

Malignant Peritoneal Mesothelioma After Thorotrast Exposure

Claudia Stey, M.D., Ursula Landolt-Weber, M.D., Wilhelm Vetter, M.D.,
Christian Sauter, M.D., and Borut Marincek, M.D.

A case of a malignant peritoneal mesothelioma in a 63-year-old male patient with a history of exposure to Thorotrast in 1945 is presented. There was no history of exposure to asbestos. The clinical manifestation was a serosal effusion, which required weekly ascites puncture until therapy with intraperitoneal bleomycin was initiated. The latter treatment led to a significant reduction of ascites without any influence on tumor progression. Unfortunately, intraperitoneal bleomycin was accompanied by pulmonary toxicity, but at a higher total dose than known for intravenous administration. Three years after diagnosis the patient is still alive, without relapse of ascites production after bleomycin had to be stopped. Considering the risk of pulmonary fibrosis with high-dose intraperitoneal bleomycin and the lack of efficacy on tumor reduction, bleomycin seems to offer no advantage with respect to cisplatin.

Key Words: Computed tomography—Peritoneal mesothelioma—Therapy—Thorotrast malignancies.

CASE REPORT

A 63-year-old man noticed an increase in abdominal circumference in September 1990, and was admitted to hospital because of massive ascites and a right-sided pleural effusion. The patient reported in his history an injury during World War II, which led to a cubital angiography with Thorotrast in 1945.

On physical examination, the patient was in good condition (176 cm, 83 kg), without fever, lymphadenopathy, or signs of cholestasis. Erythrocyte sedimentation rate was 20 mm/h, hematologic laboratory values were normal. Creatinine, ALT, AST, alkaline phosphatase, PFT, serum albumin, amylase, and alpha-fetoprotein were in the normal range. Serological tests for hepatitis revealed only previous exposure to HAV.

Chest radiograph showed a right pleural effusion but normal heart size and lung parenchyma. Abdominal ultrasound confirmed massive ascites with floating fibrinous bodies. Liver and spleen were diminished in size. Diagnostic paracentesis yielded a bloody, mucinous exudate (protein content = 45.7 g/L). Microscopic examination of the exudate revealed tumor cells, suggesting an adenocarcinoma (Fig. 1). In addition, computed tomography (CT) demonstrated characteristic findings of long-standing thorotrast-induced changes (Fig. 2A,B). The liver exhibited a subtle reticular pattern of metallic densities, which were most apparent in subcapsular areas of the right lobe. The peripancreatic and splenic hilar lymph nodes also had metallic density. Metallic deposits were greatest in the spleen, which was small and homogeneously involved. Also evident were ascites and irregular soft tissue strands infiltrating the omental fat, indicative of a peritoneal neoplasm. There was no obvious primary tumor. Upper and lower gastrointestinal tract endoscopy revealed

From the Departments of Internal Medicine (C.S., W.V., C.S.), Pathology (U.L.W.), and Radiology (B.M.), University Hospital, Zürich, Switzerland.

Address correspondence and reprint requests to Dr. Claudia Stey, Department of Internal Medicine, University Hospital of Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.



FIG. 1. High cellularity in smears of the aspirated and centrifugated ascites fluid. Round aggregates of tumor cells morphologically not to be differentiated from cells of an adenocarcinoma. Papanicolaou stain, $\times 800$.

no abnormalities. Immunostaining with anti-Lu-5, -CEA, -B12, and -vimentin antibodies of the ascites' cells and identical cells, which have been found later in an abdominal subcutaneous metastasis, were Lu-5 and vimentin-positive, but negative for B12 and CEA. This is an unusual combination for adenocarcinoma. Diagnosis of a well-differentiated peritoneal mesothelioma was made (Figs. 3 and 4). In view of the poor prognosis, conservative treatment with diuretics and periodic removal of the ascitic fluid was considered adequate.

During the first year, weekly paracentesis with albumin replacement was necessary, and the patient was stable, apart from weight loss. Because of increasing pleural effusion, a pleurodesis had to be performed in May 1992. Thoracoscopy showed tumor infiltration of the parietal and diaphragmatic pleura and the histologic appearance of the biopsy specimen was identical to the ascites. Subsequently, the patient got tired of the paracenteses and they were stopped. Within 1-2 weeks increasing ascites caused pain and dyspnea.

In September 1992, weekly chemotherapy with 30



FIG. 2. (A,B) Upper abdominal CT. Secondary changes 45 years after thorium dioxide injection: Reticular pattern of metallic densities in the liver, most apparent in subcapsular areas of the right lobe (arrowhead). Homogeneous metallic density of the spleen, which is small (S). Metallic deposits in peripancreatic lymph nodes (open arrow). Ascites (A). Omental infiltration secondary to malignant peritoneal mesothelioma (curved arrow).

FIG. 3. Aspirated cells of the abdominal wall tumor. Immunocytochemical staining with the keratin antibody Lu-5 shows the positive reaction in cells of the epithelial type of mesothelioma.



mg intraperitoneal bleomycin was initiated and the ascites decreased markedly within 4 weeks. The dose interval was prolonged to 14 days, because the cumulative dose for side effects (especially pneumonitis) with intraperitoneal bleomycin is not known. Bleomycin therapy was continued until May 1993 (cumulative dose of 720 mg). At this time, the patient started suffering from dyspnea and cough. CT of the lungs showed interstitial fibrosis and cardiophrenic lymphadenopathy (Fig. 5). In the abdomen there was evident progression of the peritoneal tumor, but ascites had decreased (Fig. 6). Bleomycin was stopped, and so far no

relapse in ascites production has occurred. Therapy with steroids and oxygen was started to reduce dyspnea. Three years after diagnosis the patient is still alive.

DISCUSSION

Malignant peritoneal mesothelioma is a rare neoplasm causing major diagnostic and therapeutic problems. Most cases are related to asbestos exposure (1). In the case of a malignant tumor in an individual with a history of Thorotrast exposure with typical deposits of thorium dioxide, a causal relationship must be considered (2-4). In our patient, there was no other known



FIG. 4. The partially positive immunoreaction of the tumor cells with vimentin demonstrates the biphasic character of the mesothelioma tumor cells.

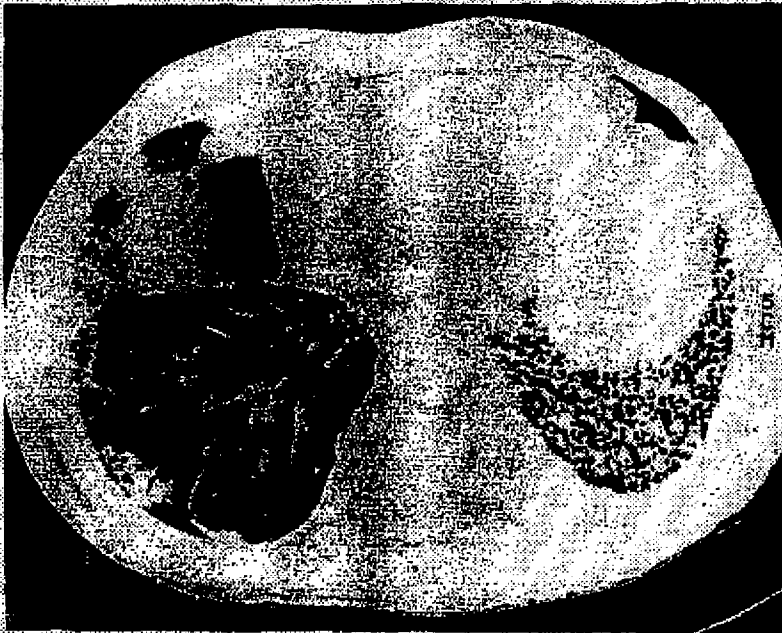


FIG. 5. Pulmonary fibrosis after bleomycin. CT shows interstitial fibrosis most marked in the caudal left lung.

carcinogenic stimulus and no exposure to asbestos. The long latency period is characteristic. Malignant tumors occur after a latency of 14-45 years (3). Thorotrast accumulates in the reticuloendothelial system, especially in the liver (60%) and in the spleen (20%), where alpha radiation is delivered in considerable

quantities over prolonged periods, because Thorotrast has an extremely long half-life (4-6). Its physical half-life is about 1.4×10^{10} years and its biologic half-life is 400 years in human beings (7). Wherever the substance accumulates, fibrous tissue is formed. Beyond this fibrogenesis, Thorotrast is carcinogenic. A positive

FIG. 6. Progression of malignant peritoneal mesothelioma (curved arrow) following intraperitoneal chemotherapy with bleomycin, but regression of ascites.



correlation between dosage, tumor incidence, and latency has been demonstrated in previous studies (6,8-11). The most frequent tumors are renal/pelvic carcinomas, sarcomas, leukemias, liver hemangioendothelioma, hepatocellular carcinoma, and carcinoma of the bile ducts (4,12-16). Up to now Thorotrast-associated peritoneal mesothelioma has been reported only once (17). The mesothelioma in our case is not in a direct irradiated area, but there is a close topographic relation between the tumor and the deposits of thorium dioxide in the liver, the spleen, and the lymph nodes.

Histologic diagnosis of mesothelioma is often difficult because mesothelial hyperplasia or other malignant tumors may mimic mesothelioma. Therefore, immunohistochemical assays, demonstrating the coexpression of vimentin, keratin, and epithelial membrane antigens, are often necessary to establish the diagnosis (18). CT is a noninvasive imaging modality in diagnosis and follow up in peritoneal mesothelioma (19). Ascites is usually present in moderate or large amounts. Omental infiltration is a prominent and valuable CT feature and the progression of omental involvement is a notable change to discern on follow-up (19).

Therapeutically, malignant peritoneal mesothelioma is still a problem. It is known to be relatively refractory to conventional intravenous chemotherapy. A subset of patients, principally those with small-volume disease, with and without surgical tumor debulking, can benefit from treatment with intraperitoneal chemotherapy. Most data available refer to cisplatin-based intraperitoneal chemotherapy (20,21). In our case, intraperitoneal chemotherapy with bleomycin had an excellent effect on ascites control, but no effect on tumor progression. The cumulative dose for intraperitoneal treatment which is not associated with side effects is unknown (22). Unfortunately, our patient developed pulmonary fibrosis after a cumulative dose of 720 mg, which is three to four times the total intravenous dose associated with pulmonary toxicity (23). Considering the side effect of pulmonary fibrosis and the lack of effect on tumor mass reduction, high-dose bleomycin given intraperitoneally seems to offer no advantage with respect to cisplatin.

REFERENCES

- Antman KH, Pass HI, Recht A. Benign and malignant mesothelioma. In: DeVita VT, Hellmann S, Rosenberg SA, eds. *Cancer, principles and practice in oncology*. Philadelphia: J.B. Lippincott; 1989:1399-417.
- Janower ML, Miettinen OS, Flynn MJ. Effects of long-term Thorotrast exposure. *Radiology* 1972;103:11-20.
- Gondos B. Late clinical and roentgen observations following Thorotrast administration. *Clin Radiol* 1973;24:195-203.
- Case Records of the Massachusetts General Hospital. Case 15: 1981. *N Engl J Med* 1981;304:893-899.
- Grampa G. Radiation injury with particular reference to Thorotrast. *Pathol Annu* 1971;6:147-69.
- Von Kaick G, Lorenz D, Muth H, Kaul A. Malignancies in German Thorotrast patients and estimated tissue dose. *Health Phys* 1978;35:127-36.
- Hersh JB, Steadman LT, Looney WB, Colodzin M. Excretion of thorium and thorium daughters after Thorotrast administration to human subjects. *Acta Radiol* 1957;47:481-98.
- Da Silva Horta J, Abbasi JD, Cayolla da Motta L, Kozia ML. Malignancy and other late effects following administration of Thorotrast. *Lancet* 1965;2:201-3.
- Da Silva Horta J, Cayolla da Motta L, Tavares MH. Thorium dioxide effects in man: epidemiological, clinical, and pathological studies (experience in Portugal). *Environ Res* 1974;8:131-59.
- Brunner HE, Rüttner JR. Die Gewebereaktion auf Thoriumdioxid im Peritonealtier. *Arch Gewerbepathol Gewerbehyg* 1975;15:236-40.
- Von Kaick G, Liebermann D, Lorenz D, et al. Recent results of German Thorotrast study: epidemiological results and dose-effect relationships in Thorotrast patients. *Health Phys* 1983;44(Suppl 1):299-306.
- Dahlgren S. Thorotrast tumours: a review of the literature and report of two cases. *Acta Pathol Microbiol Scand* 1961;53:147-61.
- Morant R, Rüttner JR. Thorotrast Spätschäden. *Schweiz Med Wochenschr* 1982;117:952-7.
- Casper L. Peritoneal hemangioendotheliomatosis after salpingography with Thorotrast. *Ann NY Acad Sci* 1967;145:798-805.
- Curry JL, Johnson WG, Feinberg DH, Updegrave JH. Thorium induced hepatic hemangioendothelioma: roentgen angiographic findings in two additional cases with clinical "inform and consent" problems. *AJRN* 1975;125:671-7.
- Levy DW, Rindberg S, Friedman AC, et al. Thorotrast induced hepatosplenic neoplasia: CT identification. *AJR* 1986;146:997-1004.
- Maurer R, Egloff B. Malignant peritoneal mesothelioma after cholangiography with Thorotrast. *Cancer* 1975;36:1381-5.
- Bollinger DJ, Wick MR, Dehner LP, et al. Peritoneal malignant mesothelioma versus papillary adenocarcinoma: a histochemical and immunohistochemical comparison. *Am J Surg Pathol* 1989;13:659-70.
- Guest PJ, Reznick RH, Selleslag D, et al. Peritoneal mesothelioma: the role of computed tomography in diagnosis and follow-up. *Clin Radiol* 1992;45:79-84.
- Markman M, Kelsen D. Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma. *J Cancer Res Clin Oncol* 1992;118:547-50.
- Vlasveld LT, Gallee MP, Rodenhuis S, Taal BO. Intraperitoneal chemotherapy for malignant peritoneal mesothelioma. *Eur J Cancer* 1991;27:732-4.
- Bitran D. Intraperitoneal bleomycin pharmacokinetics and results of a phase II trial. *Cancer* 1985;56:2420-3.
- Chisholm RA, Dixon AK, Williams MV, Oliver RTD. Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992;30:158-60.

1. Antman KH, Pass HI, Recht A. Benign and malignant mesothelioma. In: DeVita VT, Hellmann S, Rosenberg SA, eds. *Cancer*