2. Higher-power photomicrograph of Fig 1 to show histiocytic macrophages with "foamy" cytoplasm in intima and media. Note also prominence of plasma cells (*arrows*) in leukocytic exudate in artery wall (hematoxylin and eosin, ×400).

Comment

Microscopic abnormalities occurring in the renal vessels of rejected human transplanted kidneys have been well described.[1-3] These changes seem to be confined to the interlobular, arcuate, and interlobar arteries and arterioles, and vary with the length of survival and with vessel size. In the early stages, these lesions consist of a diffuse inflammatory cellular infiltrate made up chiefly of plasma cells and lymphocytes, necrosis of the media, and occasional fibrinoid necrosis of the vessel wall with fibrinous deposit on the intima.[3] In patients surviving a longer period, 25 to 28 days, the vascular damage is more pronounced and more vessels are involved, with the main renal artery spared. At this time the changes consist of medial necrosis, fibrinoid necrosis, and intimal thickening. In addition, the intima contains large vacuolated phagocytic cells which are distinctive, possibly plasma-cell derivatives, and peculiar to this type of rejection phenomenon.[3]

In the ureteral arteries of the two patients herein reported, severe vascular abnormalities were noted. These lesions are similar to those previously described in renal arteries in transplant rejection.[1-3] Rejection of the ureter may contribute to the physiological failure of the renal transplant.

The ureteral vascular changes followed closely after transplantation and consisted of focal round-cell infiltration of the vessel wall, fibrinoid degeneration of the intima, and focal medial necrosis (case 1). In the second patient, who survived for a longer period of time (20 days, case 2), the vascular abnormalities in the ureter consisted of intimal proliferation and degeneration, focal histiocytic infiltration of the media and intima, and medial necrosis. Infiltration of the artery wall by histiocytes with foamy cytoplasm (Fig 1) appears to be unique to the human renal transplantation rejection mechanism.[3] These cells are large, have vacuolated cytoplasm which does not stain with the PAS reagent, and have small, ovoid, eccentrically placed nuclei. Their origin may be from plasma cells.[3]

Summary

Degenerative changes were present in the ureteral arteries in two patients who died after having undergone renal transplantation. These abnormalities are similar to those present in arteries in the kidney. The renal vascular rejection process has been previously described, whereas vascular rejection in the human ureter has not. Round-cell infiltration and focal necrosis of the media is present in ureteral arteries in early rejection. Later findings include medial necrosis and infiltration of the media and intima with large vacuolated histiocytes and leukocytes. The histiocytes appear to be peculiar to the homotransplant rejection phenomenon.

Generic and Trade Names of Drugs

Azathioprine—*Imuran.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*
Chloramphenicol—*Chloromycetin.*

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Benign Asbestos Pleurisy

H. B. Eisenstadt, MD

THE classical picture of asbestosis has been divided into several stages.[1] At first, there is a latent period of ten or more years during which asbestos bodies are formed around the asbestos fibers. During this time the patient is completely asymptomatic, and results of his chest x-ray are normal. This stage is followed by the gradual appearance of respiratory symptoms in the form of dyspnea, cough, expectoration, and wheezing; the roentgenologist finds bilateral pulmonary fibrosis. As the disease advances, systemic complaints are added, such as fatigue, malaise, weakness, anorexia, and weight loss. Final-

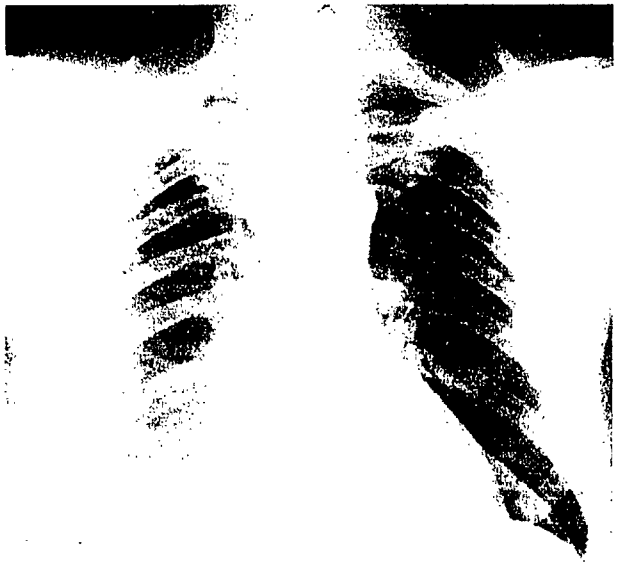
See also page 371.

From the Medical Clinic, Port Arthur, Tex.
Reprint requests to 2301 Procter St, Port Arthur, Tex (Dr. Eisenstadt).

ly, extensive destruction of lung tissue leads to respiratory and cardiac failure.

It is well known that pleural abnormalities are commonly found in asbestosis. Most experts believe that they are associated only with advanced pulmonary disease; others describe them as secondary complications or even as coincidental lesions not directly connected with asbestos inhalation.[2]

In contrast to these observations we have been able to find a small number of patients with asbestosis who present primarily the clinical picture of pleurisy in the absence of any significant pulmonary disease or respiratory dysfunction.



1. Benign pleural asbestosis (case 2).

2. Malignant mesothelioma of pleura producing rib destruction. Note pleural calcifications.

Report of Cases

CASE 1.[3]—In September 1960, a 54-year-old insulator in contact with asbestos for 15 years suffered from a left-sided pleurisy. His chest x-ray revealed a small effusion. Because he had little discomfort, no thoracentesis was done, and he was treated conservatively.

However, in March 1961, a similar attack occurred on the right side. At this time, chest pain, cough, malaise and fever were quite severe, and a friction rub was noted. A thoracentesis yielded 500 cc serous fluid with 4% protein and many lymphocytes; however, neither malignant cells nor microorganisms were encountered. The course was prolonged, and finally an exploratory thoracotomy was done. The visceral pleura was as thick as an orange peel, and the pleural cavity was partly obliterated. Fibrous and hyaline plaques covered the parietal pleura. The pathologist described large deposits of dense connective tissue in the pleura with inflammatory cell infiltration. A lung section revealed thickening of the alveolar walls with macrophages and asbestos bodies.

CASE 2.—A 58-year-old white male, working with asbestos for 12 years was seen in consultation because of right-sided pleural effusion (Fig 1). The disease had been present for three weeks and had caused chest pain, fever, cough, and dyspnea. Asbestos bodies in the sputum, a moderate leukocytosis, a fast sedimentation rate, and a positive latex test for rheumatoid arthritis were the only abnormal laboratory findings. Tests for tuberculosis and fungi gave negative results. A total of 30 cc of a blood-tinged exudate was removed by thoracentesis. Two weeks later a thoracotomy, done because of persistent symptoms, revealed pleural plaques and adhesions. A lung specimen, taken in addition to the pleural biopsy, showed asbestos bodies. After decortication and partial pleurectomy, the patient became asymptomatic, and results of his chest x-ray were normal. Eight months later the patient was seen again because of fever and chest pain due to a left-sided pleural effusion. He was treated symptomatically and had completely recovered one month later.

Two cases of malignant mesothelioma, obviously preceded by benign pleurisy, have been observed.

CASE 3.—A 57-year-old refinery foreman,[6] exposed to asbestos for a decade, was treated intermittently 12 years for a severe pain in the hemithorax on the left. He had no abnormal findings. One day, a routine chest x-ray revealed a spontaneous pneumothorax with a small pleural effusion. Because of persistent symptoms a thoracotomy was done which showed pleural thickening, plaques, and adhesions. The correct diagnosis was not established until a year later when, during a barium x-ray of the colon, osteolytic lesions were discovered in the left lower side of the thorax. At this time, malignant mesothelioma was found in the bone specimen. The patient obviously had suffered from benign pleural asbestosis for about 12 years before the development of his malignancy. This case was unusual inasmuch as a spontaneous pneumothorax was the first objective evidence of disease. This complication is rare but has been reported in association with benign[7] as well as malignant asbestosis.

CASE 4.—In 1959, a 58-year-old foreman[8] who had supervised asbestos insulation for three decades was found to have a malignant mesothelioma of the pleura on the left side. Ten years earlier he had been hospitalized for bilateral pleural effusions. The diagnosis of tuberculosis was entertained at this time but could never be proved. He had been under constant medical supervision because of the appearance of streak-like pleural calcification following his attack of pleurisy (Fig 2). His autopsy showed benign asbestosis in all portions of the pleura not involved by the malignancy. Similar case histories have been found in the literature dealing with asbestos and mesothelioma.[4]

However, nowhere has the benign disease of the pleura been recognized properly.

Comment

The pathogenesis and the pathological findings of benign asbestos pleurisy do not differ fundamentally from those of classical asbestosis. Mechanical irritation or chemical influences may affect the pleura as well as the lung parenchyma. Strangely enough, asbestos bodies have never been seen by us in the pleural tissues. This observation, shared by the majority of the investigators,[4] in no way excludes asbestos as the causative agent. In addition, the sudden appearance of a unilateral or bilateral pleural effusion after many years of exposure is more suspicious of a sensitivity response than of a direct local toxic reaction.

The clinical, laboratory, and x-ray picture of pleural asbestosis does not differ significantly from that of any other form of pleural disease. The pleurisy may be acute, subacute, or chronic; dry, serous, or hemorrhagic; unilateral, or bilateral. The appearance of an effusion on one side followed sooner or later by a similar one on the other seems to be most characteristic of asbestosis. Streak-like and patchy pleural calcifications on the x-ray films have been known to be associated with various silicatoses for a long time.[5] Their presence may be helpful in the diagnosis of asbestosis; however, they can be seen in asymptomatic patients, and are frequently absent at the time of active pleuropulmonary disease.

The history of prolonged exposure to asbestos dust is of greatest diagnostic significance. However, due to the secrecy of the various manufacturing processes the use of asbestos is not always known to the workmen nor to their physicians. Insulators, pipefitters, and boilermakers who frequently come in contact with this material may be under suspicion whenever respiratory disorders develop in them. Unfortunately, many workers have changed jobs long before symptoms of active asbestosis appear.

In the absence of any specific laboratory test the final diagnosis can only be established by thoracotomy. Fibrous, hyaline and calcified plaques, and a remarkable thickening of the pleura with pleural symphysis are highly suspicious to the experienced pathologist. However, the presence of asbestos bodies in the pulmonary parenchyma with or without fibrosis has been generally accepted as the final criterion of asbestos disease.

The differential diagnosis of asbestos pleurisy has to exclude tuberculosis, which has an almost identical course, and x-ray and laboratory appearance. In addition, several other pathological entities present a similar clinical picture and can only be distinguished after exploration. The old dictum, "idiopathic pleurisy is tuberculous unless proven otherwise," has often prevented a correct differentiation.

The prognosis of benign pleural asbestosis is generally favorable. The disease is usually self-limited and disappears within a period of weeks or months. However, sometimes the course is prolonged and occasionally, as demonstrated in cases 3 and 4, it is followed by pleural malignancy.

Due to its self-limited course, asbestos pleurisy requires only symptomatic therapy. In the past, the recovery of the patient has probably been erroneously attributed to antibiotics and antituberculous drugs administered because of suggestion of infectious etiology. In recurrent and chronic pleural asbestosis, steroids may be of value for the anti-inflammatory and antifibrotic effect. If none of the conservative methods are successful in the prolonged cases, pleurectomy should be recommended in order to avoid the development of malignancy.

At a recent conference on asbestosis of the New York Academy of Science, C. Berkley, J. Churg, W. E. Smith, and I. J. Selikoff[9] have been able to demonstrate isolated asbestos fibers with the help of fluorochrome tagging and after electronic ashing in tissues not containing asbestos bodies. It is hoped that these new procedures may further clarify the pathogenesis of pleural asbestosis. We have observed cases of benign idiopathic pleurisy as well as malignant mesothelioma among the same group of asbestos workers where the diagnosis of asbestosis could not be established because of absence of asbestos bodies.

Summary

The clinical picture of benign asbestos pleurisy differs greatly from that of classical asbestosis. It may occur in the absence of significant pulmonary disease and respiratory dysfunction. This entity must be considered in the differential diagnosis of any form of idiopathic pleurisy. The history of exposure to asbestos will aid in directing the attention to this entity; however, the final diagnosis depends on a lung tissue specimen containing asbestos corpuscles or asbestos fibers.

E. C. McRee, MD, Port Arthur, Tex, gave permission to publish case 1.

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