Family Practice Grand Rounds

Malignant Mesothelioma: An Occupational Disease

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DR. FRANK WIYGUL *(Assistant Professor of Family Medicine)*: This morning Dr. Annyce Campbell is going to tell us about malignant mesothelioma while we put away our pipes and cigarettes.

DR. ANNYCE CAMPBELL *(Third-year family practice resident)*: Today's discussion will emphasize the way a person's lifestyle and means of obtaining a living begin to play a major role in respiratory health and affect the lives of family and friends. As primary care physicians, we play a potentially integral role in the early diagnosis, referral, follow-up, and inpatient support of these patients. We can best fulfill that role by being aware of diseases that have been shown to be occupationally related and being aware of occupational risks and hazards.

With the continuing introduction of new materials and processes in an increasingly complex industrial society, it is only appropriate that emphasis be directed toward the harmful or potentially harmful byproducts of industrial growth and environmental interactions. Often the work place is a hazardous environment, causing adverse respiratory reactions. The causal relationships between environmental agents and respiratory diseases can often be suspected on the basis of anecdotal information. One approach to prevention, when a causal relationship is confirmed, is prohibition of the offending agent. However, when dealing with an industrial material of major importance to society, such as cotton or asbestos, the prevention of undesired health effects ultimately takes on new dimensions and hinges upon such elusive data as the establishment of dose-response relationships and the achievement of subthreshold exposure. Confounding factors such as cigarette smoking and host response must be addressed. Time response relationship varies from the immediate response following inhalation of an irritant to a delay of many years before the appearance of an environmentally induced malignant effect or fibrosis due to mineral dust.[1,2]

The case presentation today touches on the life of one such individual who crossed that indistinct line of subthreshold exposure and experienced a full-blown "adverse respiratory reaction."

Mr. M., a 53-year-old, was admitted to Jackson Veterans Hospital from an outlying hospital with a left pleural effusion unresponsive to parenteral antibiotics. He was a former shipyard worker at Ingalls for about 16 years with a 40 pack-year history of cigarette smoking that he had discontinued over the past 12 years. His initial presentation included chest pain, nonproductive cough, and severe exertional dyspnea of two weeks' duration. Weight was stable prior to admission, and there was no known history of previous tuberculosis exposure. Upon initial examination, the patient was afebrile with resting tachycardia of 110 beats/min. General appearance revealed a pale, diaphoretic, tachypneic (28 respirations per minute) white man with paroxysmal bouts of coughing. The head was unremarkable except for decreased visual acuity secondary to bilateral cataract formation. Neck

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Continued on page 830

0094-3509/82/050827-06$01.50

Continued from page 827

and heart examination were unremarkable. Auscultation and inspection of the chest revealed a modestly increased anterior-posterior diameter with decreased breath sounds over the left lung field and scattered rales over the right lung field. Percussion was dull over the left lung field. The remainder of the examination was unremarkable.

Past medical history showed that the patient had been retired for about seven years because of arthritic pains in the neck. He has also had treatment for herpetic keratitis and cholecystectomy.

This is the father of seven children, aged 26 to 13 years. Four children are currently living at home and are healthy. The patient's father died from hypertension and heart disease.

Laboratory findings on admission included moderate hypoxemia with the following arterial blood gas readings: PO_2, 75 mmHg; PCO_2, 34 mmHg; and pH, 7.484. Blood chemistries were all within normal limits. He had a mild anemia and a white cell count of 10,600/mm^3, with 80 percent neutrophils, 13 percent lymphocytes, and 7 percent monocytes. Urinalysis and sputum examinations were negative. Serum hyaluronidase results are pending.

We have chest x-rays here today, I would appreciate some comments from the audience.

DR. WALTER TREADWELL *(Professor of Family Medicine)*: The x-ray films of the chest show no abnormalities of soft tissues or bony thorax. The right lung appears normal. The left diaphragm is elevated, suggesting loss of volume in the left lung. There is radio-opacity over the left lower lung field with extension up the thoracic cage to the apex, suggesting pleural effusion or reaction. There are also changes in the left lung above the opacity, suggesting atelectasis or an infiltrative process.

DR. CAMPBELL: I believe the formal radiological interpretation of these x-ray films is significant left pleural effusion with some suggestion of nodularity and pleural thickening. One cannot really say whether there is an obstructive lesion with this much pleural effusion. The heart border is obliterated on the left, and there is significant loss of lung volume. Would anyone care to comment on the differential diagnosis at this point?

DR. MARCIA NEWSOME *(Second-year family practice resident)*: With this man's past history

of cigarette smoking and occupational exposure in a shipyard, a major consideration would be a primary malignancy, with or without obstruction, or a secondary infection. Bronchogenic carcinoma is statistically more likely when there is a known association with smoking and asbestos exposure,[3] to which this patient may well have been subjected in a shipyard. Mesothelioma is also a strong consideration, especially in view of the involvement of the pleura.[4] I suppose an infectious cause, such as tuberculosis or fungal disease, remains a possibility, although this is not a typical presentation.

DR. CAMPBELL: Certainly, primary bronchogenic carcinoma, particularly adenocarcinoma of the lungs, and intraabdominal malignancy with pulmonary metastasis need to be considered strongly.

Our next step in evaluation was thoracocentesis. Thoracocentesis with pleural biopsy revealed grossly bloody, acidotic fluid with pH of 7.01, total protein of 4.7 g/100 mL, LDH of 2,050 IU/L, and glucose of 8 mg/100 mL. Biopsy was not diagnostic. At that point we proceeded with bronchoscopic examination, which was negative for endobronchial lesions with class II cytological examination. Finally, this patient underwent open biopsy by way of minithoracotomy with subsequent tissue diagnosis of malignant mixed-cell mesothelioma.

At this point, I am going to bring the patient in. He has agreed to answer a few questions. (The patient entered the room and was introduced.)

Mr. M., if you would, I have a few questions about your history I would like you to clarify for us. I told the audience that you were previously employed at Ingalls for about 16 or 17 years. During your period of employment at Ingalls, what specifically did you do?

MR. M: I was a sheet metal mechanic working on ventilation systems.

DR. CAMPBELL: Was there any type of special clothing, head gear, or protection apparatus worn during those duties?

MR. M: Nothing more than a hard hat, safety shoes, and safety glasses.

DR. CAMPBELL: How about employee health? Did you have annual screening procedures, chest x-ray examinations, lung studies, anything of that sort?

MR. M: No, I did not.

DR. CAMPBELL: Mr. M. has been hospitalized since mid-March. He has currently completed his first course of radiotherapy. Do we have any questions from the audience?

DR. WIYGUL: Mr. M., what was the first symptom that you noticed before you came into the hospital?

MR. M: It was just tightness in my chest. I got really short of breath.

DR. WIYGUL: How long ago was that?

MR. M: I'll say a couple or maybe three weeks.

DR. TOM GLADFELTER *(Assistant Professor of Family Medicine)*: Mr. M., what did you think was your problem before you came into the hospital?

MR. M.: I figured it may be just a cold, you know, pneumonia or something. I went to the doctor. They put me into the hospital for a few days. They figured it was pneumonia, but they couldn't get the pneumonia to break loose. They called up here and made arrangements for me to come up here.

DR. GLADFELTER: Do you now understand what kind of problem you are having?

MR. M: Yeah. I think I understand it pretty well.

DR. GLADFELTER: What is your feeling now?

MR. M: Well, it's just, I guess, a feeling that I have to put up with so I can feel better, you know. It is not a happy occasion. There is not much I can do about it either. But I guess as for myself, I'm taking it mighty good, and I guess the family is too, but we hate to be separated.

DR. ARCHIE HOWARD *(Second-year family practice resident)*: Mr. M., were you working directly with asbestos or were you just around it?

MR. M: Well, both. We worked in a room like this, with furniture. We would have to get asbestos and cloths to cover it to avoid getting burning sparks or welding sparks on it.

DR. HOWARD: There has been a lot in the news about asbestos in the last couple years. Did you worry about it when you heard about that?

MR. M: No, not really.

DR. HOWARD: Are there any other fellow workers having the same problem or other lung problems?

MR. M: No, not that I know of, because they were all over the world. Most of them came from out of state. Actually, I have not seen very many of them since I left the shipyard, so I really don't know what happened to them.

DR. CAMPBELL: Mr. M., do you have any

other thoughts or comments that you want to share with us today?

MR. M: No, not anything particular. I just hope that I have been of some help to you. (The patient left the room.)

DR. CAMPBELL: Over the past 20 years malignant mesothelioma has been the subject of much investigation, and it will continue to be investigated in the future. It is expected that from 1970 to 2000 the incidence will peak and then will begin to fall. Prior to 1950, it was a fairly rare tumor,[5] and no code for it as a cause of death was available.

In terms of epidemiology, malignant mesothelioma is related to asbestos exposure in about 70 percent of the cases. Again it depends on how thorough the initial occupational history is.[6-8] About 3 to 7 percent of asbestos workers, most of whom were exposed during the era when no safety precautions were being taken, will develop malignant mesothelioma. There has been a significantly lower prevalence in those with lesser exposure. Roughly, 75 to 80 percent of the tumors are pleural. The remainder are peritoneal. The mean age is 50 years, usually 20 to 40 years after initial exposure. Peritoneal mesotheliomas are usually related to heavier asbestos exposure. The intensity of exposure has been shown to be related to earlier death, but some tumors have actually occurred with little or no exposure. Asbestos workers have about 300 times the risk of the general population for developing this tumor. As far as the cause goes, it has been shown that pleural injection of asbestos in animals causes mesothelioma in about 60 percent of the experimental animals. Mesotheliomas have been induced in chickens by an avian leukosis virus.[9] This tumor is currently felt to be not related to smoking. However, smoking is associated with bronchogenic cancer. Asbestos fibers are inhaled from crushed asbestos crystals. Small fibers, which are usually less than 5 μm in diameter, reach the alveoli, cause chronic irritation of the pleura, and are thought to cause eventual malignant changes.[10] The tumor invades locally, involving the lungs, the chest wall, diaphragm, pericardium, mediastinal structure, and other structures of the contralateral lung. Rarely are there distant metastases to kidney, liver, or adrenal glands. This tumor is usually fatal by way of respiratory failure, congestive heart failure, or cardiac arrhythmias.

Clinically, solitary mesotheliomas are sometimes benign and usually asymptomatic, unless they are large enough to cause chest pain and pressure symptoms. They may be associated with distal osteoarthropathy, clubbing, and hypoglycemia. This is in contrast to the diffuse mesothelioma, which usually presents with chest pain, dyspnea, and pleural effusion. Cough, weight loss, and fever are less frequent and usually occur with involvement of the mediastinum. Unfortunately, at the time medical help is sought, this tumor is usually far advanced. Physical findings are usually those of pleural effusion and occasional clubbing. Later there may be weight loss, frozen chest, vocal cord paralysis, Horner's syndrome, nodal involvement, and finally terminal events, ie, cyanosis and edema secondary to respiratory and cardiac failure.[11]

Radiographic evaluation in the solitary lesion usually reveals a discrete mass. There is rarely an effusion with solitary mesothelioma, in contrast to a unilateral effusion with diffuse mesothelioma. Gross thickening or nodularity of the pleura above the effusion or after thoracocentesis is usually obvious. One may see signs of asbestosis in the opposite side, including plaque formation, fibrosis, or calcium deposits on pleura or the diaphragm, in about 20 to 25 percent of the cases. Later there is actually rib destruction and widening of the mediastinum.[4]

Diagnostic procedures include pleural fluid studies. It is worth noting that a significant amount of force is required to actually enter the pleural space, a condition thought to be secondary to adhesion formation. The fluid is grossly bloody in about 30 to 50 percent of the cases, but the first half may sometimes be light or straw colored. Rapid reaccumulation of fluid is a characteristic of this tumor. The pleural fluid chemistry is usually consistent with an exudate, ie, elevated lactate dehydrogenase and protein. The hyaluronidase acid values are usually greater than 0.8 mg, if available.[12] Cytology of pleural fluid is limited primarily by the subtle differences between benign and malignant cells and, of course, by the problems of distinguishing this from adenocarcinoma. There is a false negative rate of about 20 percent and only about 60 percent are diagnostic.

Continued on page 837

Continued from page 832

Pleural biopsy by needle is usually of little help because one seldom gets enough tissue to make a diagnosis. By far the best method of diagnosis is open biopsy by way of thoracotomy. Multiple biopsies should be obtained for light and electron microscope study because this tumor is notorious for being confused with adenocarcinoma of the lung (ie, slender microvilli as opposed to short, blocked microvilli in adenocarcinoma).[13]

The median survival of the disease is 4 to 12 months after diagnosis and 8 to 14 months after development of symptomatology. As far as therapy goes, surgery is still considered to be possibly curative with a solitary lesion. The surgical procedure is technically very difficult for diffuse mesothelioma. An attempted curative procedure called pleurectomy has relatively high mortality (in the range of about 20 percent) and is thought not to significantly prolong survival.[14]

Radiotherapy is highly palliative therapy for effusion and perhaps delaying of superior vena cava syndrome. It has been shown that high doses of radiation, about 4,500 rads, have increased median survival by about 15 months.[15] Most studies have not shown prolonged survival at doses lower than 4,500 rads. Radioactive compounds can be instilled early prior to adhesions for the pleural or peritoneal mesotheliomas.

Extensive data has not yet been reported for chemotherapy, but the two single most important agents have been shown to be doxorubicin hydrochloride (Adriamycin) and cyclophosphamide (Cytoxan). Best results have been with surgery combined with radiotherapy and chemotherapy.[16] The median survival ranges from 12 to 24 months.

In conclusion, malignant mesothelioma is only one of the vast array of occupational diseases. Fortunately, not all of them are as deadly as this particular disease. This Grand Rounds should emphasize that a simple occupational history, including not only the patient's current occupation but also previous occupations, will serve the physician and the patient well.

The following recommendations are in order with regard to early diagnosis: (1) an annual chest x-ray examination, which early on can detect pulmonary fibrosis with pleural thickening and a gradual decrease in lung volume,[17] and (2) serial pulmonary function testing. In the patient known to have current or ongoing exposure, you might want to screen somewhat more frequently and get an interpretation by someone experienced in this field. Pulmonary function tests on this disease show decreased lung volume, impaired gas exchange, with hypoxemia made worse by exercise, reduced compliance, and low pulmonary diffusion capacity with the absence of air flow obstruction.[18]

The role of the family physician can be summarized as follows: (1) awareness of this and other occupationally related diseases, (2) development of a systematic screening and management protocol that should include a complete occupational history, radiographic studies on a periodic basis, serial pulmonary function testing with interpretation by an experienced person, (3) early referral, and (4) a strong supportive program for the patient and his family, which is equally as important as the management of the disease.

Are there questions?

DR. THOMAS MILHORN *(Assistant Professor of Family Medicine)*: Have companies such as Ingalls, employing people working with asbestos, developed a screening protocol after learning of the problems we have heard today?

DR. CAMPBELL: No, not that I am aware of.

DR. GLADFELTER: There has been a lot of publicity about the association of this tumor and asbestos. But, as illustrated in this case, the patient himself was not alarmed with all the publicity. Are you aware of any government program actively screening people who had been exposed to asbestos?

DR. CAMPBELL: As far as I know, there is no funded or active screening similar to the "black lung" program.

Again, I think probably most important is that at some point these folks are going to come in with various other complaints; this is the stage at which the family physician can actually intervene and have an impact.

DR. SHERRI LONG *(Assistant Professor of Family Medicine)*: The screening procedure is very interesting, but I wonder, with the present prognosis of this disease, is it cost effective? Are we able to catch it early enough so that patients will have more than six months to live?

DR. CAMPBELL: Malignant mesothelioma is not the only occupationally related disease. There

Continued on page 840

Continued from page 837

are other asbestos related diseases that do not carry such a grave prognosis, for instance, pulmonary fibrosis. Patients with this disease have higher morbidity and mortality with pulmonary infection and would benefit from treatment. Other diseases, such as bronchogenic cancer, colorectal cancer, and otopharyngeal cancer may also benefit from early recognition,[7] and it is hoped that with earlier diagnosis alone we can improve the survival rate.

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