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Brief Report

ABDOMINAL MALIGNANT MESOTHELIOMA FOLLOWING AUTOLOGOUS BONE MARROW TRANSPLANTATION: A Case Report

R. Miniero and I. Tardivo □ Department of Pediatrics, San Luigi Hospital, University of Turin, Turin, Italy

M. De Simone □ Department of Surgery, San Giovanni Battista Hospital, Turin, Italy

L. Gubetta □ Department of Pathology, San Luigi Hospital, University of Turin, Turin, Italy

S. Orecchia □ Department of Pathology, SS Antonio e Biagio Hospital, Alessandria, Italy

P. Cacciotti □ Department of Medical Sciences, University of Piemonte Orientale, Alessandria, Italy

G. Gorzegno □ Department of Medical Oncology, San Luigi Hospital, Orbassano, Turin, Italy

□ *Secondary malignancies are a well-known late complication occurring in patients who undergo bone marrow transplant (BMT) during childhood. A boy with acute lymphoblastic leukemia experienced a BM relapse at the age of 14 years and underwent an autologous BMT conditioned with TBI and melphalan. Sixteen years later a malignant mesothelioma of the peritoneum was diagnosed. A surgical approach according to the Sugarbaker technique and hyperthermic peritoneal perfusion with CDDP and Adriamycin were performed. The patient is alive and well after a follow-up of 20 months. To the authors' knowledge this is the first case of mesothelioma as a secondary malignancy after BMT.*

Keywords. *bone marrow transplantation, mesothelioma, second tumor*

Secondary malignancies (SMs) are well-recognized late effects occurring in children who have been treated conventionally for a solid tumor or a hematological neoplasm [1]. More recently it has been shown clearly that bone marrow transplantation (BMT) represents a further SM-related risk factor in long-term survivors. Actually, transplanted patients have to face a unique

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Address correspondence to Prof. Roberto Miniero, Department of Pediatrics, San Luigi di Orbassano Hospital, Strada Gonzole, 10, 10043 Orbassano, Turin, Italy. E-mail: roberto.miniero@unito.it

set of problems, including genetic predisposition, underlying primary cancer and related treatment, conditioning regimens with high-dose chemotherapy alone or associated with total body irradiation (TBI), immunosuppression, and viruses. Each factor has been assumed to play a role in the development of SM [2–5]. Most studies have focused on SMs following allogeneic transplant rather than on autologous BMT. However, evidence is growing that the SM rate also increases in the autologous setting. This paper outlines the case of a young adult who has been diagnosed with malignant abdominal mesothelioma 15 years from the autologous BMT he had undergone in his childhood for acute lymphoblastic leukemia (ALL).

CASE REPORT

In 1981 a 10-year-old boy with a diagnosis of ALL was treated with cranial irradiation (2400 cGy) according to the AIEOP (Italian Association of Pediatric Hematology and Oncology) Protocol 7902. Then in 1985 he experienced an isolated bone marrow relapse [6]. After a second complete remission (CR) he underwent autologous BMT, with Campact-1 purged harvest. The conditioning regimen consisted of melphalan 110 mg/m^2 and TBI as a single dose of 1000 cGy. The post-transplant course was uneventful. The patient remained in CR until March 2001, when a routine abdomen ultrasonography showed the presence of supramesocolic and submesocolic ascitic fluid. The CT scans confirmed that it was a conspicuous ascitic fluid with some peritoneal thickening, in agreement with the diagnosis of neoplasm. The paracentesis demonstrated muddy fluid with lymphocytes, some histiocytes and red blood cells. Laparoscopy showed a military peritoneal seeding present everywhere (visceral and parietal).

The histological diagnosis was epithelioid malignant mesothelioma. A cytogenetic study was performed on the short-term culture of primary cell line. Metaphases were stained with the G-banding method and analyzed in accordance with ISCN guide lines. The karyotype findings were complex and heterogeneous: aneuploidy, polyploidy, and structural abnormalities. The most frequent chromosomal abnormalities were del (1p), del (5), del (6p), del (8q), −9, −17, and chromosomal rearrangements t (7; 17) and t (10; 19). Moreover, the tumor cells were assayed for SV40 at PCR and RT-PCR and the results were negative. A thorough investigation on the patient's familiar and environmental history ruled out any asbestos exposure.

Surgery was performed according to Sugarbaker's technique. A radical greater omentectomy with splenectomy, a partial right hemidiaphragm peritonectomy, and pelvic peritonectomy without visceral resections were performed. At the end of cytoreduction many nodules less than 5 mm were present with important visceral extension. Hyperthermic peritoneal perfusion with CDDP 185 mg (100 mg/sm) and Adriamycin 50 mg (28 mg/sm) at 42°C, maintained for 60 min [7, 8]. The patient was then treated with

systemic CDDP (70 mg/m^2) and Gencytabin (1000 mg/m^2) (4 courses). At present the patient is fine without any disease progression at the 20-month of follow-up.

DISCUSSION

BMT is curative for many patients with leukemia, but there is growing concern about the late effects of the procedure, particularly the occurrence of SMs. Bhatia investigated 2150 BMT recipients (of whom 1400 were allogeneic and 750 autologous). Eight solid tumors were observed in the allogeneic transplant patients vs. 7 in the autologous BMT group [2]. Later on, the same authors evaluated 2129 patients who had undergone BMT for hematological malignancies (1157 allo and 759 auto). Twenty-seven solid tumors were found in the allogeneic transplant patients and only 2 in the autologous transplant recipients. The cumulative incidence rates for new malignancies were 6.4 and 1.6% at 10 years for the patients who had received allogeneic and autologous bone marrow, respectively. The incidence of SM increased with follow-up: the younger the patient, the higher the risk, which, however, declined with age.

The pathogenesis of post-transplant solid tumors is still incompletely understood; observations in autologous transplant recipients are of great interest because the etiological factors accounting for SM in allogeneic settings, such as chronic alloantigen stimulation, chronic graft-versus-host disease (GvHD), and severe immunosuppression, may be ruled out. The risk for solid cancer turned out to be higher with TBI containing conditioning regimens; fractionated TBI seemed to be associated with a reduced risk of secondary tumors compared to single dose TBI. In a multicenter survey on almost 20,000 recipients of allogeneic BMT, of whom 3200 had survived for 5 or more years, Curtis confirmed that conditioning regimen containing TBI, without differences in the administration of single doses or fractionated doses, is a contributing factor to an increase of 3–4 times the risk of occurrence of solid tumors compared to patients who did not undergo irradiation [4].

As for histology, the types of cancer observed following transplant are very heterogeneous. An increased risk was observed for melanoma, cancers of the oral cavity, liver, thyroid, bone connective tissue, and brain; interestingly, there is a documented association with squamous cell carcinoma and chronic GvHD has been well documented. Breast cancer, gastrointestinal tract cancer, rectal cancer, lung cancer, and mucosal malignancies were also observed. Furthermore, few rare tumors were diagnosed as meningioma, synovial sarcoma, malignant fibrous histiocytoma of the liver, Kaposi sarcoma of the visceral organs, and bone and connective tissue cancers [2–5].

To our knowledge no other case of mesothelioma has been reported so far. Mesothelioma is an uncommon malignancy in the general population; primary abdominal mesothelioma is more rare than pleural mesothelioma,

as it accounts for only 10% of all primary cases [9, 10]. The main risk factor for the occurrence of this malignancy is asbestos exposure. More recently therapeutic radiation has been recognized to be an etiological factor, as shown by a number of case reports. The interval between radiation exposure and the onset of mesothelioma ranges from several years to 41 years. Most cases of secondary mesothelioma are pleuric mesothelioma occurring in patients irradiated for breast carcinoma, Hodgkin disease, and cervical cancer. Some cases of abdominal mesothelioma following radiotherapy have been reported in adult cancer patients. Few children with Wilms tumors and Hodgkin disease have been referred; in all cases the interval between primary tumors and secondary cancer was very long (14–41 years). As for subtype, almost all cases of mesothelioma developed in irradiated area were epithelial as in our case.

The association of exposure to therapeutic radiation and the development of cancer has been well documented for many years. With Hodgkin disease and breast cancer, SMs appear more frequently in the irradiation field than in nonirradiated areas. Dose, dose rate, fractionation, and biological factors, including age, primary disease, and genetic factors, may play a role [11–16]. Radiogenetic cancers generally occur after a long period of time (in general, more than 10 years); furthermore, the risk for their occurrence is higher among patients irradiated at a young age.

In our case TBI had been performed when the patient was 15 years old and the disease-free interval after transplant was 15 years, which is consistent with the known latency period of radiation induced mesothelioma. In TBI the irradiation dose is significantly lower than the doses used to treat solid tumors but the target volume is the patient's total body and total dose is administered in a very short time. Certainly this has important consequences for the risk of SM. Finally, the subtype of the form of mesothelioma developed by this patient was epithelioid, as in most cases following radiotherapy reported by others. Epidemiological studies on malignant mesothelioma have well established that exposure to asbestos fibers is the primary cause; more recently it has been showed that SV40 virus may contribute with asbestos or alone to the development of this malignant phenotype. Our case was negative for asbestos and SV40 exposure and this strongly suggests the main role played by TBI in the development of mesothelioma in the patient. The long interval from irradiation to the occurrence of mesothelioma and the histological subtype agree with the data observed in other postirradiation forms of mesothelioma reported by previous studies.

Most mesotheliomas have complex karyotypes with different clonal chromosome alterations. Our case displayed many abnormalities of karyotype, most of them not previously observed; on the contrary, del (1p) and monosomy 9 present in this case were frequently described in malignant mesothelioma and it has been supposed to play a critical role in the pathogenesis of the

tumor. This case supports previous observations in solid tumors suggesting an association between exposure to ionizing radiation and the occurrence of this secondary peritoneal mesothelioma.

Primary peritoneal mesothelioma is usually rapidly fatal, with a median survival of less than 1 year. SMs often show a more severe prognosis than primary tumors with the same histotype and their treatment can be problematic. Most postirradiation malignant mesotheliomas had a poor outcome. Our case in now alive and well 18 months after the diagnosis. The treatment was aggressive with combined surgical technique aiming at a subtotal parietal and visceral lesion removal (peritonectomy) and at the perfusion of peritoneal cavity with chemo-drugs in hyperthermia according to the Sugarbaker technique. To our knowledge this is the first time that this approach has been tried in a patient with secondary peritoneal mesothelioma.

The length of follow-up is too short to attempt a conclusion, but the good results obtained with this technique in peritoneal carcinomatosis may be encouraging for aggressive treatment of secondary mesothelioma. The risk of secondary leukemia and lymphoma does not extend beyond the first decade after transplant; the risk of radiation-related solid tumors is expected to increase with longer follow-up, especially with children irradiated at young age. Long-term survival of transplanted children has become possible from 1980s onward; many "survivors" are entering the age at which adult cancers typically develop. SMs that have not yet been encountered are likely to be observed in the future. For this reason patients should be followed indefinitely by a dedicated team, including a pediatrician and an internal medicine specialist, to detect early cancer and precursors lesions. Finally, preventive health consideration and lifestyle characteristics like smoking, nutrition, and work are warranted to a higher degree than in the general population for long-term survivors of childhood cancer.

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