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REVIEW ARTICLE

Patient management with a solitary pulmonary nodule

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Summary

Solitary pulmonary nodules are a common problem presented to the chest physicians. In our era, with the integration of new technologies, an increasing number of smaller-sized solitary pulmonary nodules are being detected. The primary objective in evaluating a solitary pulmonary nodule is prompt identification and treatment of early-stage lung cancer. A secondary objective is the avoidance of surgical morbidity in the diagnosis of a benign lung lesion.

Key words: coin lesion, diagnosis, early detection of lung cancer, management, solitary pulmonary nodule, treatment

Introduction

A solitary pulmonary nodule is a single, usually sharply defined spherical lesion that is fairly well circumscribed. There are approximately 150,000 of these nodules detected every year in the US, and about 40-50% of the resected lesions will be malignant. With improvements in the technology of CT scanning, it is likely that more and more nodules will be detected, but unfortunately, they will be more difficult to diagnose because of their smaller size [1].

As stated by Spratt [2], the correct management of solitary pulmonary nodules often remains elusive despite the multiplicity of diagnostic tests available. At the one end of the spectrum, there are people who think that all nodules should be excised, therefore subjecting patients with benign lesions to unnecessary operations. At the other end of the spectrum are those who think that only patients with tissue-proven malignant neoplasm should undergo surgery. In this group, obviously, many malignant lesions will be allowed to grow and spread whereas a curative resection could have been performed earlier [3-5].

Short of subjecting every patient with a solitary pulmonary nodule to thoracotomy, no 100% reliable tests for the definitive diagnosis of these abnormalities exist. It is thus important to have a clear understanding of all possible causes of solitary pulmonary nodules. It is also important to have complete knowledge of the diagnostic methods available, beginning with the least invasive, such as accurate recording of clinical history. It is finally important to have a safe, cost-effective, and cohesive investigative approach so that either positive diagnosis is reached or there is a strong likelihood that the nodule is benign [6,7].

Definition and incidence

Although there are many definitions of solitary pulmonary nodules (Table 1) most agree that these are well-defined lung opacities that measure less than 4-5 cm in diameter. They may have smooth lobulated, or umbilicated contours and any shape. They are completely surrounded on all sides by aerated lung, and they are not connected with the mediastinum or pleura. They are not associated with atelectasis or adenopathies. They may contain calcifications or be cavitary, but these characteristics are not necessarily obvious on a standard chest radiograph [5-7].

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Table 1. The solitary pulmonary nodule

Must be 4-5 cm or less in diameter
Must be solitary
Must be in lung parenchyma and surrounded by aerated lung
May have any contour or shape
No obvious calcification on standard chest radiograph

Most solitary pulmonary nodules are asymptomatic; they are usually picked up incidentally on chest radiography. Radiographic surveys of adults have demonstrated nodules in 0.1-0.2% of the population; but in high-risk patients recently screened for lung cancer by low-dose spiral CT, pulmonary nodules have been found in up to 20% of individuals [4,6].

Etiology of pulmonary nodules (Table 2)

Among malignant lesions, primary bronchogenic carcinoma is the most common entity. Breakdown by cell type shows that tumors often presenting in the form of solitary pulmonary nodule are adenocarcinomas including bronchioloalveolar cell carcinomas. Pulmonary metastases from extrathoracic tumors are also common. On occasion peripheral carcinoids or low-grade lymphomas may also present as solitary nodules [6,8,9].

In virtually every series of solitary pulmonary nodules, granulomas –whether they are tuberculomas or histoplasmomas - account for the bulk of the benign nodules. These granulomatous foci are usually negative for bacteria both in culture and histologically, especially when the nodule is old and partly calcified. Other benign lesions that may present as solitary nodules include hamartomas, bronchogenic cysts, and areas of chronic pneumonitis. Hamartomas are not uncommon; the majority present as well-circumscribed nodules usually less than 4 cm in diameter. "Popcorn" calcifications are virtually diagnostic. Bronchogenic cysts are foregut developmental anomalies that can also assume the appearance of a nodule when distended with mucus. They have a predilection for lower lobe localizations.

Noninfectious granulomatous conditions such as sarcoidosis, rheumatoid arthritis, and Wegener granulomatosis usually present with multiple pulmonary nodules [8-10].

Table 2. Common causes of pulmonary nodules

Malignant
Bronchogenic carcinomas (adenocarcinomas)
Pulmonary metastasis (sarcomas, kidney, colorectal, breast)
Lymphomas
Nonmalignant
Infectious granulomas: tuberculosis, histoplasmosis, coccidioidomycosis
Noninfectious granulomas: sarcoidosis, rheumatoid arthritis, Wegener granulomatosis
Benign lung tumors: hamartomas
Congenital: bronchogenic cyst, arteriovenous malformations
Others: pneumoconiosis, scar tissue, chronic pneumonitis

Assessment of the patient with a solitary pulmonary nodule

The most relevant question posed by the presence of a solitary pulmonary nodule is whether the lesion is malignant or not. This is important because small (<3 cm) solitary primary lung cancers have a better prognosis with surgical resection than larger tumors. Indeed, the 5-year survival rate for T1N0M0 resected lung cancers is 75-80%, whereas it is 55-60% for T2N0M0 tumors [6,10].

The probability that a nodule is malignant relates to clinical factors, such as age of the patient and smoking history, and radiologic characteristics, such as presence or absence of occult calcifications and nature of the contours. Finally, definitive diagnosis is based on histological documentation of the exact nature of the nodule [7-9].

Noninvasive methods

Clinical assessment

The clinical history of a patient with a solitary pulmonary nodule may provide important clues in arriving to the actual diagnosis. Because these clues may be vague, they should not, however, affect subsequent diagnostic procedures.

If the patient, for instance, is younger than 40 years and nonsmoker, the risk of malignancy is less than 1%. By contrast, a solitary pulmonary nodule in a patient with a previous history of malignant disease has a 50% chance of being malignant (Table 3). If the previous malignant neoplasm was a sarcoma or a melanoma, this probability is increased by 10-fold; and if the tumor was from the head and neck region (squamous cell carcinoma), it is increased by 2-fold [8,9].

The presence of symptoms also favors a diagnosis

Table 3. Clinical factors in favor of malignant disease

Age >40 years
History of cigarette smoking for >20-25 years
Previous history of malignant disease
Family history of lung cancer
Presence of local symptoms: cough, hemoptysis
Presence of systemic symptoms: weight loss, osteoarthropathy

of malignancy. Symptoms such as cough and hemoptysis may be due to local encroachment on surrounding intraparenchymal airways by a malignant tumor. Systemic symptoms such as weight loss and pulmonary hypertrophic osteoarthropathy are also significant risk factors for malignancy [7,9].

Clinical factors favoring a nonmalignant diagnosis are present in only a few patients with solitary pulmonary nodules (Table 4). These include previous history of tuberculosis or close contact with individuals known to have active tuberculosis or a history of other nonmalignant disease, such as sarcoidosis, rheumatoid arthritis, or Wegener granulomatosis. Telangiectasis may suggest arteriovenous malformations. Living in regions endemic for histoplasmosis is a risk factor for a granulomatous lesion; immunosuppressed patients may develop solitary mycotic foci [10].

Radiographic assessment

The purpose of the radiographic assessment is to determine which lesion will require further work-up and which lesion can be confidently called benign and therefore not require any additional diagnostic procedure [11].

Is there a lung nodule or not?

The first issue to be addressed when a solitary pulmonary nodule is discovered is whether the nodule is indeed in the lung or originates from an adjacent structure. The differential diagnosis includes lesions from the pleura (benign pleura fibromas), from the subpleural area (lipomas, schwannomas), and from the chest wall. It also includes intrapleural fibrin deposits and localized pleural effusions within lung fissures (pseudotumors). On occasion, mediastinal lesions or diaphragmatic tumors may also be mistaken for solitary pulmonary nodules [12,13].

Comparison with previous films

Radiographic stability provides substantial evidence for the benign origin of a solitary lesion, and the absence of any detectable growth of a nodule for a prolonged time is the single most reliable way of establishing that the nodule is benign. A review of old radiographs can therefore be extremely useful because if there has been no growth for a 2-year period, the nodule is probably benign (average doubling time for a malignant neoplasm is 120 days) [14].

Appearance of the lesion

Although the radiologic appearance of the nodule cannot reliably separate malignant from benign lesions, radiologic "benignancy" can be established with some confidence if specific patterns are identified. For individual cases, however, these patterns offer no absolute guidance as to the etiology of the nodule [11-15].

In general, nodules of benign origin (Table 5) are smaller (<3 cm), have better defined borders, and have a heavier radiologic density. For instance, nodules smaller than 2 cm and dense are usually granulomas. By contrast, malignant nodules are more likely to be larger and have irregular contours, with ill-defined or irregular margins. Umbilication of the border of a solitary pulmonary nodule is usually interpreted as a sign of malignancy (Figure 1).

Calcifications within a pulmonary nodule are best seen on CT scan and generally are a reliable sign that the lesion in benign, especially if specific patterns of calcium deposition are seen. These include a dense central core of calcification, a laminated pattern with

Table 4. Clinical factors in favor of benign lesion

Age < 40 years
Patient is nonsmoker
No previous history of malignant disease
No symptoms
Personal history of rheumatoid arthritis, Wegener granulomatosis
Patient lives in endemic region for histoplasmosis
Patient is immunosuppressed

Table 5. Radiologic features in favor of benign lesion

Stability for 2 years
Size smaller than 3 cm in diameter
Well-defined borders
Heavier density
Specific patterns of calcification

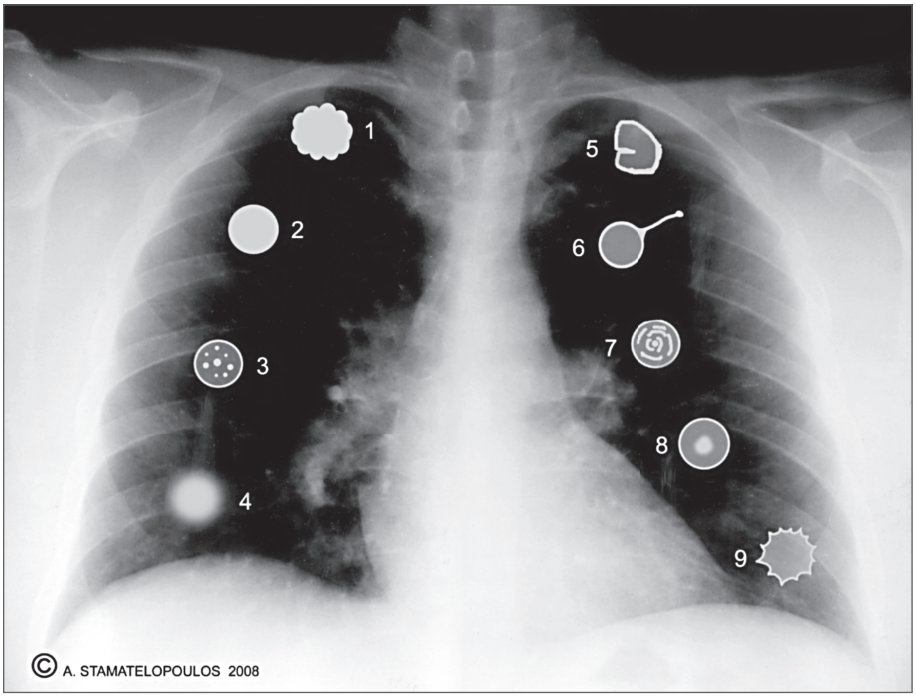

Figure 1. Imaging characteristics of different conditions that may present as solitary pulmonary nodules: 1. Lobulated with well-defined margin in hamartoma; 2. Round and well-defined margin in granuloma; 3. Round with speckled calcifications in hamartoma; 4. Ill-defined margin in pneumonia; 5. Umbilicated at the entrance of a feeding vessel in cancer; 6. Pleural tail in cancer; 7. Concentric calcifications in granuloma; 8. Central calcifications, non specific; 9. Stellate margin in cancer.

calcium in concentric layers (granuloma), and a popcorn type of calcification that is associated with hamartomas. The mere presence of calcifications, however, is inadequate evidence that the lesion is benign because microcalcifications are present in 15-25% of resected carcinomas. These calcifications may occur in necrotic areas of the tumor, or it may be a previous calcific focus that is incorporated by the tumor [11,12].

Growth rate (doubling time)

The use of growth rate is much less reliable when used in a prospective manner than retrospectively (comparison with old films). The doubling time of a lesion can be estimated by comparing two radiographs taken at an interval of 3-4 months, and this measurement can be used to determine if the nodule is benign or malignant. The calculation analyzes doubling of tumor volume rather than doubling of its diameter. It uses the formulation of a sphere, and the results are entered in a tumor volume-time graph [15]. In practice, these measurements are difficult to interpret because the volume of a given tumor may double while its diameter only increases by 25%. In general, the doubling in the volume of a malignant tumor varies from 1 to 18 months (Table 6). If a nodule shows rapid growth in a period of less than 1 month, it is usually infectious; those growing very slowly during a period of several years are often benign [12,15].

Use of CT scan

Computed tomography is the imaging technique of choice to evaluate a solitary nodule not clearly calcified on plain radiography. Because it is 10-20 times more sensitive to density differences than standard radiographs, CT can demonstrate benign calcifications not seen otherwise [13-17].

Table 6. Radiologic features in favor of malignant lesion

Evidence of growth of the lesion within 2 years or less
Volume doubling time of 1-18 months
Size larger than 3 cm in diameter
Irregular contours and margins
Umbilication of border

Nodule densitometry can also be performed, and the determination of Hounsfield numbers [15] depends on the density of the lesion. A high Hounsfield number (>600) is generally a reliable indicator of benign disease, whereas those nodules with numbers 50-150 are viewed to be the most suspicious for malignancy.

CT scan can also identify satellite nodules not seen on conventional radiographs. Unfortunately, satellite lesions can be found in both carcinomas and infectious granulomatous diseases [17,18].

Skin testing

The PPD tuberculin test and fungal serology tests are essentially unreliable because a positive test result only indicates previous exposure rather than actual disease. It does not in any way exclude the possibility of malignancy in the lesion [9,10].

Histological analysis

When clinical and radiologic clues remain vague, histological analysis becomes important.

Sputum cytology and culture

Sputum cytology is not particularly useful in the diagnosis of solitary pulmonary nodules. A diagnostic yield of less than 1% can be expected because the lesion is usually peripheral and does not exfoliate cells into the bronchial tree. Sputum cultures might be more reliable if fungal or acid-fast bacilli are recovered [9,10].

Fiberoptic bronchoscopy and transbronchial biopsy

In solitary pulmonary nodules, the yield of fluoroscopy-guided transbronchial biopsy is in the range of 40-60%, but specific benign diagnoses are established in only 10% of the nodules examined. One advantage of fiberoptic bronchoscopy is that it permits visual inspection of the bronchial tree. Samples are obtained by washing and brushing the affected segment, followed by transbronchial biopsy under biplane, fluoroscopic guidance. Results are dependent on the size of the nodule, its proximity to central airways, and skills of the operator. If the lesion is less than 2 cm in diameter, a specific diagnosis will be obtained in 10% of the cases; if the nodule is 2-4 cm, the technique will be diagnostic in 40-50% of the cases. Fiberoptic bronchoscopy is a safe procedure; significant hemorrhage occurs in less than 1% of the cases and pneumothorax in less than 10% of cases [19,20].

Transthoracic needle biopsy

Transthoracic needle biopsy (fine-needle aspiration) is performed under fluoroscopy of CT guidance. It is a safe procedure, with less than 10% of patients requiring tube drainage because of a pneumothorax.

In malignant lesions, a positive diagnosis can be established in up to 95% of cases, provided the material is handled by experienced pathologists. Limiting factors are the visibility and location of the lesion and the experience of the operator. With CT guidance, however, nodules as small as 7-8 mm in diameter can be safely sampled, with yields of positive diagnosis in the presence of malignancy in the range of 50-60% [21-23].

Specific benign lesions (e.g. granulomas, hamartomas, active infection, infarct) are diagnosed in only 10% of the cases, mostly because they are difficult to penetrate as they tend to be pushed away by the needle. These benign diagnoses are often reported as nonspecific inflammatory changes or fibrosis. A negative biopsy without a specific benign diagnosis therefore provides insufficient evidence of a nonmalignant origin of the nodule, and further diagnostic procedures may be indicated [23].

Invasive methods

By the time the initial investigations are completed, the nodule is either a known malignant neoplasm requiring surgical resection or a nodule in which no malignant cells have been found and no definitive diagnosis has been established. This uncertainly of benign diagnosis is thus the most compelling argument for thoracoscopic excision of these nodules. Video-assisted thoracoscopic surgery (VATS) has a sensitivity and specify of 100%, and it can be done with no mortality and minimal morbidity. In benign lesions it becomes a therapeutic procedure [24-26].

CT scan is used to localize the nodule, and at operation, the nodule is either visualized or palpated. A wedge excision is then carried out including surrounding normal lung parenchyma with endoscopic stapler. Other techniques, such as hook wire localization with CT or fluoroscopic imaging, can be used if the nodule is located away from the pleural surface. If a primary lung cancer is identified, formal thoracotomy and anatomic resection can be carried out [27-30].

Open thoracotomy

Thoracoscopic resection may be difficult for small nodules (<1.5 cm) or for centrally located lesions that

are close to hilar structures and suitable for thoracoscopic wedge excision. In those cases, standard limited thoracotomy is the definitive procedure to establish the diagnosis of the nodule. The mortality is low, but the morbidity is higher than that of thoracoscopy [31].

Overall approach to the diagnosis of a pulmonary nodule

The most appropriate approach for the diagnosis of indeterminate pulmonary nodules is still controversial, although everyone agrees that these nodules should be investigated until a diagnosis is reached or until there is a strong likelihood that the nodule is benign.

An observation-only approach is recommended if the patient is young (<35 years), is a nonsmoker, and has no previous history of malignant disease (Table 7). On chest radiographs, the nodule must have been present and unchanged in size or contours for at least 2 years, and it must be small (<1 cm) or have a benign pattern of calcifications. A definitive diagnosis of benign disease obtained by transthoracic needle biopsy or transbronchial bronchoscopic biopsy is also a criterion that justifies observation. The follow-up of these nodules must include serial CT scans for at least 2 years (every 4-6 months), keeping in mind the possibility that granulomas can undergo malignant changes at any time.

In most other clinical settings, a biopsy must be taken. Basically, two different approaches to obtaining tissue from the lesion exist. The first one is to use noninvasive biopsy techniques such as transthoracic needle biopsy. This approach is justified because technological advances in the field of CT-guided needle aspiration biopsy as well as skills in cytologic interpretation of small specimens have increased the diagnostic yield of the technique to 95% or better in cases of malignant neoplasms. In most cases, transthoracic needle biopsy can be rapidly performed, has low cost and few complications. The real advantage is that both patient and the surgeon know the diagnosis before surgery. That knowledge not only allows better planning of the operative procedure but also avoids relying on intraoperative diagnostic maneuvers before definitive therapy [32].

The second approach is to use invasive biopsy techniques such as thoracoscopy or open thoracotomy without prior transthoracic needle aspiration biopsy. This approach is justified by the fact that transthoracic needle biopsy may have a false-negative rate in the presence of malignancy as high as 5-7%. In addition, there may be significant difficulties in making a specific benign diagnosis. The final and most quoted argument in favor of this approach is that transthoracic needle biopsy adds another diagnostic step in a situation where operation will be warranted anyway. For those surgeons who prefer this approach is that transthoracic needle aspiration biopsy is reserved for patients who are not surgical candidates and those who have unresectable malignant neoplasms and in whom a tissue diagnosis is needed [33].

Table 7. Characteristics of benign nodules

Patient 30-35 years old and nonsmoker
No previous history of malignant disease
Nodule unchanged in size or contours for 2 years or more
Nodule is small (<1 cm)
Benign pattern of calcifications
Definitive diagnosis of benign disease by transthoracic needle biopsy

Approach to the patient with multiple pulmonary nodules

Although most patients with multiple pulmonary nodules have metastatic disease, it is important to obtain histologic confirmation. Alveolar cell carcinoma and multifocal adenocarcinomas are primary lung tumors that may regularly present with multiple nodules. On occasion, noninfectious granulomatous conditions may also present with multiple pulmonary nodules [33].

Conclusion

Because the 5-year survival for malignant solitary pulmonary nodules is high, it is important that these are diagnosed early and resected. On the other hand, thoracotomy and even thoracoscopy carry some morbidity and mortality, and these should be avoided whenever possible for benign lesions. Although multiple techniques can be used to diagnose these nodules, it is still better to resect a benign lesion than to delay the excision of a malignant tumor until there is metastatic spread.

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