

October 2005

**LUNG
CANCER****FRONTIERS**

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New Directions for Lung Cancer Frontiers

Lung Cancer Frontiers is published by The Snowdrift Pulmonary Conference and supported by a generous grant from the Flight Attendant Medical Research Institute (FAMRI) of Miami, Florida. It is hoped that the next series of issues will help to disseminate knowledge based on our experiences in early lung cancer identification and treatment, based upon studies originally conducted in Grand Junction, Colorado.

"The purpose of *Lung Cancer Frontiers* is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated."

The Editorial Board calls everyone's attention that all issues of *Lung Cancer Frontiers* beginning with their inception in 1996 are available on the internet at www.lungcancerfrontiers.org.

Recent dramatic events have focused new light on the growing and unanswered problem of lung cancer. The rather sudden deaths of ABC anchorman, Peter Jennings, and Barbara Bel Geddes, star of the famed Dallas TV series, both heavy smokers, and the announcement of the diagnosis of lung cancer in Dana Reeve, widow of the late Christopher Reeve, a young non smoker, has sent a chill to the public. What can be done about lung cancer? How can it be diagnosed early in its natural history, and be treated for cure? Why do even non smokers sometimes get lung cancer? Science has a lot of questions begging for answers.

No doubt exists that the greatest risk factor in lung cancer is tobacco smoking, responsible for about 85% of cases. But what about non smokers? We know that lung cancer clusters in families, and there are racial genetic factors involved. Asian women often have adenocarcinoma, often bronchoalveolar lung cancer without a smoking risk. These women respond better to gefitinib (Iressa), compared with non Asian women, presumably due to a specific mutation of the epidemical growth factor receptor (EGFR) (N Engl J Med 2004;350:2129-2399). But some women without this mutation respond.

cancer is in the mid to late 60s, depending on the country of diagnosis. But why ignore the aging population that could have cures, equal to other solid tumors? It just isn't fair!

We have a growing number of technologies that CAN diagnose early stage lung cancer. Early stage lung cancer has a much higher cure rate than when lung cancer is diagnosed at a later stage. We simply cannot wait until large population studies prove, to the most die hard critics, that screening high risk populations will reduce lung cancer mortality. Since survivors avoid or postpone mortality, what is the argument here?

Previous issues of *LCF* have focused on the science behind early diagnosis and treatment programs. As we approach our 10th anniversary, we are now changing our focus a bit. Each issue will present contemporary case reports that make specific points about early diagnosis and treatment. **We invite our readers to also submit cases of particular interest for publication in future issues of LCF.** We will continue to monitor the scientific literature in the English language for abstracts that will be of particular interest to the clinician. We hope this will make *LCF* more interesting to our readers, and more immediately clinically relevant.

The Editors.

The median age of diagnosis of lung

The Forum for Early Diagnosis and Treatment of Lung Cancer

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**THE TIME TO DIAGNOSE
LUNG CANCER IS NOW!**

For more than a decade we have been presenting the case for the diagnosis of asymptomatic, and hopefully, early stages of lung cancer in patients at high risk. High risk is defined as heavy smoking, family history of lung cancer, and occupational risk, always with airflow obstruction measured by simple spirometry. In several issues we have described the success of this approach by a primary care practice in Grand Junction, Colorado. The questionnaire which was used to identify a total of 12 cases from 430 questionnaires representing high risk patients has now been validated. (CHEST 2005;127:1140-1145). The questionnaire which proved to be so successful is reproduced on page five of this issue. We now have the knowledge and technology to diagnose asymptomatic and early stage lung cancer, and should be doing it as the standard of care.

New Approaches to Lung Cancer Diagnosis and Treatment

Beginning in January 2005, a multidisciplinary lung cancer clinical conference was established at Swedish Hospital in Denver, Colorado. Its central purpose is to provide consultative assistance to the specialties included in lung cancer diagnosis and treatment. Disciplines represented are pulmonology, diagnostic radiology, oncology, radiation therapy, surgery and pathology. This conference has now participated in the decisions resulting in causative or palliative care for 1007 patients in the past eight months. Outreach and early identification of asymptomatic lung cancer in primary care practice, based on the Grand Junction Model, is currently underway.

The following is the abstract of the first full report of the Grand Junction Study, which forms the evidence base for case finding in high risk patients using dual testing with CT and sputum cytology.

Lung Cancer Detection in Patients With Airflow Obstruction Identified in a Primary Care Outpatient Practice

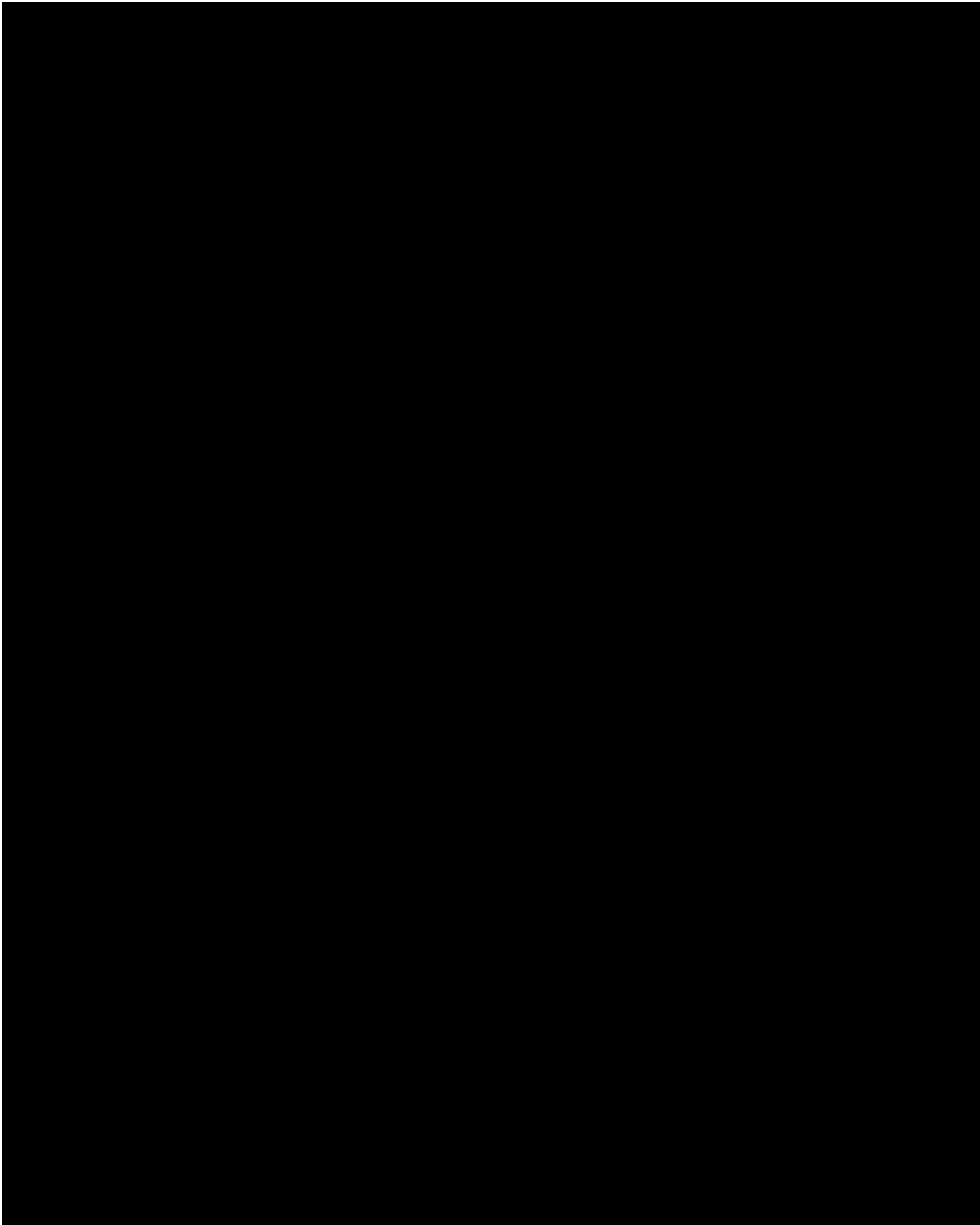
Joel J. Bechtel, MD, FCCP; William A. Kelley, MD, FCCP; Teresa A. Coons, PhD; M. Gerry Klein, MD, Daniel D. Slagel, MD; and Thomas L. Petty, MD, Master FCCP

Introduction: This prospective study describes a community-based lung cancer identification project focusing on high-risk patients who receive general care in a primary care outpatient practice. Within 1 calendar year, a simple questionnaire was completed in 1,296 patients > 50 years old to identify 430 patients at high risk of lung cancer (smoking, family history of aerodigestive tract cancer, or occupational exposures) Spirometric abnormalities were found in 126 of these patients.

Methods: Chest posteroanterior radiographs, thoracic CT scans, and sputum cytology were offered to subjects with airflow obstruction (N=126). Eighty-eight patients underwent all tests. Thirty-eight patients refused or could not consent in a timely fashion.

Results: Six cancers were found in the screened group, and all were treated. Two more cancers were found in the nonscreened patients with airflow obstruction. Both were treated by surgical resection or radiation therapy. Costs per cancer found were \$11,925 per patient.

Conclusions: Case finding in high-risk patients in a primary care population can be accomplished at a relatively low cost.



needle aspiration biopsy, and PET = positron emission tomography scan

GRAND JUNCTION QUESTIONNAIRE

Did you know that in 1999 it is estimated that 171,600 new lung cancer cases were diagnosed in the United States? Lung cancer is the most common cause of cancer deaths for both men and women in the United States. Dr. Joel Bechtel, Dr. Thomas Petty, The Saccomanno Research Institute at St. Mary's Hospital and Medical Center, and Primary Care Partners, P.C. hope to learn more about the lung cancer risks in our community. We have undertaken a community screening project with the purpose of investigating methods for detecting lung cancer at an earlier, more treatable stage. Patients choosing to take part in the project will be evaluated using spirometry (a test of lung function done by blowing into a measurement device), sputum cytology (cells coughed up from deep in the lungs are looked at through a microscope), a chest x-ray and a chest CT scan. We would appreciate your help in this important project by completing this brief questionnaire.

1) Name: _____
Date: _____ Age _____ Telephone No. _____

2) Type of Insurance Coverage: _____
No Coverage: _____

3) Please circle the answer that best describes your smoking habits:
I have never smoked.

I currently smoke.

I smoked in the past, but no longer smoke.

Packs per day: _____ Year or age started: _____ Year or age stopped: _____

Please circle the answers that apply to you:

I current work or have previously worked in one or more these occupations:

Underground Mining
Construction
Railroad

I have significant industrial and/or occupational exposure to the following substances:

Asbestos
Silica Dust
Coat Dust

4) Please circle the answer that best describes who in your family has been diagnosed with cancer of the lung and/or larynx:
No One Self Parent Brother or Sister Children

I would like to get more information about this important project:

No Yes

This study was planned in 1999 and enrolled patients between 2000 and 2001.

Based on the Grand Junction experience, the Swedish Hospital in Denver has now begun a program for early diagnosis and treatment of lung cancer in the Metropolitan Denver area. The announcement of this program is presented below.

The Swedish Hospital Lung Cancer Diagnosis & Treatment Center

Dear Doctor _____:

Today we have the knowledge and technologies to be able to change the outcome of lung cancer. In 2005, 170,000 will be diagnosed with lung cancer, often in late stages. Overall survival has been only 15% at five years using ordinary (conventional) approaches to diagnosis, based on symptoms or a lung mass diagnosed by accident. We can improve survival to 75% at five years with early diagnosis, based on many studies.

We know how to find lung cancer in patients at highest risk. A simple questionnaire, reproduced below, and office spirometry will identify a population with a risk of 6 to 10% now. At least 50% of lung cancers diagnosed by CT and sputum cytology will be early stage disease with an excellent chance for cure. The other 50% will need immediate treatment for what stage of disease is found. In EVERY case, there is the opportunity of treatment to increase survival, improve quality of life, and **save the costs of advanced lung cancer care.**

Our new and unique program at Swedish Hospital offers the latest in state-of-the-art technologies and treatment. Our efficient program is unique in the Rocky Mountain Region, and is available to all.

CONTEMPORARY CASE REPORTS

Presented by
Thomas L. Petty, M.D. (Editor)

Case No. 1

A 72-year old woman, previously in excellent health, had an episode of acute pancreatitis and was hospitalized. She had evidence of cholecystitis and scattered pancreatic calcifications. A successful cholecystectomy was performed. A chest x-ray at the time of admission showed a 7 mm nodule non-calcified in the left mid-lung field. A chest x-ray one year earlier did not have this lesion. She discontinued smoking on the event of this hospitalization, having smoked a total of 56 pack years. The patient was discharged to her primary care physician. Even though the radiologist recommended a follow-up by CT, no chest x-ray or CT follow-up was done by his physician in the five years that followed.

After the patient's primary care physician retired, she was treated by his partner. From 2001 to 2003, the patient was seen frequently with cough, wheeze, and mucus hypersecretion of varying degrees. A diagnosis of COPD was entered in the medical record, but no spirometry was done. The patient was treated with various bronchodilators including albuterol, Ipratropium, and the combination of both agents (Combivent®). At times, she received a combination of Salmeterol and Fluticasone (Advair®). She continued to be followed by the primary care physician until an episode of hemoptysis occurred in 2003. This led to a chest x-ray which showed a 6 centimeter lobular mass in the left mid lung fields. A biopsy revealed a squamous cell carcinoma. The patient had pulmonary function tests done at this time which were

FVC of 1.67 L (63%) and FEV₁ 1.07 (55%). Following inhalation therapy of Albuterol, the FVC elevated to 2.61 liters and FEV₁ 1.31 liters. The patient's diffusion test was 72% of predicted. Residual volume was 220% of predicted. The total lung capacity was 145% of predicted.

At the time of surgery, a large mass adherent to the left pulmonary artery was resected. A patch of the pulmonary artery was accomplished. Histologic examination revealed a well differentiated squamous cell carcinoma with invasion of the pulmonary artery. Three nodes were positive for squamous cell carcinoma in the left hilar region. Subsequently, the patient had numerous complications and over the ensuing three months, and developed evidence of myelodysplasia with thrombocytopenia and anemia. She developed a chest infection, became septic, uremic and died five months after her resectional surgery.

Comment on Case Report:

The issues here are simple. A new small non-calcified nodule, which appeared between 1995 and 1996, did not result in any followup imaging. In addition, when this patient presented with chronic symptoms of cough expectoration, the diagnosis of COPD was made, but no spirometry was done for confirmation or assessment of severity. There was no consideration that lung cancer could be the underlying diagnosis. Only when the patient developed hemoptysis did her physicians obtain a chest x-ray which demonstrated a 6 centimeter lobulated mass in the left lung fields, which is the location of the original small nodule. Very likely early identification and treatment would have averted this unhappy outcome. Cases such as this may result in litigation for failure to diagnose lung cancer when a chest x-ray is suspicious and requires follow-up.

A chest x-ray at the time of admission showed a 7 mm nodule non-calcified in the left mid-lung field.

... no chest x-ray or CT follow up was done ...

The issues here are simple. A new small non-calcified nodule, which appeared between 1995 and 1996, did not result in any follow-up imaging.

A diagnosis of COPD was entered in the medical record, but no spirometry was done.

Case Presentation of a “Solitary Pulmonary Mass”

S. Arnold, M.D. and D.E. Doherty, M.D. (Lexington, Kentucky)

Case No. 2

A 55 year old male smoker presented to the Emergency Room of his local hospital with a two-week history of right-sided chest pain and a fever to 102.5 degrees F. that had occurred last evening. He had also noted bloody sputum in the past month, but assumed it was due to “chronic bronchitis, because it cleared up without me seeing a doctor.” His past medical history is remarkable for long-standing arthritis and chest pain necessitating a cardiac catheterization four months prior (the results of which were normal according to the patient. His social history reveals a 60 pack-year tobacco history.

In the ER the patient appeared well His respirations were not labored and no wheezes or rhonchi were heard on auscultation of the lungs. His physical examination was otherwise unremarkable, as were his laboratory values, except for a slightly elevated white blood cell count of 14.0. A chest x-ray obtained in the emergency room revealed a 3 cm right upper lobe mass (Figure 1) and the patient was given Trimethoprim/Sulfamethoxazole for acute bronchitis, and sent home to follow-up in the multidisciplinary lung cancer clinic. At the time of his clinic visit, a CT of the chest confirmed a 2.5 cm spiculated mass in the right upper lobe without apparent adenopathy, and a PET scan demonstrated a malignant-appearing mass in the right lung (SUV of 7.0) without any other sites of abnormality (Figure 2). Pulmonary function tests done at this time were FEV₁ of 2.1 (78% of predicted), a FVC of 2.8 (80% of predicted), and an FEV₁/FVC of 75%, with-

out a significant change in airflow in response to one time bronchodilator (inhaled Albuterol). The patient’s diffusion test was 87% of predicted and his was scheduled for surgical resection.

On the day prior to surgery, the patient reported transient left arm weakness and again came to the ER. A neurological examination revealed 4/5 strength in the left grip, bicep and tricep, with no other focal deficits. A contrasted MRI of the brain was performed and a 3.0 cm right temporal lesion was found (Figure 3). The patient underwent a craniotomy which revealed a moderately differentiated adenocarcinoma, consistent with a lung primary. He recovered and was discharged on post-op day 2 and completed a course of whole brain radiation. One month after his brain resection, a repeat CT scan showed no change in the pulmonary lesion, and the patient underwent a resection of the lung mass. At the time of surgery, a solitary adenocarcinoma was removed with a full node dissection, with a final pathologic stage T1N0M1.

Discussion:

This case highlights that not all stage IV lung cancers are equal, and while resection of a lung cancer in a patient with a known brain metastasis may not always be appropriate, there are times that surgery is indicated. This patient had no significant co-morbid illnesses, a low cardiac risk stratification and excellent pulmonary reserve. In other words, he was an excellent surgical candidate for resection. He had a solitary brain

He had also noted bloody sputum in the past month, but assumed it was due to “chronic bronchitis . . .

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. . . And a PET scan demonstrated a malignant-appearing mass in the right lung (SUV of 7.0) . . .

Patients with a solitary brain metastasis that is controlled locally, may benefit from surgical resection of their lung cancers . . .

metastasis, which when resected and followed by whole brain radiation, provided a 5-year survival of 10 to 20%.— Patients with a solitary brain metastasis that is controlled locally, may benefit from surgical resection of their lung cancers, with case series reporting a 5-year survival rate from 5 to 20%.— While controversial, an aggressive approach in highly functional patients with a surgically resectable lung cancer (T1-2 N0-1) and an isolated brain metastasis can lead to long term survival (up to 5 years, in some cases). The general recommendation is to treat the primary lung tumor according to the T and N status in the setting of a solitary brain metastasis. Adjuvant chemotherapy is controversial in this setting and remains of unproven benefit. [The availability of new chemotherapy agents such as Tarceva® and Avastin® offer additional hope of lung cancer survival. (ed)]

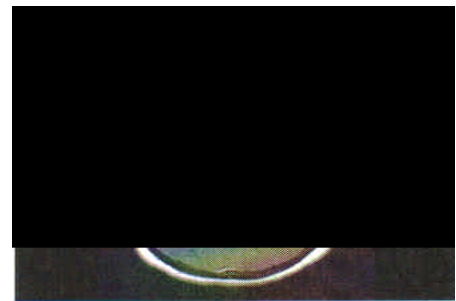


Figure 2—

Figure 1—



a Patient with Solitary Pulmonary Nodule

- 55 year old smoker presents with right-sided chest pain, hemoptysis
- PMHx:
 - Cardiac catheterization 2 months prior: normal coronaries
 - 60 pack-year tobacco history
 - Arthritis

Solitary Pulmonary Nodule

- CT of the chest confirms a solitary nodule (2.5 cm in right upper lobe) without adenopathy
- FEV₁ = 2.1
- Physical examination and laboratory assessment are normal

A chest x-ray showed a small right pleural . . .

Chest x-ray scan six months after beginning therapy showed growth of the mass with new multiple right sub-pleural nodules.

Figure 3—Solitary Pulmonary Nodule

- On the day prior to surgery, the patient complains of transient left arm weakness

Case Presentation by Thomas A. Hyers, M.D. of St. Louis, Missouri

Case No. 3

JRM: 46-year-old African-American man is evaluated for persistent cough and 10 pound weight loss. Physical examination shows only a pale thin man in no acute distress. A chest x-ray showed a small right pleural effusion with right middle lobe collapse associated with a right hilar and paratracheal mass. No pleural plaque or parenchymal opacities were observed.

Past medical history was unremarkable. Patient had been in generally good health and takes no medications. He was a lifelong non-smoker. There was no personal or family history of cancer.

Occupational and environmental history: He had been a railroad machinist and inspector for 19 years. He worked inside diesel cabs, engine rooms and radiator rooms on a daily basis. He was often in the radiator room when diesel exhaust is blown into the room during engine tests. His inside work was usually done at high idling rates as he looks for fuel, oil or fume leaks. He also does welding on truck (wheel) assemblies and outside inspection of idling diesels in the rail yards. He described himself as a compulsive worker who would work overtime

without pay to “get the job done.” He had never done underground or surface strip mining, smelter or factory work, or worked in the plastics industry. He lived in a home with a basement. He reported that radon gas testing on two occasions had shown “slightly elevated” radon gas levels in his basement.

Case disposition: CT-guided fine needle aspirate of the mass showed poorly differentiated large cell carcinoma, favor poorly differentiated squamous cell carcinoma. He was staged further and considered non-resectable. He received combined external beam irradiation therapy and systemic chemotherapy with cisplatin and etoposide. Chest CT scan three months after beginning therapy showed some decrease in the right hilar and mediastinal mass with decrease in the pleural effusion. Chest CT scan six months after beginning therapy showed growth of the mass with new multiple right sub-pleural nodules.

Comment (T. Hyers): This is the “cleanest” case I have seen implicating diesel exhaust as a cause of lung cancer. Many of the patients I see with lung cancer and diesel exhaust exposure also smoked cigarettes, which is a big confounding factor. I don’t think the radon gas issue is very important because many homes in the Midwest have minimally elevated radon gas levels in their basements. However, as this case goes to litigation, his radon gas exposure will likely be discussed at length.

Selected References:

1. Garshick E, Schenker MB, Munoz A, et al: A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 1988;137:820-825.
2. Hayes RB, Thomas T, Silverman DT: Lung cancer in motor exhaust-related occupations. *Am J Ind Med*

He worked inside diesel cabs, engine rooms and radiator rooms on a daily basis.

He reported that radon gas testing on two occasions had shown “slightly elevated” radon gas levels in his basement.

1989;16:685-695.

3. Dockery DW, Pope CA III, Xiping X, et al: An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-1759.

- .. A chest x-ray showed a round left upper nodule of roughly 1.7 centimeters.

Case Presentation by James T. Good, Jr., M.D. of Englewood, Colorado

Case No. 4:

A 43-year old white woman was referred to a pulmonologist because of an abnormal CT scan. She was being evaluated for laparoscopic surgery for assistance in weight control because of severe obesity.

During her evaluation, a chest x-ray showed a round left upper nodule of roughly 1.7 centimeters. The borders were smooth. A chest x-ray taken one month earlier at another hospital showed the same abnormality. The CT scan showed a small cavity within a medical proportion. A PET scan showed partial radial uptake of FTG. The patient's only symptoms were related to recurrent sinusitis. She had required multiple courses of antibiotics and finally, just before the present evaluation, the symptoms had evolved. She previously had had sinus surgery and removal of polyps.

A strong family history of cancer on the mother's side was reported. The patient had aunts and uncles with various cancers including stomach, bowel, ovarian, pancreas, liver, lung and bone cancer. The patient was a nonsmoker and did not use recreational drugs. The patient's physical examination was normal except for severe obesity. Because of the solitary nodule, the PET scan isotope uptake, and the strong family history for lung cancer, a needle biopsy was per-

formed. The patient had hoped to avoid a thoracotomy in view of the extensive other pending surgery. A large core biopsy revealed the features of hamartoma.

Comment:

Hamartoma is a slow growing, benign lesion containing multiple tissues. The small cavity seen in the CT scan was shown to be adipose tissue. The justification of the extensive work-up and biopsy section was the strong family history of lung cancer. It is well known that more women, non-smokers, are being diagnosed with lung cancer today due to heightened public awareness.

SELECTED ABSTRACTS FROM THE RECENT LITERATURE

1. Clinical Cancer Research 2005;11:537-543

The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

Roderick H. Breuer, Arifa Pasic, Egbert F. Smith, et al

Purpose: To study the natural history of preneoplastic lesions in the bronchial mucosa of the individuals at risk.

Patients and Methods: White light and autofluorescence bronchoscopy examinations have been done in 52 individuals harboring 134 preneoplastic lesions (WHO criteria). End points were the de-

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Because of the solitary nodule, the PET scan isotope uptake, and the strong family history for lung cancer, a needle biopsy was performed.

However, when analyzed per individual, no significant difference of progression rate between individuals with or without severe dysplasia was seen (39% versus 26%; P = 0.36).

The initial WHO classification of any preneoplastic lesion cannot be reliably used for accurate risk assessment of field carcinogenesis.

velopment of carcinoma in situ (CIS) or squamous cell cancer (SCC) or the highest category of dysplasia up until March 1, 2003 for the remaining preneoplastic lesions.

Results: Distribution and outcome of preneoplastic lesions have been found to be unrelated to various risk factors such as smoking history, past history of cancer, or chronic obstructive pulmonary disease. Nonstepwise changes of preneoplastic lesions are seen. Regression rate has been 54%. Progression to CIS/SCC has been 13.4% (18 of 134) and was for severe dysplasia, significantly higher (P = 0.003) than preneoplastic lesions showing lower-grade dysplasia (squamous metaplasia, mild and moderate dysplasia). Time to progression was not significantly different. However, when analyzed per individual, no significant difference of progression rate between individuals with or without severe dysplasia was seen (39% versus 26%; P = 0.36). Conclusions: The 54% regression rate of all preneoplastic lesions, 26% to 39% progression rate to CIS/SCC of individuals with no significant difference in progression rate and time to progression combined with nonstepwise histologic changes unrelated to the initial histologic grading indicate that one cannot differentiate the potentially more malignant preneoplastic lesions among the many preneoplastic lesions present in the bronchial mucosa. The initial WHO classification of any preneoplastic lesion cannot be reliably used for accurate risk assessment of field carcinogenesis.

Editorial Comment (TLP):

Clinicians need to have a reliable marker of the presence of a small occult malignancy in the large conducting airways. This study indicates that the stage of dysplasia may not be a marker of a progressively malignant lesion. See following abstract.

Lung Cancer 2005;49:187-191

High prevalence of occult endobronchial malignancy in high risk patients with moderate sputum atypia.

[Kennedy TC](#), [Franklin WA](#), [Prindiville SA](#), [Cook R](#), [Dempsey EC](#), [Keith RL](#), [Hirsch FR](#), [Merrick TA](#), [Shroyer KR](#), [Petty TL](#), [Byers T](#), [Bunn PA Jr](#), [Miller YE](#).

University of Colorado Comprehensive Cancer Center, University of Colorado Health Sciences Center, Denver, CO, USA.

Early stage radiographically occult lung cancer has a high cure rate, but comprises a small fraction of all lung cancer. Abnormal sputum cytology is one indication for bronchoscopy in patients with chest imaging that is not suspicious for lung cancer. While there is good evidence that sputum cytologic findings of carcinoma, carcinoma in situ or severe atypia predict high rates of diagnosis of lung cancer, less is known of the frequency in which lung cancer is diagnosed in bronchoscopies carried out for the indication of moderate sputum atypia. One small series, published in abstract form only, reported an 8% rate of diagnosis of lung cancer in subjects bronchoscoped for moderate atypia. We tested the hypothesis that moderate sputum atypia is an indicator of occult central airway cancer in a retrospective analysis of a group of high risk subjects, defined as current or former smokers with >30 pack-years tobacco smoking and airflow obstruction with moderate atypia sputum cytology. Seventy-nine such subjects with no evidence of malignancy on chest radiograph at the time bronchoscopy was scheduled underwent white light and autofluorescence bronchoscopy. Lung cancer was found in five subjects; three had invasive squamous cell carcinomas and two had carcinoma in situ. Seven additional subjects had severe dysplasia found on endobronchial biopsy. Moderate sputum atypia may be an important marker of risk for occult endobronchial malignancy in high risk subjects.

Editorial Comment (TLP):