Malignant Peritoneal Mesothelioma Associated with Deep Vein Thrombosis Following Radiotherapy for Seminoma of the Testis


Abstract

A 52-year-old man developed malignant peritoneal mesothelioma 17 years after radiotherapy for seminoma of the testis. Although asbestos exposure is considered to be the major risk factor for the development of malignant mesothelioma, prior therapeutic radiation has also been postulated as a causative factor. The unexplained appearance of ascites or pleural effusion within a previously irradiated area should be considered suggestive of malignant mesothelioma in any long-term survivor of cancer. In addition, the patient suffered a deep vein thrombosis four years before the diagnosis of mesothelioma. Deep vein thrombosis is a common complication of malignant disease, and is often the first clue to occult malignancy.

Case Report

In July 1999, a 52-year-old Japanese man was referred to us for evaluation of ascites and bilateral common iliac vein obstruction. He had worked for over 30 years as a plasterer, but had no history of exposure to asbestos. In 1982, he had been treated for a seminoma of the right testis. Orchiectomy had been performed, followed by radiation therapy, to the iliac region (32 Gy), to the paraaortic region (61 Gy), and to the right kidney (51 Gy). He was doing well until 1995, when he was admitted to another hospital with lower leg edema. He was diagnosed as having right common iliac vein obstruction by angiography. Anticoagulation therapy with warfarin was administered and the edema disappeared. Warfarin administration was stopped in 1996. In December 1998, he was readmitted with lower leg edema and ascites, and treated with furosemide 20 mg. On admission to our hospital, a physical examination revealed cutaneous venous dilatation of the abdominal wall and massive ascites, but no lower leg edema. A hematological examination revealed a white blood cell count of 5,700/μl, a red blood cell count of 254×10^4/μl, a hemoglobin concentration of 6.7 g/dl, a hematocrit of 21.6% and a platelet count of 44.4×10^4/μl. The erythrocyte sedimentation rate was 164 mm/h, and the serum level of C-reactive protein was 16.5 mg/dl. Coagulation studies revealed an elongation of activated partial thromboplastin time (44.8 seconds, vs 31.6 seconds in control) and a high concentration of fibrinogen (434 mg/dl) and fibrin degradation product (40 μg/ml). Prothrombin time, protein C and protein S activities were normal. Serologically, antinuclear antibodies, lupus anticoagulant, and anticardiolipin - β2-glycoprotein I complex antibodies were negative. Total protein was 7.8 g/dl with 31.5% γ-globulin. Serum levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase were 27 IU/l, 22 IU/l, and 312 IU/l, respec-
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The serum level of sialyl Lewis X-i was 216 U/ml (negative<38 U/ml). Other tumor markers were not elevated. Magnetic resonance angiography revealed an obstruction from the bilateral common iliac vein to the lower end of inferior the vena cava, and a compensatory development of the left gonadal vein (Fig. 1). Abdominal computed tomography and magnetic resonance imaging (Fig. 2) demonstrated massive ascites and a mass (2x1.5 cm) near the gastric lesser curvature.

A 67Ga scan revealed an abnormal uptake at the mass and omentum lesion (Fig. 3). Further examination of ascites disclosed an exudative effusion with elevated levels of sialyl Lewis X-i and hyaluronic acid, 2,580 U/ml, and 21,000 ng/ml, respectively. Cytological study of the ascites revealed atypical mesothelial cells, but was otherwise non-diagnostic. Laparoscopically, all surfaces of the parietal and visceral peritoneum were thickened, granular, and pale brown (Fig. 4). Histologic examination of laparoscopic biopsy specimens disclosed a well-differentiated epithelial variant of malignant mesothelioma. Microscopic examination showed that the tumor was composed of relatively large polygonal epithelioid cells that coalesced to form a papillary pattern (Fig. 5). Immunohistochemical staining with keratin, vimentin, and thrombomodulin were posi-

Figure 1. Magnetic resonance angiography showing an obstruction from the bilateral common iliac vein to the lower end of the inferior vena cava (arrowhead), and a compensatory development of the left gonadal vein (arrows).

Figure 2. Abdominal computed tomography showing massive ascites and a mass near the gastric lesser curvature (arrow).

Figure 3. 67Ga scintigraphy showing abnormal uptake at the mass (arrowhead) and omentum lesion.

Figure 4. Laparoscopic finding of the visceral peritoneum showing thickened, granular, and pale brown surfaces.
Figure 5. Laparoscopic biopsy specimen of the peritoneum showing a well-differentiated epithelial variant of malignant mesothelioma. (A) The tumor was composed of large epithelioid cells arranged in a papillary pattern (HE stain, ×60). (B) Immunohistochemical staining (×30) with keratin, vimentin, and thrombomodulin were positive. CEA staining was negative.
tive. CEA staining was negative. These findings indicated that the tumor was a malignant epithelioid mesothelioma.

After confirmation of the diagnosis, the patient received two courses of intraperitoneal infusion of cisplatin. Although the chemotherapy reduced the ascites, the overall response was poor. The chemotherapy has been continued for six months.

**Discussion**

Long-term cancer survivors treated with chemo- and/or radiotherapy, are at a high risk of developing secondary malignancies. As the population of cancer survivors is increasing, treatment-related secondary malignancies are a growing concern. Although exposure to asbestos is considered the major risk factor for the development of malignant mesothelioma, prior therapeutic radiation has been postulated as a causative factor. There are currently more than 20 reports in the literature of patients who developed mesothelioma after exposure to radiation, including three in Japan (5–7). Cavazza et al reviewed 35 such cases from the literature and their own files (2). They found the most frequently described initial cancer to be Hodgkin’s disease (11 patients): five cases in which mesotheliomas developed after radiation therapy for Wilms’ tumor or breast carcinoma and four after radiotherapy for seminoma. The mean time between exposure and the appearance of mesothelioma was approximately 19.5 (range, 5 to 41) years. This latency is characteristic of radiation-related solid tumor’s, a minimum of 10 years is typically required for development (8). As with asbestos-related mesotheliomas, post-irradiation mesotheliomas are primarily of the epithelial type (22 of 28 patients). The present case shows certain similarities to previous cases of malignant mesothelioma after radiation exposure. No history of asbestos exposure could be elicited from the patient or his relatives. The initial diagnosis was seminoma of the testis, with an epithelial type of malignant mesothelioma developing in a previously irradiated area. The interval from the time of irradiation to the diagnosis of mesothelioma was 17 years. It is highly likely that this malignant peritoneal mesothelioma was a secondary neoplasia related to radiotherapy.

Experimental studies support a role for radiation in the pathogenesis of malignant mesothelioma. Sanders and Jackson (9) reported the development of malignant mesothelioma in rats after intraperitoneal administration of radioactive plutonium. Warren et al (10) noted an increased incidence of mesothelioma in rats after irradiation and administration of asbestos, compared with animals that received asbestos alone.

Neugut et al (3) reported that there was no significant elevation in the risk of developing mesothelioma after thoracic radiotherapy. They performed a retrospective cohort study utilizing 251,750 women registered with breast carcinoma and 13,743 people with Hodgkin’s disease. However, there were several limitations to their study. One was the relatively short follow-up (maximum, 20 years). Another was the possibility that a significant number of pleural effusions were misdiagnosed as breast carcinoma or Hodgkin’s disease rather than as new primary malignant mesothelioma.

In the present case, the right common iliac vein obstruction was found four years before the diagnosis of malignant peritoneal mesothelioma. It is likely that the obstruction was caused by thromboembolism, not by tumor embolism. Because the $^{68}$Ga scan did not reveal an abnormal uptake at the obstructed vein, in contrast to the strong uptake at the mass near the gastric lesser curvature and the omentum lesion. Thromboembolism is the most common complication in patients with a malignant disease. The incidence of clinical episodes of thromboembolism in patients with cancer varies from 1% to 11% (11). Mucin-secreting adenocarcinomas of the gastrointestinal tract are most often associated with thromboembolism, but cases in patients with lung, breast, ovarian, and prostate tumors are also reported (11). In cases with malignant mesothelioma, it is described that clotting abnormalities occur in 10–20% (4). Antman et al (12) reported that clotting abnormalities complicated the course of five patients with malignant peritoneal mesothelioma: disseminated intravascular coagulation in two, extensive thrombosis and concurrent pulmonary emboli in two, hemolytic anemia and phlebitis in one. Carrington and Adams (13) also reported a case of jugular vein thrombosis associated with malignant pleural mesothelioma. Aderka et al (14) reported that in 34% of the cases, idiopathic deep vein thrombosis was the first clue to occult malignancy and preceded its diagnosis by 4 to 68 months. In the present case, a diagnosis of malignant mesothelioma was established 4 years after the thrombotic episode.

It is also known that patients who have received radiation therapy are at increased risk of deep vein thrombosis (15–17). Graf et al (15) reported that the incidence of deep vein thrombosis was 7.6% in patients with gynecological cancer treated with primary and postoperative radiotherapy. Of these, 60% occurred during radiotherapy, and 10% in the postoperative period. The remaining occurred in patients with additional risk factors such as tumor progression. In the present case, the interval from the time of irradiation to the diagnosis of thrombosis was 13 years. The radiotherapy might have played a role in the deep vein thrombosis in cooperation with the progression of peritoneal mesothelioma.

**Conclusion**

We reported a rare case of malignant peritoneal mesothelioma associated with deep vein thrombosis following radiotherapy for seminoma of the testis. Idiopathic deep vein thrombosis in an otherwise healthy patient should be followed up and examined periodically for occult cancer. The unexplained appearance of ascites or pleural effusion within a previously irradiated area should be considered suggestive of malignant mesothelioma in any long-term survivor of cancer.

**References**

2) Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant me-