Peritoneal Mesothelioma with Elevated Serum Ferritin and β_2 -microglobulin levels

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Peritoneal mesothelioma was diagnosed in a 54-year-old female, who had never been exposed to asbestos. The clinical picture was dominated by progressive abdominal distension due to the development of ascites as well as tumor, severe right hypochondralgia and intermittent fever. Abnormal laboratory findings were; elevated ESR, positive CRP, mild leukocytosis with normal differential, high serum levels of ferritin and β_2 -microglobulin, and an abnormal accumulation of isotope in the right upper quadrant of the abdomen on Ga scintigram. On exploratory laparotomy, the liver was found to be surrounded by tumor tissue, but histological examination was not diagnostic. A saliva test of the tissue was positive, indicating a high glycogen content. At autopsy the tumor was found to consist of two elements, epithelial and sarcomatoid. The final diagnosis was peritoneal mesothelioma.

Key Words: Peritoneal mesothelioma, Glycogen, Ferritin, β_2 -microglobulin

Mesothelioma is a mesenchymal neoplasm which originates in the lining membrane of various serous cavities; pleural, peritoneal and pericardial. It may also occur in the tunica vaginalis testis and around the fallopian tube¹⁾. Peritoneal mesothelioma is extremely rare and usually occurs in middle to old age, especially in men. Since the suggestion by Wagner et al (1960) that mesothelioma is related to exposure to asbestos, there have been many reports describing the histological appearance and asbestos exposure²⁻⁶⁾. The treatment of mesothelioma is difficult since these tumors are not radio-sensitive^{7,8)} and, because of their diffuse nature, they are not amenable to surgery. The role of chemotherapy in the management of this disease is difficult to ascertain⁹⁻¹¹⁾. We report a case of peritoneal

mesothelioma which was diagnosed at autopsy.

CASE REPORTS

A 54-year-old housewife was admitted on Sept. 3, 1979 because of right hypochondralgia and fever. The provisional clinical diagnosis was cholecystopathy. The patient had been well until approximately two months prior to admission when she developed right upper quadrant abdominal pain. The pain was dull, radiated to the right back, was unrelated to meals, and accompanied by intermittent fever. She had been constipated for an unknown interval but had not had melena. She had no definite history of exposure to asbestos. Her social history included heavy cigarette smoking and moderate alcohol abuse in the past.

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Her family history was not contributory.

The patient was normally developed and well nourished with a pulse rate of 66/min and a temperature of 37.8°C. Physical examination disclosed a slightly protuberant abdomen due to meteorism with normal bowel sounds and diffuse tenderness, especially marked in the right hypochondrium. no fluid wave was detected. The remainder of her physical examination was unremarkable.

Abnormal laboratory findings upon admission were; an elevated ESR of 61 mm/h, CRP 5(+), mild leukocytosis with normal differential, increased α_1 and α_2 -globulin and a decreased serum iron level. The so-called oncofetal antigens, carcinoembryonic antigen (CEA) and α -fetoprotein (AFP), were normal. Serum levels of ferritin and β_2 -microglobulin were abnormally high (Table 1). A chest X-ray revealed slight elevation of the right leaf of the diaphragm, and an abdominal plain film demonstrated a moderate amount of intestinal gas. An upper GI series showed no significant abnormalities except for mild extrinsic pressure on the bulb. Cholecystography and scintigraphy with ^{99m}Tc PI showed normal visualization of the biliary tract and gallbladder. A liver scintigram with ^{99m}Tc Sn-coll. showed a slightly elevated right lobe and an enlarged left lobe without any space-occupying lesions. ERCP showed a normal pancreatic duct. A Ga scintigram revealed abnormal accumulation in the right upper quadrant of the abdomen (Fig. 1). Cultures of urine, sputum and blood were negative. A stool specimen was negative for occult blood. The following tests remained normal during the patient's hospitalization: urinalysis, amylase (serum & urine), ASLO, RA, STS, T. Bil., GOT, GPT, Al-p, LAP, γ -GTP and serum electrolytes.

Although the presence of malignancy could not be ruled out, the patient was first treated with various antibiotics for possible infection in the hepatobiliary tract. About 3 weeks after admission, transient reduction of fever was achieved by the administration

Table 1. Cancer related proteins

	Oct. 4	Nov. 13	Nov. 22	Nov. 27 (ascites)
CEA (0-2.5 ng/ml)	1.8	1.4	1.4	
α -Feto (0-20 ng/ml)	0	0.4	0.4	
β_2 -microglobulin (0.8-2.4 mg/dl)		7.6	7.0	9.9
Ferritin (3.3-86.3 ng/ml)		4950	3850	2350

Fig. 1. Ga scintigram showing abnormal accumulation in the right upper quadrant of the abdomen.

of Minocycline HCl and Amikacin. However, an irregularly shaped, elastic hard tender mass gradually became palpable 3 cm beneath the right costal margin. The patient's general condition continued to deteriorate with recurrence of fever, severe right upper quadrant pain, vomiting, progressive anemia, ascites and pleural effusion. The ascitic fluid was an exudate containing malignant cells of various sizes.

Exploratory laparotomy disclosed a large amount of thick, straw-colored ascitic fluid. A diffuse, white nodular elastic mass was adherent to the liver, ligamentum teres, mesentery and duodenum. The site of the primary growth could not be established. Many small implants were seen on the peritoneum and omentum, but the pancreas, spleen, ovaries and uterus were not involved. Curative resection was impossible because

of the diffuse infiltration and adhesion of the tumor tissue. Biopsies of the tumor tissue revealed a necrotized malignant process with large pleomorphic neoplastic cells containing pale granular cytoplasm and irregularly enlarged vesicular nuclei of various shapes. Silver impregnation revealed nest-like structures. Tumor cells were arranged in sheets. These features were entirely compatible with those of a malignant vascular tumor.

The immediate postoperative course was uneventful, but ascitic fluid reaccumulated quickly, and the tumor grew rapidly. She received combined immuno-chemotherapy: OK-432 (a streptococcal preparation, Picibanil) 5 KE twice a week intraperitoneally, vincristine sulfate 1 mg intravenously once a week and PS-K (a protein polysaccharide, Krestin) 6 g a day orally. Accumulation of ascites and tumor growth seemed to be depressed by this therapy, but the patient died 3 months after admission.

AUTOPSY FINDINGS

The peritoneal cavity was completely obliterated and diffusely infiltrated with smooth, coarsely nodular, white fleshy tumor tissue. The loops of the upper bowel were stuck together by the tumor, and white tumor nodules up to 1 cm in diameter were present on the serosa of the large intestine and parietal peritoneum. The liver was completely surrounded by a thick layer of the tumor but there were no intrahepatic metastasis (Fig. 2). Microscopically, tumor cells consisted of two elements, spindle cells (sarcomatous lesion) and epithelium like cells (pseudogranular lesion composed of cuboidal and polygonal cells). The nuclei were round or oval, and often contained a prominent nucleolus (Fig. 3). The cytoplasm of the tumor cells and the extracellular material prestained with PAS showed a marked reduction in color intensity following treatment with saliva. Plasma cells were moderately increased in the bone marrow, spleen, lymphnodes and lungs. The final diagnosis was (1) malignant peritoneal

Fig. 2. Cut surfaces of liver surrounded by a thick layer of tumor.

Fig. 3. Tumor cells showing spindle cell and epithelial cell elements. H and E $\times 100$.

mesothelioma, (2) metastasis to the para-aortic and mesenteric lymphnodes and (3) fatty changes in the liver.

DISCUSSIONS

The clinical picture of peritoneal mesothelioma is relatively nonspecific. Abdominal distension due to tumor infiltration and ascites, usually serosanguinous or grossly bloody, or perhaps more localized abdominal pain are the outstanding symptoms. It seems unlikely that we can diagnose it early

enough for a useful trial of therapy. Laparotomy usually reveals very extensive growth, and at this stage surgical palliation is not feasible. It is difficult to determine the natural course of the disease, because in most of the reported cases various diagnostic and therapeutic measures have been taken which may have affected the course. The average duration of the disease until death is six months. This is much shorter than the over one year survival rate for pleural mesothelioma¹²⁾. The disease is invariably fatal.

Mesothelioma that has spread extensively through the peritoneum almost invariably penetrates the diaphragm and invades the pleural surface. The visceral pleura of the lungs is usually spared. The absence of liver metastasis in cases of diffuse peritoneal mesothelioma is obviously different from primary tumors of the stomach, gut or pancreas. Cytologic evaluation of peritoneal fluid is useful in the diagnosis of mesothelioma; large atypical mesothelioma cells may be seen, but they are not diagnostic.

We tested for several cancer related proteins. Ferritin and β_2 -microglobulin concentrations were abnormally high in serum and ascitic fluid of our patient. An increased serum level of β_2 -microglobulin is found in cases of renal tubule damage as well as in various diseases¹⁴⁾. Ferritin, the major iron-storage protein in the body, is found chiefly in the cytoplasm of cells of the reticulo-endothelial system. Recently it has been reported to be increased in malignant diseases such as leukemia, lung cancer, hepatoma and pancreatic seminoma¹⁵⁾. Although no reports on mesothelioma have mentioned increased serum levels of ferritin and β_2 -microglobulin, the extremely high levels in the serum and ascitic fluid in the present case may reflect the rapid growth of the mesothelioma.

Mesothelial tumors are characteristically pleomorphic, and the microscopic morphology forms a spectrum from highly characteristic pure epithelial and sarcomatoid types through nonspecific, although relative-

ly differentiated, to pleomorphic anaplastic proliferations. The appearance may vary in different parts of the tumor in the same individual, and small biopsies may fail to show this characteristic variation. In this case, exploratory laparotomy failed to identify the variety of histological patterns because only a few small biopsy specimens could be examined. Mesothelioma is rich in mucopolysaccharide which helps to define it histologically¹⁶⁾. The saliva test was positive in this case, indicating a high glycogen content. There have been scattered reports of responses to chemotherapy, but generally the disease has been found to be resistant to drugs. In our case, immuno-chemotherapy (the administration of OK-432 into the peritoneal cavity) seemed effective in delaying the reaccumulation of ascites.

The following criteria seem to be important in the diagnosis of malignant peritoneal mesothelioma: (1) a compatible clinical history, (2) characteristic gross features with intermittent fever, (3) absence of primary carcinoma, (4) peritoneal biopsy at different places to show the characteristic features, (5) histochemical studies, (6) extremely high levels of ferritin and β_2 -microglobulin, and (7) progressive growth of the tumor.

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REFERENCES

- 1) Ackerman, L. V.: Tumour of the retroperitoneum, mesentery and peritoneum. In AFIP Atlas of Tumour Pathology, Sec. 6, Fas. 24: 97, 1954.
- 2) Churg J, Rosen SH, Moolten S: Histological characteristics of mesothelioma associated with asbestos. Ann. N.Y. Acad. Sci. 132: 614, 1965.
- 3) Harries PG, Jones JSP, Skidmore JW, et al: Summary of Symposium on Diseases Asso-

- ciated with Asbestos Dust Exposure.
- 4) McDonald AD, Harper A, EI Attar OA, et al: Epidemiology of primary malignant tumours in Canada. *Cancer* 26: 914, 1970.
 - 5) Selikoff IJ, Churg J, Hammond EC: Relation between exposure to asbestos and mesothelioma. *N Engl J Med* 272: 560, 1965.
 - 6) Stanton MF, Wrench C: Mechanism of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 48: 797, 1972.
 - 7) Campbell WN: Pleural mesothelioma. *Am J Pathol* 26: 473, 1950.
 - 8) Semb G: Diffuse malignant pleural mesothelioma. *Acta Chir Scand* 126: 78, 1963.
 - 9) Yap BS, Benjamin RS, et al: The value of Adriamycin in the treatment of diffuse malignant pleural mesothelioma. *Cancer* 42: 1692, 1978.
 - 10) Elmes PC: Therapeutic openings in the treatment of mesothelioma. *I. A. R. C. Sci. Publ* 8: 277, 1973.
 - 11) Spremulli E, Wampler G, Regelson W.: Chemotherapy of malignant mesothelioma. *Cancer (Philadelphia)* 40/5: 2038, 1977.
 - 12) Elmes PC: The natural history of diffuse mesothelioma. *I. A. R. C. Sci. Publ.* 8: 267, 1973.
 - 13) Donna A: Proposal of a method for the cytologic identification of mesothelioma. *Pathologica* 68/985, 493, 1976.
 - 14) Kawai T.: β_2 -microglobulin. *Jap J Clin Path*, 28: 38, 1980.
 - 15) Krause, JR, et al: Serum Ferritin and Bone Marrow Iron Stores. 1. Correlation with absence of Iron in Biopsy Specimens. *Am J Clin Pathol* Nov, 72(5): 817, 1979.
 - 16) Kannersein M, Churg J, Magner D: Histochemical studies in the diagnosis of mesothelioma. *I. A. R. C. Sci Publ* 8: 62, 1973.
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