


SALVATORE MAUGERI FOUNDATION, AND
UNIVERSITY OF PAVIA

Asbestos-Induced Peritoneal Mesothelioma in a Construction Worker

Rodolfo Fonte,[1] Salvatore Gambettino,[1] Mario Melazzini,[1] Mario Scelsi,[2] Claudio Zanon,[3] and Stefano M. Candura[1,4]

[1]Division of Occupational Medicine and [2]Laboratory of Pathology and Cytodiagnostics, Salvatore Maugeri Foundation, Work and Rehabilitation, IRCCS, Scientific Institute of Pavia, Pavia, Italy; [3]Division of Oncological Surgery and Medical Technology, S. Giovanni Battista Hospital, Turin, Italy; [4]Department of Preventive, Occupational and Community Medicine, University of Pavia, Pavia, Italy

Occupational and environmental asbestos exposure continues to represent a public health problem, despite increasingly restrictive laws adopted by most industrialized countries. Peritoneal mesothelioma is a rare and aggressive asbestos-related malignancy. We present the case of a 65-year-old man who developed recurrent ascites after having been exposed to asbestos in the building industry for > 40 years. Liver function and histology were normal. Abdominal computed tomography initially excluded the presence of expansive processes, and no abnormal cells were found in the ascitic fluid. Laparoscopy showed diffuse neoplastic infiltration of the peritoneum. Histopathology of bioptic samples revealed epithelioid neoplastic proliferation with a tubulopapillary pattern, falsely suggesting metastatic adenocarcinomatosis. In consideration of the occupational history, and after further diagnostic procedures had failed to identify the hypothetical primitive tumor, immunostaining of the neoplastic tissue was performed. Results were negative for carcinoembrionary antigen and the epithelial glycoprotein Ber-EP4, whereas results were positive for the mesothelial markers cytokeratins, calretinin, epithelial membrane antigen, and HBME-1, thus leading to the correct diagnosis of peritoneal epithelial mesothelioma. The Italian Workers' Compensation Authority recognized the occupational origin of the disease. Cytoreductive surgery associated with continuous hyperthermic peritoneal perfusion (cisplatin at 42°C, for 1 hr) was performed. The disease relapsed after 4 months and was later complicated by a bowel obstruction requiring palliative ileostomy. The patient died 23 months after diagnosis. This case illustrates the insidious diagnostic problems posed by peritoneal mesothelioma, a tumor which often simulates other malignancies (e.g., metastatic carcinomas) at routine histopathological examination. Occupational history and immunohistochemistry are helpful for the correct diagnosis, which, in turn, is important in relation to prognosis and treatment (adoption of new integrated procedures that seem to promise prolonged survival and increased quality of life), and in relation to medicolegal issues and occupation-related compensation claims following asbestos exposure. *Key words:* **calretinin, cisplatin, HBME-1, intraperitoneal chemotherapy, occupational cancer, peritonectomy.** *Environ Health Perspect* **112:616–619 (2004). doi:10.1289/ehp.6542 available via** *http://dx.doi.org/* **[Online 1 December 2003]**

Case Presentation

In June 2000 a 65-year-old man was hospitalized for recently developed ascites, indefinite abdominal pain, dyspepsia, and mild hepatomegaly (echographic finding). He reported occasional abuse of alcoholic beverages and lifelong heavy smoking (40 cigarettes/day). The patient had worked in the building industry from 14 to 55 years of age (1949–1990), when he retired. His duties (installation of industrial roofing, pipes, flues, and tanks) required cutting and shaping asbestos-cement panels with an electric saw and a rotating abrasive disk, exposing him to the inhalation of asbestos fibers. Routine blood and urine analyses (including indicators of liver function) were normal. Viral hepatitis (B and C) markers were negative. Chest radiography and lung function tests revealed chronic obstructive pulmonary disease (COPD). Esophagogastroduodenoscopy disclosed mild gastroduodenitis. Abdominal computed tomography (CT) excluded the presence of expansive processes. Evacuative paracentesis was performed: the ascitic fluid was clear, and cytologic analysis did not detect abnormal cells.

In the following months, ascites reformed quickly after repeated paracentesis. Percutaneous liver biopsy (December 2000) showed normal hepatic histology. Laparoscopy (April 2001) revealed diffuse neoplastic infiltration of the peritoneum and greater omentum, with a carcinomatous aspect. Several bioptic samples were collected; standard histopathologic examination demonstrated epithelioid neoplastic proliferation with a tubulopapillary pattern (Figure 1), suggesting metastatic peritoneal adenocarcinomatosis. Further diagnostic procedures (colorectal radiology and endoscopy, magnetic resonance imaging of the abdomen, chest CT, and pelvic, transrectal, and testicular ultrasonography) failed to identify the hypothetical primitive tumor. The occupational history of long-term asbestos exposure prompted us to conduct immunohistochemical tests on the neoplastic tissue samples. Staining for the carcinoembrionary antigen (CEA) and the epithelial glycoprotein Ber-EP4 was negative, whereas results for the mesothelial markers cytokeratins, calretinin (Figure 2), epithelial membrane antigen (EMA), and HBME-1 (Figure 3) were positive, leading to the diagnosis of peritoneal epithelial mesothelioma.

In May 2001 the patient underwent bilateral subphrenic peritonectomy, partial pancreasectomy, splenectomy, appendicectomy, and cytoreductive debulking of neoplastic nodules larger than 3 mm. This was followed by peritoneal perfusion with cisplatin heated at 42°C for 1 hr. After overcoming severe postoperative complications (delayed adynamic ileus, *Candida tropicalis* septicemia, and *Clostridium difficile* bowel infection), the

Address correspondence to S.M. Candura, Division of Occupational Medicine, Salvatore Maugeri Foundation, Work and Rehabilitation, IRCCS, Scientific Institute of Pavia, Via Ferrata 8, I-27100 Pavia, Italy. Telephone: 39 0382 592740. Fax: 39 0382 592096. E-mail: scandura@fsm.it

The authors declare they have no competing financial interests.

Received 24 June 2003; accepted 1 December 2003.

patient was discharged in fairly good conditions (July 2001). He remained apparently free of disease for 4 months, after which ascites reformed. Abdominal ultrasonography indicated disease relapse.

In February 2003 the subject was readmitted to the hospital with a clinical picture suggestive of intestinal obstruction, which was confirmed at colonoscopy. Surgery revealed the presence of diffuse peritoneal neoplastic infiltration involving the intestinal loops. Palliative ileostomy was performed. The subject died 1 month later at 67 years of age.

Discussion

Malignant peritoneal mesothelioma was first described in 1908 by Miller and Wynn; it is a rare, locally aggressive neoplasm arising from the abdominal serosal lining, and exposure to asbestos fibers has been recognized as a principal etiopathogenetic agent (Antman 1993; Vogelzang 2002). The disease is more common in men, possibly because of the higher male occupational exposure to asbestos (Antman 1993; Attanoos and Gibbs 1997).

Diagnosis of peritoneal mesothelioma (particularly the differentiation from the more common metastatic peritoneal cancers) is often difficult and delayed, both for the nonspecific clinical manifestations of the disease (abdominal pain, ascites, abdominal masses) and its extreme morphologic variability (Attanoos and Gibbs 1997; Sugarbaker et al. 2002). In the reported patient, the clinical picture was dominated by recurrent ascites. Normality of both liver function and histology excluded the presence of hepatic disease. Definition of the neoplastic nature of ascites required exploratory laparoscopy. Routine histologic examination of neoplastic tissue was initially misleading, suggesting metastatic invasion of the peritoneum by occult adenocarcinoma. Besides mesothelioma, a variety of other abdominal and pelvic malignancies (e.g., gastrointestinal or genitourinary cancer) may in fact present with peritoneal seeding. With hematoxylin-eosin staining, epithelial (epithelioid) mesothelioma (the most common histopathological subtype, 50–75% of cases) may present the same morphology of glandular carcinomas, as in this case. Sarcomatous (or sarcomatoid) mesothelioma (15–20%) may in turn simulate sarcomas originating from connectival tissue (e.g., fibrosarcoma). The only pathognomonic phenotype is the mixed (or biphasic) mesothelioma (20–30%), where epithelioid and sarcomatoid tissues coexist. Histologic diagnosis of rare morphologic variants (e.g., small-cell, desmoplastic, or lymphohistiocytoid mesothelioma) may also be problematic (Attanoos and Gibbs 1997; Sugarbaker et al. 2002).

In this patient, the negative results of CEA and Ber-EP4 immunohistochemistry allowed us to exclude reactivity of the bioptic samples with epithelial-binding antibodies, whereas results of immunohistochemistry for cytokeratins, calretinin, EMA and HBME-1 indicated reactivity of the neoplastic tissue with antibodies that preferentially bind cells of mesothelial origin (Attanoos and Gibbs 1997; King and Hasleton 2001). As a discriminant marker, calretinin (a calcium-binding protein) shows high sensitivity and specificity for mesothelioma (Doglioni et al. 1996; Leers et al. 1998), particularly for the epithelial subtype (Attanoos et al. 2001). Thus, immunostaining allowed us to formulate the correct diagnosis of primary peritoneal mesothelioma (epithelial subtype) excluding metastatic adenocarcinomatosis.

Besides immunohistochemistry, one element that significantly helped us formulate the diagnosis was the patient's occupational history of prolonged asbestos exposure in the building industry. Due to its physicochemical characteristics (resistance to mechanical agents, electricity, chemicals, heat, and fire and textile, insulating, and hygroscopic properties) and relatively low cost, asbestos was widely used until recently in a variety of industrial processes. Other than construction (asbestos-cement, fireproof panels), asbestos has also been used in the automobile, railway, naval, and aerospatial industries (insulating and fireproof coatings, brake and clutch linings); metallurgy (shields, protective clothing); the textile industry (asbestos-made blankets and overalls; linings of warping, looming, and combing machines; Chiappino et al. 2003); and food processing (asbestos filters). In 1990, the estimated worldwide production of asbestos (used in approximately 1,500 industrial processes) was 4,500,000 tons/year (Candura and Candura 2002).

Occupational and environmental asbestos exposure may cause asbestosis (evolutive lung fibrosis), pleural fibrosis and calcification, lung cancer, and mesotheliomas, with a risk proportional to the duration and intensity of exposure (Antman 1993; Magnani et al. 1998; Rom et al. 2001; Rubino et al. 1972; Selikoff 1978). The first reports on the carcinogenic effect of asbestos on the lung date back to 1935 (Gloyne 1935; Lynch and Smith 1935), whereas asbestos-related mesotheliomas, both pleural (Wagner et al. 1960) and peritoneal (Keal 1960), were first described in 1960. The mechanisms underlying asbestos-induced oncogenesis are not completely understood. Apparently, asbestos plays a cocarcinogen role in lung cancer, with promoter-like activity and synergism with smoking, whereas in mesothelioma it acts as a complete carcinogen. Oxygen free radicals appear to have a pivotal role in the process, exerting direct and indirect genotoxic effects on the mesothelial cells (Attanoos and Gibbs 1997; Walker et al. 1992).

The implication of asbestos in the causation of peritoneal mesothelioma is less evident than in pleural mesothelioma (Peterson et al. 1984). The abdominal localization seems to require a particularly intense and prolonged exposure (Browne and Smither 1983; Selikoff 1978). Several hypothesis have been formulated to explain the mechanism by which asbestos reaches the peritoneum. In experimental animals, asbestos fibers penetrate the gastrointestinal wall after ingestion (Masse et al. 1980), and asbestos bodies have been found within some human peritoneal mesotheliomas (Hourihane 1965). It has therefore been postulated that ingestion of fibers, either directly from contaminated food or indirectly from expectorated sputum, may be one route for asbestos transmission to the peritoneum (Craighead and Mossman 1982).

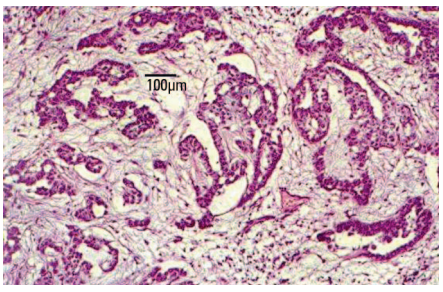

Figure 1. Bioptical peritoneal sample showing neoplastic proliferation with papillary and glandular features and stromal infiltration (hematoxylin-eosin; magnification, 100×).

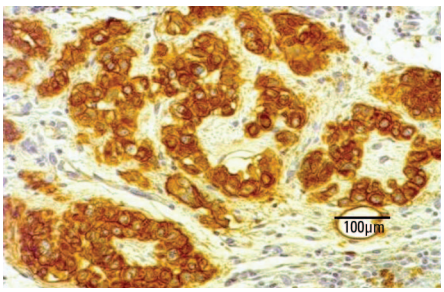

Figure 2. Bioptical peritoneal sample showing positive diffused immunoreactivity for calretinin (magnification, 200×).

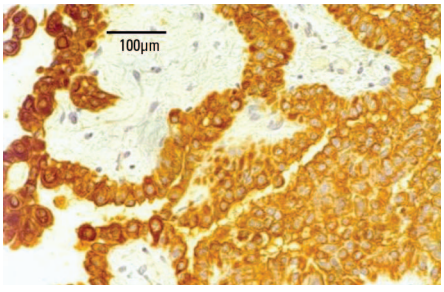

Figure 3. Bioptical peritoneal sample showing immunohistochemical reaction for HBME-1, indicated by intense and diffuse positivity of cytoplasmatic membranes (magnification, 200×).

Other possible mechanisms are permeation of diaphragmatic stomata and hematic/lymphatic transport (Auerbach et al. 1980).

Beginning in the 1970s, both the United States and the European community progressively introduced restrictive laws concerning the sale and use of asbestos. Italy definitively banned its extraction, import/export, and use in 1992. Nevertheless, asbestos continues to represent a public health concern for at least three reasons (Chiappino 1998). First, people exposed in the past (especially in the work environment) are still at risk because asbestos-induced desease, especially cancer, may develop up to 40 years after exposure (Lanphear and Buncher 1992; Vogelzang 2002). Projections based on epidemiologic data suggest that the number of men dying from pleural mesothelioma in Western Europe each year will almost double until around 2018 (Peto et al. 1999). Second, removal of preexisting asbestos is a current source of occupational exposure. Third, a large portion of the asbestos used in the past is still present in the general environment and inevitably causes release of fibers into the air because of aging and disintegration. The asbestos concentrations that may currently be encountered in the home environment are much lower than those previously present in the occupational setting; however, such microdoses should not be disregarded because of the apparent lack of a safety threshold for the risk of mesothelioma. Low asbestos doses, insufficient to cause asbestosis and lung cancer, may express high pathogenetic potential for mesothelioma (Selikoff 1978).

Thus, clinicians should be aware of the possibility of mesothelioma, pleural or peritoneal, among patients with previous asbestos exposure. In such cases, careful occupational and environmental anamnesis may correctly address diagnosis and, consequently, treatment and prognosis. Discovery of a causal link between asbestos exposure and disease implies important medicolegal duties. The case described here had to be reported to the judicial authority (as established by the Italian Penal Code) and was referred to the Italian Workers' Compensation Authority, which recognized the occupational origin of the disease.

After the correct diagnosis was formulated, the patient was treated with cytoreductive surgery associated with continuous hyperthermic peritoneal perfusion (CHHP) and survived 23 months. Until recently, peritoneal mesothelioma was considered incurable, with a median survival of less than 1 year from diagnosis. Several different approaches had been unsuccessfully attempted in the past, including surgery, systemic chemotherapy, whole abdominal irradiation, and intraperitoneal administration of radioisotopes (^{32}P, ^{198}Au) or antiproliferative drugs (thiotepa, bleomycin) (Antman et al. 1983; Sridhar et al. 1992). No dominant therapeutic guideline currently exists. During the last few years (de Bree et al. 2000; Ma et al. 1997; Sebbag et al. 2000; Sugarbaker et al. 2002), a new integrated therapeutic strategy has been introduced in which the diffused abdominal tumor is removed by peritonectomy and resection of the involved organs; the peritoneal cavity is then successively inundated with a solution containing antitumor drugs (cisplatin, doxorubicin) heated to 41–42°C. During this phase, the surgeon manually distributes the liquid into the peritoneal cavity to allow the drugs to reach all the surfaces. Early postoperative intraperitoneal paclitaxel treatment may also be associated (Sugarbaker et al. 2002). Regional treatments avoid systemic toxicity and take advantage of the peritoneal–plasma barrier and first-passage clearance of cytostatic drugs by the liver. Tumor debulking before intraperitoneal chemotherapy is essential for the effectiveness of treatment because the penetration depth of the drugs is limited to < 5 mm (Averbach and Sugarbaker 1996). This multimodality technique has resulted in successful palliation of ascites and in median survivals up to 50–60 months, with projected 3-year survival rates up to 60% (Sugarbaker et al. 2002). Survival has been reported more than 5 years after treatment (Sebbag et al. 2000; Sugarbaker et al. 2002). This implies that, when diagnosed early, peritoneal mesothelioma is treatable with reasonable expectations for high quality of life and potential cure.

Conclusion

The patient reported here illustrates the diagnostic problems posed by peritoneal mesothelioma. The epithelial subtype of this tumor often assumes a papillary and/or glandular cytoarchitecture, falsely suggesting the presence of metastatic adenocarcinoma at routine histopathological examination. In such cases, the doubts can be resolved using occupational history and immunohistochemistry. The restrictive laws recently introduced by several countries have reduced but not eliminated the risk of asbestos-induced mesothelioma. Because of the long latency of this disease, individuals exposed in the past, either in the workplace or in the general environment, require careful surveillance.

Correct diagnosis of peritoneal mesothelioma allows the adoption of innovative therapeutic procedures (cytoreductive surgery plus CHHP), which offers prolonged survival and increased quality of life. When asbestos is involved in the causation of the disease, accurate diagnostic assessment is also important in relation to medicolegal issues and occupation-related compensation claims.

References

Antman KH. 1993. Natural history and epidemiology of malignant mesothelioma. Chest 103(suppl 4):373S–376S.

Antman KH, Pomfret EA, Aisner J, MacIntyre J, Osteen RT, Greenberger JS. 1983. Peritoneal mesothelioma: natural history and response to chemotherapy. J Clin Oncol 1:386–391.

Attanoos RL, Gibbs AR. 1997. Pathology of malignant mesothelioma. Histopathology 30:403–418.

Attanoos RL, Webb R, Dojcinov SD, Gibbs AR. 2001. Malignant epithelioid mesothelioma: anti-mesothelial marker expression correlates with histological pattern. Histopathology 39:584–588.

Auerbach O, Conston AS, Garfinkel L, Parks VR, Kaslow HD, Hammond EC. 1980. Presence of asbestos bodies in organs other than the lung. Chest 77:133–137.

Averbach AM, Sugarbaker PH. 1996. Peritoneal mesothelioma: treatment approach based on the natural history. Cancer Treat Res 81:193–211.

Browne K, Smither WJ. 1983. Asbestos-related mesothelioma: factors discriminating between pleural and peritoneal sites. Br J Ind Med 40:145–152.

Candura F, Candura SM. 2002. Principles of Industrial Technology for Occupational Medicine Scholars' Use [in Italian]. Piacenza, Italy:Casa Editrice La Tribuna.

Chiappino G. 1998. The problem of asbestos today [in Italian]. G Ital Med Lav Erg 20:200–202.

Chiappino G, Mensi C, Riboldi L, Rivolta G. 2003. Asbestos risk in the textile industry: final confirmation of data from the Lombardy Mesothelioma Register [in Italian]. Med Lav 94:524–530.

Craighead JE, Mossman BT. 1982. The pathogenesis of asbestos associated disease. N Engl J Med 306:1446–1455.

de Bree E, Christodoulakis M, Tsiftsis D. 2000. Malignant peritoneal mesothelioma treated by continuous hyperthermic peritoneal perfusion chemotherapy. Ann Oncol 11:753–756.

Doglioni C, Tos AP, Laurino L, Iuzzolino P, Chiarelli C, Celio MR, et al. 1996. Calretinin: a novel immunocytochemical marker for mesothelioma. Am J Surg Pathol 20:1037–1046.

Gloyne SR. 1935. Two cases of squamous carcinoma of the lung occuring in asbestosis. Tubercle 17:5–10.

Hourihane D. 1965. A biopsy series of mesotheliomata, and attempts to identify asbestos within some of the tumors. Ann NY Acad Sci 132:647–673.

Keal EE. 1960. Asbestosis and abdominal neoplasm. Lancet 2:1211–1216.

King JE, Hasleton PS. 2001. Immunohistochemistry and the diagnosis of malignant mesothelioma. Histopathology 38:471–476.

Lanphear BP, Buncher CR. 1992. Latent period of malignant mesothelioma of occupational origin. J Occup Med 7:718–722.

Leers MPG, Aarts MMJ, Theunissen PHMH. 1998. E-Cadherin and calretinin: a useful combination of immunohistochemical markers for differentiation between mesothelioma and metastatic adenocarcinoma. Histopathology 32:209–216.

Lynch KM, Smith WA. 1935. Pulmonary asbestosis. III: carcinoma of lung in asbesto-silicosis. Am J Cancer 24:56–64.

Ma GY, Bartlett DL, Reed E, Figg WD, Lush RM, Lee KB, et al. 1997. Continuous hyperthermic peritoneal perfusion with cisplatin for the treatment of peritoneal mesothelioma. Cancer J Sci Am 3:174–179.

Magnani C, Mollo F, Paoletti L, Bellis D, Bernardi P, Betta P, et al. 1998. Asbestos lung burden and asbestosis after occupational and environmental exposure in an asbestos cement manufacturing area: a necropsy study. Occup Environ Med 55:840–846.

Masse R, Sebastien P, Monchaux G, Bignon J. 1980. Experimental demonstration of the penetration of fibres into the gastrointestinal tract. IARC Sci Publ 30:321–328.

Miller J, Wynn WH. 1908. A malignant tumor arising from the endothelium of the peritoneum, and producing a mucoid ascitic fluid. J Pathol Bacteriol 12:267–278.

Peterson TJ Jr, Greenberg SD, Buffler P. 1984. Non-asebstos-related malignant mesothelioma. Cancer 54:951–960.

Peto J, Decarli A, La Vecchia C, Levi F, Negri E. 1999. The European mesothelioma epidemic. Br J Cancer 79:666–672.

Rom WN, Hammar SP, Rusch V, Dodson R, Hoffman S. 2001. Malignant mesothelioma from neighborhood exposure to anthophyllite asbestos. Am J Ind Med 40:211–214.

Rubino GF, Scansetti G, Donna A, Palestro G. 1972. Epidemiology

of pleural mesothelioma in north-westerm Italy (Piedmont). Br J Ind Med 29:436–442.

Sebbag G, Yan H, Shmookler BM, Chang D, Sugarbaker PH. 2000. Results of treatment of 33 patients with peritoneal mesothelioma. Br J Surg 87:1587–1593.

Selikoff IJ. 1978. Asbestos and Disease. New York:Academic Press.

Sridhar KS, Doria R, Raub WA Jr, Thurer RJ, Saldana M. 1992. New strategies are needed in diffuse malignant mesothelioma. Cancer 70:2969–2979.

Sugarbaker PH, Acherman YIZ, Gonzalez-Moreno S, Ortega-Perez G, Stuart OA, Marchettini P, et al. 2002. Diagnosis and treatment of peritoneal mesothelioma: the Washington Cancer Institute experience. Semin Oncol 29:51–61.

Vogelzang NJ. 2002. Emerging insights into the biology and therapy of malignant mesothelioma. Semin Oncol 29(suppl 18):35–42.

Wagner JC, Sleggs CA, Marchand P. 1960. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 17:260–271.

Walker C, Everitt J, Barret JC. 1992. Possible cellular and molecular mechanisms for asbestos carcinogenicity. Am J Ind Med 21:253–273.