YALE JOURNAL OF BIOLOGY AND MEDICINE 74 (2001), pp. 159-163.

CASE REPORT

A Case of Pleural Mesothelioma with Effusive-Constrictive Pericarditis

Nargues A. Weir[a] and Brett Gerstenhaber

Division of Pulmonary and Critical Care, Department of Medicine, Yale School of Medicine, New Haven, Connecticut

INTRODUCTION

Mesothelioma infrequently causes pericardial constriction and rarely symptomatic pericardial tamponade. Most commonly, a primary pleural malignancy will extend locally, but primary involvement of pericardium is also well-recognized. However, pericardial fibrosis in conjunction with pleural mesothelioma has not been described before in the literature. We report a case of pleural mesothelioma with simultaneous development of benign effusive-constrictive pericarditis.

CASE REPORT

S.H., a 76-year-old man, presented for consultation after the incidental finding of a pleural effusion. In preparation for a hip replacement, a chest radiograph was performed revealing a moderate sized left-sided effusion. He denied any history of pneumonia, bronchitis, asthma, tuberculosis, cough, hemoptysis, weight loss, orthopnea, or paroxysmal nocturnal dyspnea. His past medical history was significant for a left carotid endarterectomy, peripheral vascular disease, and bilateral knee replacements. Medications included chlorthalidone and occasional alprazolam. He denied allergies to any medications. Social history was significant for a remote history of smoking (40 pack years) and moderate daily alcohol consumption. He was a retired telephone installer and denied any known exposure to occupational inhalants. His family history was significant for two siblings dying from cancer (patient did not know the primary sources) and one sibling dying from a myocardial infarction.

Physical examination revealed a well-nourished, afebrile man with a pulse of 94, blood pressure of 150/90 mmHg, and a respiratory rate of 14 breaths per minute. The head and neck examination were normal, most notably for the absence of neck vein distention and lymphadenopathy. Dull breath sounds were heard over the left lung base with decreased tactile fremitus and absent egophony. The remainder of the cardiopulmonary examination was otherwise

[a] *To whom all correspondence should be addressed:* Nargues A. Weir, M.D., Division of Pulmonary and Critical Care, Department of Medicine, Yale School of Medicine, 333 Cedar Street, LCI 105, P.O. Box 208057. Tel.: 203-281-7037. E-mail: narguesnscottweir@msn.com.
[b] *Abbreviations:* CT, computed tomography.
Received: Received: February 1, 2001; Accepted: April 18, 2001.

unremarkable. The abdominal, extremity and neurological examinations were also unremarkable.

Laboratory evaluations revealed a white blood cell count of 8.10 K/ul, with 58 percent granulocytes, 33 percent lymphocytes, and 5 percent monocytes. Hemoglobin was 13.8 g/dl, and the platelet count was 520 K/ul. Hematologic indices were significant for a mean corpuscular volume of 94 fl, red blood cell distribution width of 15.2 percent, and a sedimentation rate of 66 mm/hr. Coagulation, urinalysis and chemistry studies were normal, with the exception of an alkaline phosphatase of 100 U/l (reference range 36-92). Thyroid studies were also within normal ranges. Electrocardiogram showed a normal sinus rhythm, normal intervals and axis, with an inverted T wave in lead III, which was unchanged from prior studies. A chest radiograph showed enlargement of the cardiac silhouette, bilateral pleural effusions left considerably larger than the right, and pleural thickening. A persantine thallium scan showed a small inferobasilar defect without ischemia.

At thoracentesis of the left chest, 500 ml of serosanguinous fluid were removed; analysis of the fluid demonstrated 2,100 RBC's, 5,100 white blood cells (80 percent lymphocytes, 12 percent granulocytes), lactate dehydrogenase of 307 U/l (fluid/serum ratio of 1.88), protein 4.5 g/dl (fluid/serum ratio of 0.625), and glucose 111 mg/dl. Gram stain and acid fast smear were negative, and cultures failed to grow any organisms. Cytopathology was negative for malignant cells. A computed tomogram of the chest was obtained which revealed pleural thickening and calcification without any masses or significant adenopathy. The patient again denied any history of exposure to asbestos, but

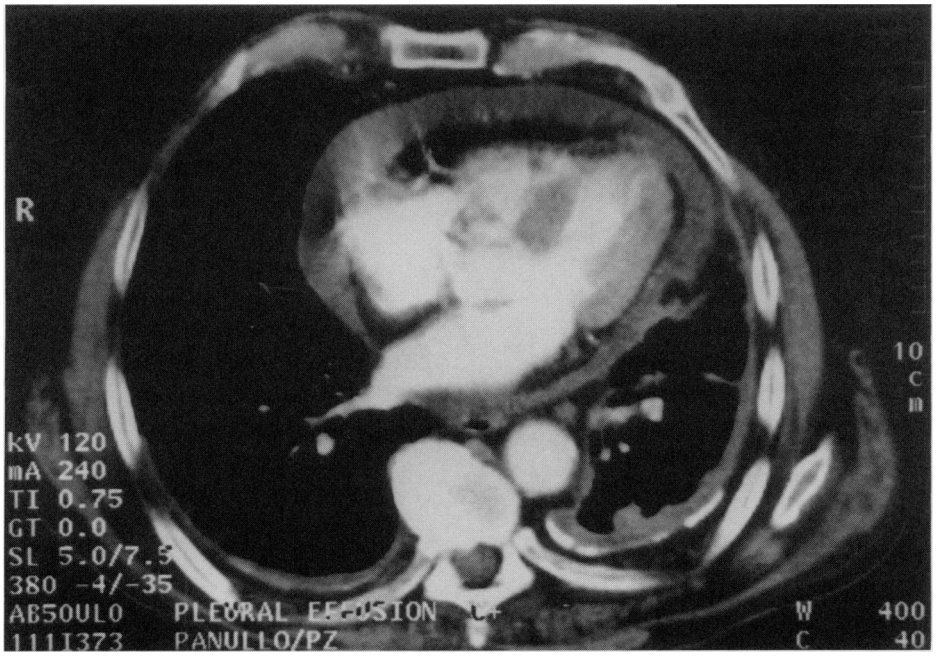

Figure 1. Left pleural thickening with a rounded pleural mass suggestive of a pleural malignancy. Calcifications within the pleura indicate prior exposure to asbestos. Pericardial thickening and effusion are also noted.

nevertheless was felt to most likely have had a benign asbestos-related effusion given the pleural abnormalities on the computed tomography (CT)[a] scan.

S.H. was followed serially with physical examination and chest radiographs. The pleural effusions did not reaccumulate and he remained asymptomatic. Two years later, he was admitted to hospital for new onset atrial fibrillation with liver enzyme abnormalities. He now reported dyspnea on exertion, peripheral edema, and weight loss. A repeat chest CT scan (Figure 1) at that time showed a new right-sided pleural effusion with a moderate sized pericardial effusion. Physical examination was now remarkable for an irregular pulse of 60, blood pressure of 110/60 mmHg, respiratory rate of 22 breaths per minute, distended neck veins without Kussmaul's sign, distant heart sounds without a diastolic knock, hepatomegaly without ascites, and moderate pedal edema. Electrocardiogram now showed diffuse nonspecific T wave abnormalities with diminished voltage. Echocardiogram demonstrated the pericardial effusion without right heart compromise. Both visceral and parietal pericardium were thickened with fibrinous stranding, and a thick pericardial peel adherent to the surface of the epicardium was noted.

The patient's dyspnea improved with diuresis, anticoagulation, and rate control. A right and left heart catheterization revealed elevated pressures in all chambers and equalization of diastolic pressures. A coronary arteriogram showed minimal three-vessel disease with preserved left ventricular systolic function.

With the diagnosis of constrictive pericarditis and persistence of pleural effusions, there was rising concern for mesothelioma of the pleura and pericardium. An open video-assisted thoracoscopy and pericardial biopsy were performed, with creation of a pericardial window. The pathologic evaluation of the parietal pleura was consistent with malignant mesothelioma, but the pericardial tissue showed only chronic inflammation and fibrosis. The pericardial fluid was bloody, and cytologic examinations demonstrated reactive mesothelial cells without malignant features. Concomitant biopsies of the peritoneum and diaphragm also failed to show malignancy.

Clinically, S.H. continued to deteriorate steadily. Treatment with chemotherapy and/or radiation was declined, and S.H. died three weeks later of respiratory insufficiency.

DISCUSSION

Mesothelioma is a well recognized malignancy of mesodermal tissue. It commonly affects the pleura and peritoneum, and less commonly the pericardium. The association between asbestos exposure and mesothelioma was first alluded to in the 1940s. Later observations of the higher incidence of mesothelioma in workers exposed to asbestos solidified this association. A rising incidence of this malignancy is now seen due to the latent development of the disease after exposures 20 to 40 years ago. The most common reaction to asbestos is pleural plaque formation seen 20 years or longer after exposure [1]. Pleural effusions are seen less commonly. The effusions are typically exudative and bloody [2]. A similar response may occur in the pericardium. The latter reaction was first noted in the 1950s, when Beck's procedure was performed for myocardial revascularization. The operation entailed opening the pericardial sac, scoring the epicardial layer and sprinkling asbestos onto the epicardium in hopes of generating collateral circulation. A fibrotic reaction then ensued, occasionally creating a constrictive pericardium [3, 4]. More recently, several cases of occupational asbestos exposure have been described that have also resulted in constrictive pericarditis [5, 6]. Our patient had a bloody

pleural effusion in the setting of calcified pleural plaques, thrombocytosis, and an elevated sedimentation rate. Initially, his history, physical examinations, radiographs and laboratory results of the pleural fluid ruled out other plausible causes of exudative effusion. He was diagnosed with a benign asbestos-related effusion, and for two years, he showed no further evidence of pleural disease. Subsequently, he developed dyspnea and failure to thrive. He demonstrated recurrent pleural effusions, and malignancy was confirmed by an open biopsy. He eventually died from constrictive pericarditis which was surprisingly not of malignant etiology.

The finding of pericardial constriction and cardiac tamponade has previously been described in case reports of patients with pleural mesothelioma [7]. However, those reports have always shown the constriction due to local invasion from the pleural primary malignancy, not from benign fibrosis of the pericardium itself. Asbestos-induced involvement simultaneously of the pleura and pericardium is frequently due to either an effusive-constrictive reaction [6] or due to mesothelioma with local extension [8]. Mesothelioma usually develops within the pleura and grows contiguously, although hematogenous and lymphatic metastases are possible. It is unusual to see, however, a mesothelioma and benign fibrotic reaction together (although mesotheliomas can be associated with an intense desmoplastic reaction).

Our patient had clear evidence of pleural mesothelioma on biopsy, with a likely related benign effusive-constrictive pericarditis. Even though an autopsy was not performed, the open biopsy of the pericardium with sampling of all related tissues and fluid failed to offer an alternate explanation. Cultures of the tissue and fluid failed to demonstrate an infectious etiology for the fibrosis. It is conceivable that the pericardium was invaded by the mesothelioma, and the fibrosis seen in the biopsied tissue was due to a local desmoplastic reaction to malignant invasion. Perhaps autopsy would have proven this. However, the pericardial biopsies showed chronic inflammation, and the parietal pleura showed an epithelial mesothelioma without fibrotic reaction. The only case reported in the literature that is similar to ours was by Yilling and co-workers in 1982. They described a case of primary pericardial mesothelioma with benign reactive fibrosis of the pleura [9].

A review of several series of patients with pleural mesothelioma also failed to reveal any mixed reactions to asbestos as described in our patient. Roberts reviewed 32 cases of pleural mesothelioma in 1976. Involvement of the heart occurred in six percent of their series, specifically pericardial and epicardial involvement by tumor without benign fibrosis [10]. Chahinian and co-workers in 1982 published a prospective evaluation of 69 patients with mesothelioma [11]. The pericardium was replaced by tumor in 12 percent, and the heart was invaded in 4 percent of their patients. None had benign fibrotic involvement. Ruffie and co-workers in 1989 reviewed 332 patients with pleural mesothelioma [12]. In their series, 49 percent of patients had pericardial involvement at autopsy, and 5 percent died from pericardial constriction or tamponade. The pericardial involvement, however, was not described as a fibrotic or benign process. Two other series of 140 and 180 patients, respectively, with pleural mesothelioma did not find pericardial involvement [13, 14].

The pericardium can rarely be the primary source of mesothelioma. Although several cases have described this subtype of mesothelioma [15, 7], the incidence is likely lower than case reports would have us believe given the definition of a true primary pericardial mesothelioma, as

described by Anderson and Hansen in 1974 [16]. In conclusion, we report a unique case of asbestos-related bloody pleural effusions with later development of pleural mesothelioma. The patient's death, however, was due to a benign effusive-constrictive pericarditis, more likely than not caused by asbestos.

ACKNOWLEDGEMENT: *We would like to thank Dr. Richard A. Matthay for his assistance in completing this paper.*

REFERENCES

1. Ehler, G.R., McLoud, T.C., and Gaensler, E.A. Prevalence and incidence of benign asbestos pleural effusion in a working population. JAMA. 247:617-622, 1982.
2. Rom, W.N. Asbestos-related lung disease. In: *Fishman's Pulmonary Diseases and Disorders*. New York: McGraw-Hill Companies; 1998, pp. 1422-1426.
3. Weg, J.G. A 77-year-old man with progressive dyspnea on exertion. Chest 113:521-522, 1998.
4. Fraker, T.D., Walsh, T.E., Morgan, R.J., and Kim, K. Constrictive pericarditis late after the Beck operation. Am. J. Cardiol. 54:93, 1984.
5. Davies, D., Andrews, M.I.J., and Jones, J.S.P. Asbestos induced pericardial effusion and constrictive pericarditis. Thorax 46:429-432, 1991.
6. Fischbein, L., Namade, M., Sachs, R.N., Robineau, M., and Lanfranchi, J. Chronic constrictive pericarditis associated with asbestosis. Chest 94:646-647, 1988.
7. Meysman, M., Noppen, M., Demeyer, G. and Vandincken, W. Malignant epithelial mesothelioma presenting as cardiac tamponade. Eur. Heart J. 14:1576-1577, 1993.
8. Churg, A., Warnock, M.L., and Bensch, K.G. Malignant mesothelioma arising after direct application of asbestos and fiber glass to the pericardium. Am. Rev. Resp. Dis. 118:419-424, 1978.
9. Yilling, F.P., Schlant, R.C., Hertzler, G.L., and Krzyaniak, R. Pericardial mesothelioma. Chest 81:520-523, 1982.
10. Roberts, G.H. Distant visceral metastases in pleural mesothelioma. Br. J. Dis. Chest 70:246-250, 1976.
11. Chahinian, A.P., Pajak, T.F., Holland, J.F., Norton, L., Ambinder, R.M., and Mandel, E.M. Ann. Int. Med. 96:746-755, 1982.
12. Ruffie, P., Feld, R., Minkin, S., Cormier, Y., Bouton-Laroze, A., Ginsberg, R., Ayoub, J., Shepherd, F.A., and Evans, W.K. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. J. Clin. Oncol. 7:1157-1168, 1989.
13. Law, M.R., Hodson, M.E., and Turner-Warwick, M. Malignant mesothelioma of the pleura: clinical aspects and symptomatic treatment. Eur. J. Resp. Dis. 65:162-168, 1984.
14. Antman, K., Shemin, R., Ryan, L., Klegar, K., Osteen, R., Herman, T., and Lederman, G. Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and the Brigham and Women's Hospital experience over two decades, 1965-1985. J. Clin. Oncol. 6:147-153, 1988.
15. Llewellyn, M.J., Atkinson, M.W., and Fabri, B. Pericardial constriction caused by primary mesothelioma. Br. Heart J. 57:54-57, 1987.
16. Anderson JA, Hansen BF. Dan. Med. Bull. 21:195-200, 1974.