Pulmonary Nodule in an Asymptomatic 64-Year-Old Woman

HAROLD STERN, M.D.,a DARRYL CARTER, M.D.,b AND ASIM DIKENGIL, M.D.c

aDepartment of Surgery, bDepartment of Pathology, cDepartment of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut

Received April 25, 1986

The unexpected finding of a pulmonary nodule in an asymptomatic patient is a common clinical event. This paper examines the case of a 64-year-old woman who was discovered to have a small pulmonary nodule on routine examination. Differential diagnosis, modes of examination, and pathological findings are examined.

CLINICAL PATHOLOGICAL CONFERENCE

A 64-year-old woman was admitted to Yale–New Haven Hospital (Y–NHH) because of an abnormal chest X-ray.

History

One week prior to admission, the woman had been scheduled for surgical removal of a bunion at a nearby hospital. Admission chest films showed a 1.5 cm "coin" lesion in the right upper lobe. Surgery was postponed and the patient was admitted to Y–NHH for evaluation. The patient stated that she had been healthy all her life and had no recent complaints. She specifically denied cough, hemoptysis, sputum production, dyspnea, chest pain, fever, and weight loss. Review of systems was completely negative, and the patient took no medications.

She had been a housewife and stenographer all her adult life and had not been exposed to dusts or fumes. She had never smoked cigarettes. A brother had died at age 68 of a stroke. A sister had died five years ago with tuberculosis; the patient had had no contact with her sister for many years.

Two separate physical examinations demonstrated a healthy appearing, well-nourished woman with normal vital signs. There was no lymphadenopathy. Eyes, ears, nose, and throat were unremarkable. The thyroid was not palpable. Lungs were clear to percussion and auscultation. Heart sounds were normal, with no murmurs, gallops, or rubs.

The abdomen was soft with no tenderness, masses, or palpable organs. The remainder of the physical exam was entirely normal.

Routine admission laboratory data included complete blood count, chemistries, and urinalysis, all within normal limits. Chest X-ray demonstrated a normal heart and normal pulmonary vasculature. Lung fields were clear except for a rounded 1.5 cm density in the anterior segment of the right upper lobe. No significant adenopathy was identified.

Bronchoscopy demonstrated no lesions, but green pus was seen in the anterior segment of the right upper lobe. Stains of this material showed no acid-fast organisms.
or fungi. Routine bacterial cultures yielded only normal flora. Cytologic examination was also unremarkable. Chest films following bronchoscopy demonstrated no change in the appearance of the lesion. Nuclear scans of brain, bone, and liver-spleen were all normal.

On the fourth hospital day, a procedure was performed.

Clinical Discussion

DR. HAROLD STERN (Clinical Associate Professor of Surgery, Yale University School of Medicine and Associate Chief of Cardio-Thoracic Surgery, Y–NHH): As I was coming here today, I was wondering how can an otherwise asymptomatic patient presenting with a solitary pulmonary nodule best be approached? This is quite a difficult problem for the physician and certainly for the patient, since by definition the lesion is asymptomatic and noted only on routine films. I thought it would be best to defer a detailed presentation of this patient until I give a short discourse about isolated pulmonary nodules.

The asymptomatic pulmonary nodule has long been of interest to surgeons and pathologists. In considering this entity in an individual case, the first item is the history. There is a high incidence of histoplasmosis in the Ohio Valley and residence there tremendously increases the possibility of a histoplasmosa. Most important is a history of prior carcinoma in any organ. We see many patients who have had breast carcinoma many years ago present with asymptomatic pulmonary nodules. Often these lesions represent new carcinomas, though others are metastatic from the original breast lesion.

The criteria which define pulmonary nodules are very important. The lesion should not be irregularly outlined or asymmetric. It should be well demarcated from the surrounding lung. It should not be fused with the hilum or pleura. Lesions over 3 cm in diameter are no longer categorized as nodules. Certainly, lesions 5 to 10 cm in size are almost always malignant. The term “coin” lesion should be discarded, since the actual lesion is spherical or ovoid, not circular. The presence of satellite lesions suggests a benign process such as pulmonary granuloma.

Compilations of data with proven diagnoses have been noted repeatedly. One of the most detailed analyses is by Steele [1]. Of 887 patients presenting with solitary pulmonary nodules, 316 had malignant lesions, of which 26 were metastatic from other primaries, 65 were benign tumors, and 475 were granulomas, including tuberculosis, histoplasmosis, coccidiomycosis, and the like.

Some classic radiographic findings suggest benign lesions. These include the target sign which appears exactly like a target with concentric calcification. This distinctive appearance represents phases of growth and calcification in a histoplasma. Popcorn-type calcification suggests hamartoma. Eccentric calcifications can be seen in carcinomas and should certainly not be included as part of criteria for a benign process.

An important aid for the thoracic surgeon prior to recommending surgery are old films with which the growth rate of the lesion can be established. Almost everyone has had an old chest roentgenogram. Retrieving old films can be difficult, but the reward of finding an unrecognized lesion many years old speaks for itself.

Some years ago Dr. Spencer described a series of patients who had adenocarcinomas associated with prior scars [2,3]. Spencer assumed that a previous scar was responsible for dysplasia and eventual carcinoma formation. At the operating table, these lesions
have a classic appearance of being puckered, with local areas of anthracosis. Commonly, adenocarcinomas are seen in similar areas of chronic inflammatory lesions. Subtle changes in size, however slight, may represent the occurrence of a new adenocarcinoma in an old granulomatous lesion.

Now to consider the patient in question. Tuberculin testing was not done and I cannot fault this omission, since this testing generally is not helpful. A few years ago, we would have ordered tomograms. It is of interest that some of the earliest tomography apparatus was located at Y-NHH. Nowadays, a CT scan would be performed. I find CT particularly helpful in discovering any unsuspected mediastinal involvement of metastases; as well, multiple nodules too small for conventional radiography may be delineated. Haunesfeld density is not used here to differentiate benign from malignant lesions.

Bronchoscopy has a minor role in the evaluation of pulmonary nodules. Some people prefer a transbronchial needle biopsy with a flexible endoscopic needle. I find this approach difficult and have abandoned this technique.

The transthoracic needle biopsy is probably the best method for definitive diagnosis. There are complications, particularly pneumothorax. The major problem as I see it, however, is the negative needle biopsy result. To be confident with a negative diagnosis of malignancy, one must not only see no tumor cells, but also make another diagnosis by discerning cell histology.

Another method of obtaining a diagnosis is the so-called limited thoracotomy, or mini-thoracotomy. The nodule is removed and, as a bonus, the mediastinum is examined for evidence of malignancy. In the event that pulmonary resection is indicated, the incision may be enlarged to perform the definitive operation at the same sitting.

I should again mention the patient with breast carcinoma presenting with a new pulmonary lesion. It is imperative that the nodule be removed. Estrogen receptor studies can be performed if the lesion is metastatic from the breast, and if the lesion represents a new primary (as many as 50 percent are), it may be removed.

May we see the films?

DR. ASIM DIKENGIL (Resident in Radiology, Yale-New Haven Hospital): The admission X-ray (Fig. 1) is a P-A view which shows a sharply circumscribed nodule in the anterior segment of the right upper lobe. There is no adenopathy of the hila or mediastinum. There are no calcifications within the nodule. The pleura is normal.

Looking at the tomogram (Fig. 2), we can see the nodule to be well delineated, without calcifications. The lesion was not present on earlier films from 16 months ago. Thus we have an unstable nodule which is highly suspicious for malignancy.

DR. STERN: Can I ask your opinion about these tentacles extending from the lesion?

DR. DIKENGIL: This is a soft sign for carcinoma. Corona radiata is another such sign for malignancy. The only two reliable signs of a benign lesion are a benign pattern of calcification and stability over at least two years.

DR. STERN: At this stage, a CT scan would be helpful. One remote possibility is that of dog heartworm, though I do not suspect it here. I would be highly suspicious of malignancy. Though in this case I am not sure of this diagnosis, I would operate in any case.

Clinical Diagnosis

Malignancy?
Pathological Discussion

DR. DARRYL CARTER (Professor of Pathology, Yale University School of Medicine): The patient discussed today has a peripherally located nodule in the lung on chest X-ray examination. Dr. Stern has discussed the differential diagnosis of these lesions, which is quite wide-ranging. It includes inflammatory diseases, benign neoplasms, and primary and secondary malignant neoplasms of the lung.

Among the benign neoplasms which Dr. Stern discussed are the various granulomatous processes which may occur in the lung. Tuberculosis, of course, is the most common but other granulomatous infections, including histoplasmosis and coccidiomycosis, may occur and produce a solitary nodule in the lung. Frequently these lesions are multiple and their multiplicity is helpful in the differential diagnosis.

Dr. Stern mentioned the relatively unusual occurrence of infarct-like nodules which occur in the periphery of the lung following an infection or infestation with the dog heartworm, *Dirofilaria immitis*. Over the past few years we have seen several of these lesions. Their overall appearance is similar to that of an infarct, but in the pulmonary vessels of the infarcted tissue there is evidence of the parasite. Fortunately, these organisms do not multiply in the human as they do in the dog. The filarial worms end their life cycle in humans and break off into the pulmonary circulation where they infarct the lung and produce a radiographic image similar to a primary pulmonary neoplasm.

Two benign lesions mentioned in the differential diagnosis are the so-called hamartoma of the lung and benign fibrous mesothelioma. The hamartoma of the lung presents as a rounded nodule which grows very slowly. It is the most common benign tumor of the pulmonary parenchyma. The term hamartoma is a misnomer in that the lesion is a benign interstitial growth of mesenchymal tissue which usually differentiates toward cartilage, but which may differentiate toward adipose tissue. A similar lesion which is usually found directly under the pleura is the so-called fibrous
mesothelioma. This is composed of cells which are apparently fibroplastic but recently have been shown in many instances to contain elements of smooth muscle. Occasionally and classically, these lesions are pedunculated from the visceral pleura but may extend into the central portion of pulmonary parenchyma along the fissures.

Having ruled out these lesions, the primary consideration for a peripheral nodule is primary adenocarcinoma of the lung. From a morphologic standpoint, it is extremely difficult to distinguish those adenocarcinomas which arise in the periphery of the lung and those which are metastatic to the lung, particularly in the presence of a previous adenocarcinoma as of the colon or stomach. In this patient, there was no such preceding lesion.

The lesion which was shown on this patient's chest film was indeed an adenocarcinoma of the lung associated with a central scar. As Dr. Stern pointed out, the nature of the scar and the relationship between the scar and carcinoma have been a subject of considerable interest for many years. The concept of scar cancer of the lung was first popularized in 1939 by Friedrich [4]. The interpretation of the lesion was that of an adenocarcinoma growing in the regenerating epithelium at the periphery of a scar. Over the years, numerous authors have discussed and refined this concept. Most recently, Auerbach et al. have associated adenocarcinomas of the lung with scars produced by either infarcts or tuberculosis [5].

Recently, however, the concept of carcinoma developing at the periphery of the scar has been replaced with the concept that most such lesions represent an adenocarcinoma with a desmoplastic central portion. Shimosato et al. have suggested from both radiographic and histologic evidence that the scar formed as a result of the growth of the carcinoma rather than vice versa [6]. These authors also suggested that the extent of the scar correlated inversely with the survival of the patient.

Joe Madri and I recently published a study of the nature of patients presenting with scars in the central portion of the peripheral adenocarcinoma of the lung by studying the types of collagen which were present [7]. In this study, it was found that burned-out scars present in the periphery of the lung and not associated with neoplasia had undergone a process of maturation so that there was a large amount of types I and V collagen present but a decrease in the type III collagen. Type III collagen is usually laid down in the early stages of the scarring process. Conversely, in all of the patients with "scar" cancers studied in this series (and the patient discussed here), there was a marked increase in type III collagen and relatively small amounts of types I and V collagen. This indicated that the scar present was being actively laid down, presumably as a result of the tumor and therefore a desmoplastic reaction to the tumor. This work has been confirmed subsequently by other laboratories using collagen probes.

It is clear that there are some carcinomas which do develop at the periphery of pre-existing scars. The classic case presented by Raeburn and Spencer of a carcinoma which was growing around a bullet which had been present in the pulmonary parenchyma for some twenty years is certainly evidence that scar cancers do occur [8]. It is of interest that the carcinoma growing around the bullet in that report was a small cell carcinoma and not an adenocarcinoma, as is typical of "scar" cancer.

The reinterpretation of the nature of the scar has implications for the etiology of peripheral carcinoma of the lung as well as for the interpretation of chest films for neoplastic disease.

Pathological Diagnosis

Pulmonary adenocarcinoma
REFERENCES

1. Steele JD: The solitary pulmonary nodule. J Thorac Cardiovasc Surg 46:21–39, 1963
2. Spencer H: Pathology of the Lung, 2nd edition. Elmsford, NY, Pergamon Press, 1968, p 826
3. Rauburn C, Spencer H: A study of the origin and development of lung cancer. Thorax 8:1–10, 1953
4. Friedrich G: Periphere Lungenkrebs auf dem Boden Pleurahäher Narben. Virchow's Arch 304:230–247, 1939
5. Auerbach O, Garfinkel L, Parks VR: Scar cancers of the lung. Cancer 43:636–642, 1979
6. Shimosato Y, Hashimoto T, Kodama T, Kameya T, Suzuki A, Nishiwaki Y, Yoneyama T: Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. Amer J Surg Path 4:365–373, 1980
7. Madri J, Carter D: Scar cancers of the lung: Origin and significance. Human Path 15:625–631, 1984
8. Raeburn C, Spencer H: Lung scar cancers. Brit J Tuber 51:237–245, 1957