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Clear cell sarcoma of the gastrointestinal tract after very low-dose therapeutic radiation therapy: a case report

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Abstract Childhood cancer survivors are at risk for developing second malignant neoplasms. Very-low-dose therapeutic radiation therapy (RT) may be used to treat infants with Stage 4S neuroblastoma. We report a case of a patient who subsequently developed clear cell sarcoma of the gastrointestinal tract nearly 15 years after treatment with very low-dose therapeutic RT (4.5 Gy) for Stage 4S neuroblastoma.

Second malignant neoplasms (SMNs) are a well-recognized occurrence in childhood cancer survivors exposed to chemotherapy and radiation [1]. We present a case report of a 15-year-old male who developed clear cell sarcoma of the gastrointestinal tract after treatment with very low-dose therapeutic radiation therapy (RT) for Stage 4S neuroblastoma as an infant.

1. Case report

A 15-year-old male presented to his local emergency department with a one-week history of intermittent fevers. He also reported a three-month history of headaches, fatigue, night sweats and a 13-pound weight loss. On physical exam, he was below the fifth percentile for height and weight and pale with oral thrush. Laboratory tests were significant for microcytic anemia.

The patient's past medical history was notable for Stage 4S neuroblastoma limited to the liver diagnosed at 2 months, which presented initially with massive hepatomegaly. Subsequent imaging revealed a multi-nodular liver and elevated urine catecholamines. Molecular biology studies showed the tumor was hyperdiploid and n-MYC-non-amplified. As the patient had massive hepatomegaly with clinical compromise, RT was indicated to prevent respiratory distress, bowel necrosis, and renal failure due to oliguria. The patient received 4.5 Gy in three 1.5 Gy fractions to the liver as well as systemic therapy with cyclophosphamide (7350 mg/m^2), doxorubicin (245 mg/m^2), cisplatin (180 mg/m^2), and etoposide (400 mg/m^2) per Pediatric Oncology Group Study 9243. He achieved complete remission seven months after initiation of therapy.

The patient underwent extensive medical evaluation, which ruled out all suspected diagnoses including

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inflammatory bowel disease and infection. Finally, positron emission tomography (PET) scan revealed an FDG-avid soft-tissue mass within the distal ileum. A subsequent exploratory laparotomy with resection of the 4 cm mass and distal ileum and mesenteric lymph node dissection was performed. Surgical margins and lymph nodes were negative. The specimens were described as sheets of round cells with focal clear cell and rhabdoid features staining positively for S100 protein and vimentin. Fluorescent in-situ hybridization was positive for EWSR1 gene rearrangement, confirming clear cell sarcoma of the GI tract. As the tumor was localized and there are no standardized therapy guidelines for clear cell sarcoma, the patient did not receive adjuvant chemotherapy and a conservative watchful waiting approach with serial imaging every 3 months was taken.

Approximately 1 year after the initial surgical resection, the patient was found to have biopsy-proven metastatic clear cell sarcoma in the liver. He underwent an exploratory laparotomy and resection of a 1 cm liver nodule, and was referred to the National Cancer Institute for enrollment on trial 08-C-0007, a pediatric phase I trial of ipilimumab.

2. Discussion

Clear cell sarcoma of the gastrointestinal tract, first described in 2006, is a rare disease characterized by an EWS-CREB1 fusion and strong S100 protein reactivity. Melanoma markers such as HMB45, which are common to non-gastrointestinal clear cell sarcomas, otherwise known as melanomas of the soft parts, are not present [2]. To the best of our knowledge, there have been no reports of clear cell sarcoma of the gastrointestinal tract as SMNs in childhood cancer survivors.

Childhood cancer survivors are at increased risk of developing a variety of subsequent neoplasms as a result of their therapy. In the Childhood Cancer Survivor Study cohort of 14,358 patients, 30-year cumulative incidence of SMNs was 9.3% [3]. While hematologic, central nervous system, and soft tissue SMNs are typical, subsequent gastrointestinal malignancies have been seen as well, especially in patients who received direct abdominopelvic irradiation. The British Childhood Cancer Survivor Study reported 105 digestive SMNs in their cohort of 17,981 patients and 1.4% cumulative incidence of subsequent colorectal cancer in survivors who were treated with direct abdominopelvic irradiation [4]. Similarly, the Childhood Cancer Survivor Study reported gastrointestinal SMN risk was 4.6-fold higher in childhood cancer survivors than the general population, and even higher for those who received abdominal radiation [5].

Interestingly, though the association of increased risk of SMNs and treatment with RT has been described in the literature, the dose-risk relationship is not well-defined [6]. A recent multi-center study examining 4568 childhood cancer survivors reported the risk of developing a secondary malignancy in a digestive organ exhibited a strong dose–response relationship: patients who received between 10 to 29 Gy and patients who received greater than 30 Gy had odds ratios of 5.2 and 9.6, respectively, when compared to survivors who had not received RT [7]. The cumulative incidence rate of secondary sarcoma was similarly found to be radiation dose-dependent among 266 Ewing sarcoma patients with no SMNs developing in patients receiving <48Gy [8]. Likewise, the German Childhood Cancer Registry cohort only experienced increased risk of SMNs for doses ≥65 Gy [9]. In contrast, childhood Hodgkin's lymphoma survivors treated with low-dose radiation of 15 to 25.5 Gy remained at significant risk for sarcomas, breast, and thyroid cancers at frequencies similar to those of their peers treated with high-dose radiation [10].

Though our patient was treated with very low-dose therapeutic RT of 4.5 Gy to the abdomen, he may have developed a secondary malignancy. However, given our patient's unique medical history, the possibility of Li-Fraumeni syndrome cannot be excluded and it is possible that the patient was predisposed to developing two different, unrelated malignancies. Of note, patients with Li-Fraumeni syndrome are known to be at increased risk of developing radiation-related SMNs [11]. Further, neuroblastoma has been reported to be weakly associated with germline TP53 mutations [12].

While very low-dose therapeutic RT is less commonly used today, it may be necessary to save the life of an infant with Stage 4S neuroblastoma. Though this patient's presentation was unique, it is a reminder of the importance of ongoing surveillance of late effects and SMNs in our growing population of childhood cancer survivors.

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