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Asbestosis and Neoplastic Disorders of the Hematopoietic System

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Abstract. Gerber, Michael A.: Asbestosis and neoplastic disorders of the hematopoietic system. Am. J. Clin. Path. 53: 204–208, 1970. Five cases of asbestosis associated with tumors of the hematopoietic system in a series of 35 cases of asbestosis proved by autopsy are reported. Two were cases of multiple myeloma; two, myeloproliferative disorders, including a case associated with reticulum-cell sarcoma; one, Waldenstrom's macroglobulinemia. The incidence of this association is significantly higher than the overall incidence of such disorders in the corresponding age group of patients without asbestosis.

BEGINNING in 1935 with the reports of Lynch and Smith[7] and of Gloyne[4] a large body of data on the association of asbestosis with cancer of the lung has accumulated. Wagner,[16] Webster,[17] and Selikoff and associates[12] have drawn attention to the striking correlation between asbestosis and mesothelioma of the pleura and peritoneum. The increased incidence of carcinomas of the gastrointestinal tract in persons with asbestosis has been reported by Hammond and associates.[5] The purpose of this paper is to bring to attention the association of asbestosis with tumors of the hematopoietic system. During a period of 11 years, five such cases were encountered in the autopsy experience of a single hospital.

Report of Cases

Case 1

A 54-year-old Caucasian male machinist was admitted because of generalized weakness, marked weight loss, and chest pain of two months' duration. Biopsy of the left hip, performed one month previously, had shown multiple myeloma. On physical examination the patient was poorly-nourished, weak, and anemic. The hemoglobin was 7.68 Gm. per 100 ml. There were areas of swelling and tenderness over the right chest laterally and over the left lower ribs posteriorly. Roentgenographic examination showed partial destruction of several ribs bilaterally. The liver, spleen, and lymph nodes were not palpable. The urine contained 1+ albumin. The patient died 12 days after admission.

Autopsy findings. The lungs contained moderate fibrosis with asbestos bodies and anthracotic pigment, as well as bullous emphysema. There was slight hypertrophy of the right ventricle of the heart. The leaves of the diaphragm contained a few large pearly-white dense hyaline plaques. The vertebrae showed extensive destruction by compact masses of fairly mature myeloma cells.

Final diagnoses: 1) multiple myeloma with destruction of vertebrae and ribs; 2) pulmonary asbestosis with secondary bullous emphysema and hyaline plaques of diaphragmatic pleura; 3) hypertrophy of the right ventricle of the heart.

Case 2

A 69-year-old Negro man with an occupational history of 12 years as a miner (phosphate) and eight months as a laborer in an asbestos plant was admitted because of productive cough, shortness of breath, weakness, and weight loss. Physical examination disclosed marked clubbing of the fingers and signs in the right upper lung consisting of dullness, increased vocal fremitus, and absence of breath

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sounds. The hemoglobin was 10 Gm per 100 ml., hematocrit 32%, leukocyte count 5,100 with a normal differential. The sedimentation rate was 28 mm. per hr. Urinalysis revealed moderate proteinuria and pyuria. Other laboratory tests disclosed no abnormalities.

Roentgenogram of the chest showed atelectasis of the right middle lobe and base of the right upper lobe. Bronchoscopy revealed a tumor at the orifice of the right-upper-lobe bronchus. Biopsy disclosed highly anaplastic epidermoid carcinoma. The tumor was regarded as inoperable. The patient died four months after admission.

Autopsy findings. The parietal pleura contained numerous hyaline plaques bilaterally. There was a fist-size tumor in the area of the hilus of the right lung, causing partial obstruction of the right main bronchus. Histologic study confirmed the biopsy findings of a highly anaplastic epidermoid carcinoma. Disseminated fibrosis containing asbestos bodies was found in the pulmonary tissue. The right ventricle was hypertrophied. The liver weighed 1,270 Gm. Microscopically, the portal fields were found to contain diffuse plasma-cell infiltration. The spleen weighed 100 Gm. Microscopically, the splenic trabeculae and blood vessels were found to be infiltrated diffusely by large numbers of plasma cells. Much hemosiderosis was present. Both adrenals contained scattered nodules of metastatic carcinoma. The kidneys appeared unremarkable grossly. Microscopic examination disclosed dense deposits of plasma cells within the stroma and hyaline alteration of the media of veins, suggestive of amyloid. The bone marrow was partially replaced by compact homogeneous infiltrations of plasma cells.

Final diagnoses: 1) anaplastic epidermoid carcinoma of the right main bronchus with metastases to both adrenal glands; 2) plasma-cell myelomatosis with diffuse infiltration of bone marrow, liver, spleen and kidneys*, 3) pulmonary asbestosis with pleural plaque formation; 4) hypertrophy of the right ventricle of the heart.

Case 3

A 58-year-old Caucasian, male, bank clerk had a history of gouty arthritis, proved histologically in 1962. In 1965 he was admitted to the hospital because of progressive mental confusion, severe left temporal headache, and attacks of syncope. The liver was palpable 10 cm. below the costal margin. Neurologic examination showed right hemiparesis. Laboratory tests gave essentially normal results except for elevated blood uric acid (11 mg. per 100 ml.) and a weakly positive Latex test for rheumatoid factor. A brain tumor was suspected and proved by cerebral arteriography. Craniotomy was performed and a hemorrhagic, partly-necrotic tumor was excised from the left frontal lobe. Microscopic examination indicated a poorly-differentiated microglioma (reticulum-cell sarcoma). Eight days postoperatively the patient died.

Autopsy findings. Remnants of the left frontal lobe of the cerebrum contained an infiltrating tumor composed of medium-sized cells with large round, oval, or lobulated, hyperchromatic nuclei, occasionally having giant-cell characteristics, and minimal cytoplasm. The neoplastic cells were clustered most densely about blood vessels. The adrenal glands were markedly enlarged weighing 36 and 42 Gm., and the cells in them had been almost totally replaced by tumor cells identical to those in the brain, which had infiltrated freely into the surrounding adipose tissue. The liver weighed 2,560 Gm., showing on section pale brown-tan parenchyma with somewhat obscured lobular architecture. Histologic examination disclosed extensive infiltration of the portal fields and adjacent parenchyma by proliferating myeloblasts, myelocytes, granulocytes, plasma cells, and lymphocytes. The spleen weighed 1,140 Gm., and contained hyperplasia of the reticulum framework and widespread myeloid metaplasia including megakaryocytes and myeloblasts. The endothelium of the large veins had been replaced by leukemic cells. The vertebral bone marrow was hypercellular, with a cell–fat ratio of approximately 5:1, and contained an abundance of large atypical megakaryocytes and many primitive cells resembling myeloblasts. There were scattered areas of early fibrosis. Examination of the lungs showed severe chronic bronchitis and patchy interstitial fibrosis containing occasional asbestos bodies accompanied by much anthracotic pigment. The leaves of the diaphragm and the parietal surfaces of both pleural cavities posteriorly were covered with extremely hard, gray-white plaques of avascular hyaline scar tissue.

Final diagnoses: 1) a myeloproliferative disorder involving the liver, spleen, and bone marrow†; 2) reticulum-cell sarcoma with massive involvement of the brain and adrenals†; 3)

* Confirmed by S. E. Moulton, M.D., New Brunswick, N. J.

† Confirmed by AFIP, kindness of Dr. Bruce H. Smith (Captain USN).

asbestosis with pleural plaques; 4) tophaceous gout, secondary.

Case 4

An 82-year-old Caucasian newspaper reporter was admitted in January 1969 because of a subtrochanteric fracture of the right femur and hypertension. He had worked as a tile manufacturer for several years until 10 years previously. On several previous admissions following an attack of gout in 1958 polycythemia vera had been diagnosed. The patient developed thrombosis of several digital arteries in 1962, cerebrovascular insufficiency in 1966, epistaxis in January 1967, and upper gastrointestinal bleeding in October 1967. He was treated with phlebotomies and several injections of radioactive phosphorus (^{32}P). In 1964 he underwent segmental resection of the sigmoid for villous adenoma.

Physical examination revealed mild hepatosplenomegaly. The hemoglobin was 12 Gm. per 100 ml., hematocrit 43%, leukocyte count 176,000 with 96% neutrophils and occasional hypersegmented cells. The reticulocytes were 2.4%; platelets, 632,000. Other laboratory tests gave essentially normal results except for elevation of blood uric acid (11.2 mg. per 100 ml.). Roentgenogram of the chest revealed diffuse pulmonary emphysema and fibrosis and slight cardiomegaly. Hip-pinning was performed. The patient died suddenly the following day.

Autopsy findings. The brain contained several small old cystic infarcts in the white matter and diffuse ischemic nerve cell change. The lungs were grossly emphysematous and showed patchy interstitial fibrosis histologically. Numerous megakaryocytes were impacted within the pulmonary capillaries. Occasional asbestos bodies were observed in the wet preparation of ground ‡ lung tissue. The parietal pleura of the posterior thoracic wall and diaphragm contained several large white hyaline plaques. The heart weighed 450 Gm. and the left ventricle was moderately hypertrophied. The liver weighed 1,400 Gm.; microscopic examination disclosed centrilobular necrosis and a few megakaryocytes within its sinusoids. The spleen weighed 800 Gm. and contained a firm, red-brown, well-circumscribed nodule 4 cm. in diameter. Histologic examination proved this to be a hamartoma characterized by thick Billroth cords with relatively few trabeculae and no lymphoid follicles. The remaining splenic tissue contained scattered small foci of extramedullary hematopoiesis composed largely of erythroid and myeloid precursors accompanied by a few hyperchromatic megakaryocytes within the sinusoids, fibroblastic proliferation, and enormous numbers of lipid-laden histiocytes in the red pulp. The lymphoid follicles were reduced in number and size. Numerous large collections of completely mature granulocytes were found in some fields. The vertebral bone marrow was hypercellular with a fat-to-marrow ratio of 1:9 and contained myeloid hyperplasia with a myeloid–erythroid ratio of 6–8:1 and increased numbers of basophilic and eosinophilic granulocytes and their precursors. Large numbers of megakaryocytes, many of which were immature and atypical, were found. Examination of the blood vessels disclosed subintimal and adventitial fibrosis.

Final diagnoses: 1) a myeloproliferative disorder, manifested predominantly as polycythemia vera with pronounced hyperleukocytosis, 2) pronounced lipoid histiocytosis of the spleen, possibly secondary to platelet phagocytosis; 3) hamartoma of the spleen; 4) pulmonary asbestosis with pleural plaque formation, 5) multiple small old cystic infarcts of the cerebrum; 6) moderate left ventricular hypertrophy; 7) segmental resection of colon for villous adenoma, remote.

Case 5

A 72-year-old Caucasian woman with a two-year history of diabetes mellitus was admitted in 1968 for elective removal of a cataract of the right eye. She had worked from 1924 to 1942 as a pipe coverer in an asbestos plant. On physical examination mild hepatosplenomegaly was found. The patient's serum was extremely viscous with a positive Sia test, total protein 9.5 Gm. per 100 ml., albumin 2.3 Gm. per 100 ml. Ultracentrifugation of serum protein showed an elevation of 19S macroglobulin to 0.7 Gm. per 100 ml. (9.3% of total), atypical macroglobulin, class S 9.7 in the amount of 1.9 Gm. per 100 ml. (25.3% of total), normal 7S globulins, and reduced albumin. Immunoelectrophoretic analysis showed a paraprotein in the gamma-A fraction, decreased gamma-M fraction, and normal gamma G, beta-1C, alpha-2 globulin, beta lipoprotein, and albumin. The hemoglobin was 11.4 Gm. per 100 ml., hematocrit 34%, leukocyte count 7,500 with 56 neutrophils, 37 lymphocytes, 1 eosinophil, 6 monocytes. Platelet count was 125,000; reticulocytes 1.6%; sedimentation rate 4 mm. per hr. Bone marrow examination revealed roulcau formation and atypical lymphocytic and plasmacytoid infiltrate consistent with Waldenström's macroglobulinemia. Skeletal roentgenographic studies showed diffuse osteoporosis. There were no punched-out lesions.

‡ Waring Blender × 30 sec.

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Nineteen days after admission the patient became comatose, developed cyanosis and Biot's respiration, and died the next day.

Autopsy findings. The posterior parietal pleura and both surfaces of the diaphragm contained multiple, pale-gray, hyaline plaques. The lungs were edematous and numerous patches of interstitial fibrosis containing many asbestos bodies were found microscopically. The liver weighed 1,660 Gm. Microscopic examination disclosed nodular transformation of its architecture by an irregular tracery of narrow bands of fibrous tissue heavily infiltrated with lymphoid and plasmacytoid elements. There was no significant bile duct proliferation or fatty infiltration. The spleen weighed 650 Gm. and was markedly congested. Microscopic examination disclosed prominent plasmacytoid infiltration of the trabeculae and perivenous areas. Microscopically, the adrenal glands showed *focal infiltration of* lymphoid and plasmacytoid cells. The lymph nodes, particularly in the periaortic area, were enlarged and congested. Microscopically, the capsule and trabecular cords were found to be infiltrated by lymphocytes and large numbers of mature and immature plasma cells, with occasional binucleate forms. No tumor nodules were found in the vertebrae. The vertebral marrow showed much loss of bony trabeculae, and marked hypercellularity. Section of marrow from a rib revealed occasional nests of lymphoid cells. Direct marrow imprints showed a relative predominance of lymphoid and plasmacytoid cells with occasional binucleate forms.

Final diagnoses: 1) a lymphoproliferative disorder (atypical macroglobulinemia, Waldenström); 2) pulmonary asbestosis with pleural plaque formation; 3) hepatic fibrosis with nodular transformation secondary to lymphoproliferative cellular infiltration.

Discussion

The diagnosis of asbestosis in each of our five cases was based upon pulmonary fibrosis, hyaline plaques upon the parietal pleura, including the leaves of the diaphragm, and the presence of characteristic asbestos bodies in the lungs. In Case 1 and Case 2 the associated malignancy was multiple myeloma. Case 2 was noteworthy for the presence of carcinoma of the lung also. In Case 3 malignant lymphoma was combined with a myeloproliferative disorder. In Case 1 the myeloproliferative disorder was represented by polycythemia vera and splenoma, with terminal extreme hyperleukocytosis. The patient previously had had a surgical operation for villous adenoma of the colon. In Case 5 the clinical picture and cytology of the bone marrow were consistent with Waldenström's disease. The macroglobulin isolated by ultracentrifugation was atypical, as in the cases reported by Kappeler and colleagues.[3]

In the 11 years between February 1, 1958, and January 31, 1969, 37 tumors of the hematopoietic system were found in 1,334 autopsies in patients 50 years old or older at Middlesex General Hospital, comprising 2.8%. In the same autopsy series there were 35 cases of asbestosis, comprising 2.6%. The five cases of asbestosis associated with tumors of the hematopoietic system amounted to an incidence of 14.3%, which is significantly higher than the 2.8% overall incidence of such tumors in the same age group.

A review of the literature reveals several reports of tumors of the hematopoietic system associated with asbestosis. In 1940 Vigliani found one case of mediastinal malignant lymphogranuloma among 76 cases of asbestosis.[15] In a cohort study of employees of an asbestos company, Mancuso found two leukemias among 58 neoplasms in 1963[6] and one lymphosarcoma of the lung among 96 neoplasms in 1967.[7] The most impressive series is that of Lieben, who reported 21 malignant tumors in a study of 68 hospital admissions with asbestosis; among these were two cases of lymphatic leukemia, and one case each of acute leukemia, lymphoblastoma, and multiple myeloma.[4] Selikoff found two malignant lymphomas and one lymphatic leukemia in 380 consecutive deaths among 632 asbestos insulation workers.[11] In addition, one man with proved multiple myeloma is under observation. Our five cases were part of a series of 33 tumors associated with asbestosis.[8]

Incidentally, only three of our five patients were known to have had occupational exposures to asbestos (labor in asbestos plant; tile manufacturing; pipe insulation). The other two presumably belong in the category of asbestosis of unrecognized origin. Asbestos bodies have been found at autopsy in the lungs of a large proportion of males without occupational exposure, the incidence in this country ranging from 25 to 97%.[13, 15, 14]

It is now clear that less intense grades of asbestosis, even minor or trivial ones, cannot be excluded from consideration in the background of these malignant tumors. Duration rather than extent of asbestosis appears to be decisive. An average interval of 38.7 years has been observed between initial exposure to asbestos and death from lung cancer.[15] Less intense grades of asbestosis are more likely to be associated with malignant mesothelioma. According to Selikoff the intervals between initial exposure to asbestos and pleural or peritoneal mesothelioma average 34.8 and 43.0 years, respectively.[11] Perhaps the amount of asbestos fibers inhaled by an ordinary urban dweller is sufficient to cause minor grades of pulmonary asbestosis. Asbestos fibers may become widely disseminated by the blood and lymph throughout the human body. Selikoff has found them in bone marrow, kidney, liver, adrenal glands, and spleen.[9] The possibility that they also enter the circulation by penetrating the mucosal barrier of the gastrointestinal tract after ingestion with contaminated food must also be considered.

The first step in proving the development of malignant tumors as a result of occupational or environmental exposure to chemical or physical carcinogens is the compilation and presentation of data such as these. The association of such exposure with increased incidence of tumors does not conclusively prove *per se* their etiologic relationship. Final proof must await the experimental induction of tumors by the incriminated agent. Experience in man already suggests the propensity of many types of tissue to develop malignant tumors in the presence of asbestosis. These and other hazards of asbestosis, one of man's additions to his own environment, are indeed numerous—and frightening.

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ASBESTOSIS

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