Multiple non-metastatic pulmonary nodules: additional CT findings that may provide the differential diagnosis

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Learning objectives

Multiple pulmonary nodules is a finding that is often difficult to interpret, challenging even for experienced professionals. Although the main hypothesis in this setting is metastatic disease, different etiologies may lead to similar findings. Thus the objectives of this paper are to:

- Define the concept of pulmonary nodules

- Present the Chest X-Ray (CXR) findings of skin lesions that mimic lung nodules

- Present non-neoplastic pathologies that are associated with multiple pulmonary nodules.

- Present some nodular pathologies, and specific findings, that may aid radiologists in establishing the differential diagnosis between these.

Background

Multiple pulmonary nodules is a finding that is often difficult to interpret, challenging even for experienced professionals. Although the main hypothesis in this setting is metastatic disease, different etiologies may lead to similar findings. Thus, the knowledge of the imaging singularities of the different nodular pathologies, can assist the radiologist in establishing a correct diagnosis.

To research this scenario, we selected twelve patients referred to the department of radiology and diagnostic imaging for investigation of multiple pulmonary nodules, identified on CT or CRX, which already had metastatic disease ruled out (after clinical correlation, imaging and biopsy). The patients were divided into three groups according to radiological findings: (1) cutaneous lesions simulating pulmonary nodules (2) nodules without cavitation (3) cavitated nodules.

1. Concept of pulmonary nodule

The glossary of terms for Chest CT, following the recommendations of the Fleischner Society of Radiology naming Committee is; (1) nodule is defined as a well defined circular opacity measuring between 2 - 30mm in diameter. This recommendation will be used in this paper.

2. Skin lesions simulating pulmonary nodules

2.1- Lesions of the ribs
Fracture of ribs with formation of a bony callus (Figs. 1 and 2), metastases to the ribs (Figs. 3 and 4) and osteochondromas (Figs. 5 and 6). These are some of the lesions found on the thoracic and bone structure that can simulate nodules in the lung parenchyma.

Image features:

The role of computed tomography is to demonstrate that the lesions observed in the projection of the lung fields on the CXR, is actually on the chest wall.

2.2 - Neurofibromatosis nodules (Fig. 7 and 8)

They are lesions of the peripheral nerves. Affect patients between 20 and 30 years, with no sex predilection. Sixty to ninety percent of these patients are diagnosed with type I neurofibromarose (2)

Such lesions can develop in the intercostal nerves and on roots of the spinal nerves. Thus can be projected in lung field

Imaging features:

Enlargement of the neural foramina and compressive bone erosions are seen on imaging studies. The lesions are hypodense on CT, with heterogeneous enhancement after contrast (2). CT shows the topography of the lesion demonstrating its distribution along the path of the nerve and the bone changes associated with it.

3. Cavitated nodules

3.1 Wegener's Granulomatosis (Fig. 9 to 12)

The first cases of Wegener's granulomatosis (WG) were reported in 1931 by Klinger (3). It is believed that WG is an autoimmune vasculitis characterized by the triad of: upper respiratory tract granulomatosis, pulmonary angiitis and glomerulonephritis. These findings are manifested as purulent rhinorrhea, hematuria and respiratory disorders. In 90% of cases it is associated with nodules and/or lung masses. (2)

Imaging features:

Radiologically presents as multiple nodules and/or lung masses, usually bilateral and located mainly in the peripheral regions of the middle and lower lung fields. May have different sizes (up to 8 cm) and in 50% of cases there is cavitation resulting from central necrosis (Figs. 11 and 12). Computed tomography can demonstrate other findings that may aid the diagnosis, such as scattered areas of consolidation, which may be peribronchial, focal peripheric or pleural based. Diffuse distribution occurs in about 10%, generally reflecting the presence of alveolar hemorrhage (Figs. 13 and 14) (3).

3.2 Rheumatoid Arthritis (Fig. 13 and 14)
Rheumatoid arthritis is a systemic disease that manifests as a common inflammatory arthritis of multiple joints and produces a large variety of intrathoracic lesions. Yousem et al (4) described a wide range of histopathology in the lungs of patients with rheumatoid arthritis. These findings include rheumatoid nodules, usual interstitial pneumonia, organizing pneumonia, lymphoid hyperplasia and nonspecific interstitial pneumonia.

**Imaging features**

Associated with clinical findings of inflammatory arthritis in multiple joints, CT demonstrates important information. Nobuyuki Tanaka, Jeung Sook Kim et al. (5) observed that ground-glass opacities and reticulation (98%) were the most frequent findings. Honeycombing (60%), traction bronchiectasis (75%), and architectural distortion (62%) were also frequent. Nodules were observed in 31 (49%) patients. Four predominant interstitial patterns of TC were identified: usual interstitial pneumonia (26 patients), nonspecific interstitial pneumonia (19 patients), bronchiolitis (11 patients), and organizing pneumonia (five patients). In two other patients, the images showed: diffuse alveolar damage and lymphoid interstitial pneumonia. Increased pulmonary artery diameter was observed in 26 (46%) of 57 patients in which the diameter of the pulmonary artery was measured.

Rheumatoid nodules manifest as circumscribed opacities, generally multiple, subpleural, that measure between 0.5 and 7 mm in diameter. These lesions tend to appear and disappear along with the sub-cutaneous nodules. Cavitation is common and may be complicated by pneumothorax, bronchopleural fistula and hydropneumothorax.

3.3 Tuberculose

Tuberculosis is a chronic granulomatous infectious disease (caused by the bacillus Mycobacterium tuberculosis or occasionally by the Mycobacterium bovis), which is characterized by impaired cell-mediated immunity. It can affect almost any organ, but the lung is most frequente location (2). It can be classified into primary and post-primary.

The primary tuberculosis is of variable severity and difficult to diagnose. In our country it is more common in children and has an insidious character, and may have nonspecific clinical manifestations, including malaise, irritability, loss of appetite and weight loss. The fever is usually moderate and in the evening, and may persist for several days or weeks. Symptoms most common are respiratory cough and dyspnea possibly due to tracheobronchial obstruction, caused by mediastinal lymphadenopathy.

The post-primary tuberculosis has a great spectrum of presentations, and they relate to the organ involved. In the pulmonary form, the patients have presente with a insidious clinical picture, sometimes with no complaints valued and a duration of symptoms before the diagnosis, of one to three months, in most cases. The constitutional findings are observed in about 70% of cases, the most common being represented by loss of appetite, low fever and afternoon, night sweats and weight loss.
The most common respiratory manifestation is dry cough, that later becomes productive with yellowish or bright sputum. Spitting blood and hemoptysis occurs in less than a quarter of the patients, and may in some cases be the consequence of a ruptured Rasmussen Aneurysm. Pleuritic chest pain is occasionally referred.

Imaging features:

The most common patterns found in primary tuberculosis are; parenchymal opacities, lymphadenopathy, atelectasis, diffuse miliary disease (miliary pattern), and pleural effusion.

In secondary tuberculosis distinct patterns may also be observed, including some that feature pulmonary nodules:

The most common findings are focal opacities or heterogeneous consolidations that predominate in the apical and posterior segments of the upper lobes (Fig. 15 and 16) as well as superior segments of the lower lobes. Such opacities may be bilateral in up to two thirds of the cases, have an average size between 2 and 3 cm in diameter and may often be associated with cavities (2).

Such parenchymal opacities may present as nodular (about 5%). These opacities may occur in different forms:

- Well defined solid nodules (Fig. 17).
- Cavitated nodules with or without fungus ball inside (Fig. 18 and 19).
- Spiculated opacities with retraction of the adjacent parenchyma (Fig. 20).

Other common findings are; the Tree in Bud pattern, and fibrosis with architectural distortion predominanting in the apices (Fig. 21). Spondylodiscitis (Fig. 22 and 23) might also be observed in some cases.

Thus the combination of findings of multiple nodules, some being cavitated (with or without fungus ball), associated with tree in Bud pattern, architectural distortion, predominantly in apices helps to establish the diagnosis of tuberculosis. Thoraco-lumbar spondylodiscitis is also sometimes associated.

Other tuberculosis patterns, that don’t form nodules may also be seen, such as the pneumonic pattern and miliary pattern (which develops because of hematogenous spread of bacilli and may occur many years after the infection), being characterized in the standard radiography by micronodules, diffuse and randomly distributed.

3.4 - Septic Embolism

Septic pulmonary embolism occurs when fragments of thrombus infected by microorganisms reach and clog the pulmonary vasculature (2). Risk factors include
intravenous drug use, presence of intravascular catheter, widespread infection in immunodeficient patients, congenital heart disease, septic thrombophlebitis, and supplicative processes of the head and neck. The majority of emboli originate in the heart, usually in association with tricuspid valve endocarditis, or peripheral veins. The bacteria most frequently isolated in blood cultures is Staphylococcus aureus, with Streptococcus pneumoniae and Klebsiella being less common causes (2).

The diagnosis of septic embolism is based on radiological findings and positive blood culture.

Imaging features:

Scattered nodules (Fig. 24 and 25), usually between 0.5 and 3 cm diameter, in various stages of cavitation, presenting well or ill-defined contours. Such lesions are more numerous in the peripheral regions of the lower lobes. One can see some areas of consolidation, generally cuneiform, often subpleural and central regions of heterogeneous attenuation or cavitation, with or without peripheral enhancement after administration of the contrast IV (2). Unilateral or bilateral pleural effusion, with or without pleural thickening and enhancement (empyema) and associated with hilar or mediastinal lymphadenopathy, are commonly observed. In rare situations intracardiac vegetations are observed (Fig. 26).

3.5 - Laringotraqueo Bronchial Papillomatosis (Fig. 28 e 29)

Laryngeal papillomatosis is an uncommon lesion, usually seen in children between 18 months and 3 years of age, caused by the human papilloma virus (HPV, the human papilloma virus english). Occasionally it can result in an impairment of trachea, bronchus and lung parenchyma (laryngotracheobronchial papillomatosis). The mean delay of the disease between the appearance of lesions in the larynx and the detection of bronchopulmonary disease is 10 years. In childhood, the symptom usually consists of hoarseness, progressing to stridor. Findings in the adult include; previous history of laryngeal papillomas, cough, hemoptysis, and recurrent pneumonia.

Imaging Features:

CT scan may show small nodules that project into the airway lumen or multifocal nodular thickening of the trachea and/or bronchi (2). Nodules can cause bronchial obstruction that produces atelectasis, obstructive pneumonitis and bronchiectasis.

The parenchyma can also be affected by the presence of circumscribed nodules, generally 1 to 3 cm in diameter, they often cavitate and present with walls that have 2 to 3 mm in thickness (2). The nodules tend to be located in the perihilar lung parenchyma. The nodules and cavities may represent papillomas or squamous cell carcinomas.

4. - Non-cavitated nodules
4.1 - Histoplasmosis (Fig. 30 a 32)

Histoplasmosis is an endemic mycosis caused by the fungus Histoplasma capsulatum. Infection occurs through inhalation of the fungus, commonly found in caves inhabited by bats, or soil inhabited by birds. In AIDS (Acquired immunodeficiency syndrome) patients, histoplasmosis manifest as an opportunistic disseminated disease, affecting approximately 2%, occurring in patients with a CD4 + lymphocyte count <100 cells/mm3 in over 80% of cases (2).

While it may be asymptomatic in immunocompetent persons in the immunocompromised this disease is usually severe, and often has a acute fatal outcome. Patients present with high fever, malaise, anorexia, mucosal and cutaneous lesions, lymphadenopathy and hepatosplenomegaly. Neurological and gastrointestinal symptoms may also be present.

Imaging features:

Up to 40% of the patients may have normal imaging studies of the chest. Among the imaging findings that may be found are; nodules, miliary nodules (most common manifestation of the disease in the immunocompromised population), consolidation (seen in up to 15% with lobar or segmental distribution), pleural effusion (10%), lymphadenopathy (<5%) (2).

Thus, patients that present with pulmonary nodules, which follow a lobar or segmental distribution, that have associated lymphonodomegaly, and present a significant epidemiology (history of exposure to birds or bats) have a high probability of histoplasmosis.

4.2 - Pulmonary Leiomyomatosis (Fig. 33 e 34)

Leiomyomatosis is a rare, benign disease, characterized by leiomiomatous extraterine lesions without cytological or histological signs of malignancy. Fewer than 200 cases have been reported so far. The pathogenesis is not well defined. It is speculated that it can be due to primary pulmonary leiomyomatosis, or even a condition secondary to uterine leiomyomas that colonize the lungs (6).

Most reported cases presents asymptomatic pulmonary nodules and a history of hysterectomy for treatment of uterine leiomyomas. Usually the lung lesions are small and peripheral, and do not cause any symptoms, but large or central tumors may cause dyspnea, chest pain, dry cough, bronchiectasis or obstructive pneumonitis. Generally, the disease has a good prognosis.

Imaging features:

Imaging tests show multiple noncalcified pulmonary nodules, bilaterally distributed, with well-defined borders that may have a few millimeters to several centimeters in diameter
(6). An important feature is that, in general, there is no enhancement by iodinated contrast media.

On chest radiographs, the lesion is indistinguishable from a metastasis. Thus, confirmation should be made by means of histopathology performed on samples of a needle biopsy.

4.3 - Pulmonary Langerhans Cell Histiocytosis (Fig. 35 e 36)

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon disease of unknown etiology, that occurs predominantly in young adults, with a peak incidence between 20 and 40 years. The PLCH has a high relationship with smoking, with 90% to 100% of patients being smokers. PLCH patients are at increased risk for malignancy, especially lymphoma and bronchogenic carcinoma. The incidence of lung cancer in patients with PLCH is 5% to 14%.

The patients with PLCH may be asymptomatic in 10% to 25% of cases. When symptoms are present, they may be systemic or pulmonar. Systemic symptoms may be the only clinical manifestation in up to one third of patients, including fever, fatigue and weight loss. The pulmonary symptoms are the most common and classically include dyspnea and dry cough. Chest pain may be present, associated with episodes of pneumothorax and, rarely, hemoptyysis might occur.

Imaging Features:

The image features depend on the stage of the disease. The initial pattern are small cystic lesions, associated with centrilobular nodules. The cysts have dimensions ranging from millimeters to centimeters and may have rounded, oval or bizarre forms (for example, bilobed and branched forms, such as clover-shaped), reflecting their etiology which is related to the distended airway lumen, associated with areas of coalescence and emphysema paracatricial. Nodules usually measure up to 5 mm, although bigger nodules may occur in up to 30% of cases, which measure up to 1 cm and rarely up to 2 cm. These nodules are dense, have well-defined margins and initially have regular borders or slightly irregular, without associated calcifications, but these can progressively evolve with hypoattenuating areas and small cavities inside. The cavitation may disappear or develop into thick-walled cavities or thin. In rare cases, we observed the initial presence of nodules without associated cysts as seen in Figure 36.

Pneumothorax can coexist with other findings and is easily characterized by CT.

In advanced stages, fibrosis, characterized by irregular linear opacities and reticular pattern, is also a form of presentation. This fibrosis is usually most evident in the apices, but may progress to involve the entire lung. Usually the lung bases are spared.

The temporal progression of the disease is highly variable, there are cases with spontaneous remission and cases which are rapidly progressive. Nodules usually
characterize lesions with greater reversibility, while older lesions are cysts and are less reversible. Rare forms of presentation, such as consolidations, lymphadenopathy, solitary nodules and lesions of the central airways, have been described in the literature.

Pulmonary hypertension, with increased caliber of the pulmonary arteries, may be a secondary complication of PLCH.

4.4 - Hyperplasia of neuroendocrine cells

The pulmonary neuroendocrine cells are widely distributed within the airway's mucosa and plays a multifunctional role in lung homeostasis, because they produce serotonin and a variety of neuropeptides. Recent studies suggest an important role for these cells during lung development, in the sensitivity to oxygen, and in the regeneration of distal lung epithelium.

The focal hyperplasia (located) in neuroendocrine cells can be observed in association with various lung diseases such as COPD, lung abscess, and cystic fibrosis bronchiectasis.

Differently, diffuse neuroendocrine cell hyperplasia of the lung is a rare disease. In their study Davies, SJ et al (9) showed that, to date, 66 cases have been published.

Patients present with tachydyspnea, hypoxemia and persistent respiratory crackles with good performance in five years. The pathologic evaluation of lung tissue by surgical biopsy is the gold standard for diagnosis of diffuse neuroendocrine cell hyperplasia of the lung.

Imaging features:

Due to its histological characteristic of linear or multifocal proliferation, nodules are the most common findings (Fig. 37), associated to areas of air trapping. Areas with Mosaic attenuation, associated with nodules, are the typical findings in high resolution computed tomography (Fig. 38) (7).

**Images for this section:**
Fig. 1: Fig 1 and 2: Fracture of the ribs with bone callus formation jutting in the lung fields. Computed tomography note that injuries are bone.
**Fig. 2:** Fig 1 and 2: Fracture of the ribs with bone callus formation jutting in the lung fields. Computed tomography note that injuries are bone.
**Fig. 3**

![Image of a medical scan showing a rib injury on the right side.]

**Fig. 4:** Rib injury right
Fig. 5
Fig. 7: Figure 7 and 8. Protruding lump in the lung fields in patients with neurofibroma in the intercostal nerves. In figure 7 can be seen protruding lesions in soft tissues of the left hemithorax.
Fig. 8: Figure 7 and 8. Protruding lump in the lung fields in patients with neurofibroma in the intercostal nerves. In figure 7 can be seen protruding lesions in soft tissues of the left hemithorax.
Fig. 9: Figure 9 and 10: patient with clinical hematuria and hemoptysis
Fig. 10: Figure 9 and 10: patient with clinical hematuria and hemoptysis
**Fig. 11:** Figure 11 and 12: consolidation areas with halo sign corresponding to alveolar hemorrhage
**Fig. 12:** Figure 11 and 12: consolidation areas with halo sign corresponding to alveolar hemorrhage
Fig. 13: Figure 13 and 14: a patient with rheumatoid arthritis presenting with pulmonary cavitations chest CT
**Fig. 14:** Figure 13 and 14: a patient with rheumatoid arthritis presenting with pulmonary cavitations chest CT
Fig. 15: Figure 15: focal opacities, consolidations and architectural distortion
Fig. 16: Figure 16: pulmonary nodules
Fig. 17
Fig. 18: Figure 18: pulmonary nodules
Fig. 19: Figure 19: cavitary nodules
Fig. 22: Figure 22 and 23: spondylodiscitis transition thoracolumbar
Fig. 23: Figure 22 and 23: spondylodiscitis transition thoracolumbar
**Fig. 27:** Figure 29: pulmonary nodules
Fig. 35
Imaging findings OR Procedure details

The images were obtained with CT scan 16 channels. The protocol included acquisitions in the axial and coronal planes after infusion of iodinated contrast media.

Conclusion

Computed tomography helps the development of differential diagnoses mainly provide additional information not noted in radiography.

References


Personal Information