

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The authors declare no conflicts of interests.