Asbestos-Induced Peritoneal Mesothelioma in a Construction Worker

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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 bioponic 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 carcinoembryonic 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, peritoneectomy. 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 gastroesophageal reflux. 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 formed 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 bioponic 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 carcinoembryonic 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 pancreatectomy, 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
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 non-specific 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 connective 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 bioplastic 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, loomign, 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 asbestos (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 (Glyone 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, exciting 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 (Brownie and Smithie 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 (Mase 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).
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 disease, 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 asbestososis 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 Italian Penal Code (as established by 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 (³²P, ¹⁹⁸Au) or antiproliferative drugs (thiotepa, bleomycin) (Antman et al. 1983; Sridhar et al. 1992). No dominant therapeutic guide-line 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 peritoneectomy 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 post-operative 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 cytarchitesture, 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

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