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Case Report

Secondary Malignant Non-Rhabdomyosarcoma Soft Tissue Sarcomas After Hematopoietic Stem Cell Transplantation in Childhood for Acute Leukemia

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Abstract

People surviving after a hematopoietic neoplasm treated in childhood carry a higher risk of developing a second cancer. Few cases of Soft Tissue Sarcomas (STS) as a second malignancy have been described in the literature. We report four non-rhabdomyosarcoma soft tissue sarcomas as second malignancy in three patients treated for acute leukemia in childhood, with a median duration from the end of the treatment of 11 years (6 to 14). All of them had hematopoietic cell transplantation including total body irradiation. First, we describe the unusual case of a 29-year-old man who developed two soft tissue sarcomas 12 years after the successful treatment of his acute leukemia with allogenic hematopoietic stem-cell transplantation. Then, we complete our report with two other cases of non-rhabdomyosarcoma STS after successful treatment of acute leukemia.

Keywords: Acute Leukemia; Hematopoietic Cell Transplantation; Soft Tissue Sarcoma; Total Body Irradiation

Abbreviations: AL: Acute Leukemia; ALL: Acute Lymphoblastic Leukemia; CNS: Central Nervous System; COPADM: Vincristine, Methotrexate, Cyclophosphamide, Doxorubicin and Prednisone; CT: Computed Tomography; DDIT3: DNA Damage-Inducible Transcript 3; DFSP: Dermatofibrosarcoma Protuberans; FISH: Fluorescent in Situ Hybridization; FNCLCC: French Federation of Cancer Centers Sarcoma Group; GVHD: Graft Versus Host Disease; HCT: Hematopoietic Cell Transplantation; HLA: Human Leukocyte Antigen; HPS: Hematoxylin, Phloxine and Saffron; IHC: Immunohistochemical; IT: Immunosuppressive Therapy; MPNST: Malignant Peripheral Nerve Sheath Tumor; STS: Soft Tissue Sarcoma; TBI: Total Body Irradiation; VEDA: Vincristine, Etoposide, Cytarabine and Dexamethasone

Background

People surviving after hematopoietic neoplasm carry a high risk of developing a second cancer, in particular skin and mucosal carcinomas, and hematopoietic neoplasms [1, 2]. This oncogenicity is attributed to exposure to chemotherapy, partial or total body irradiation and Hematopoietic Cell Transplantation (HCT), which are often associated in aggressive treatment protocols and are used to treat Acute Leukemia (AL) [3-6]. Skin neoplasms seem to be more frequent after HCT [7]. Few data are available concerning Soft Tissue Sarcomas (STS) as a second malignancy following treatment of acute leukemia [8]. STS are rare and form a heterogeneous group of malignant mesenchymal tumors with an incidence evaluated at 3.6/100 000 cases per year [9]. STS account for approximately 1% of all cancers in adults [10].

The current World Health Organization classification of STS includes more than 50 histological subtypes that are associated with specific clinical and therapeutic features [11]. We herein report four non-rhabdomyosarcoma STS as second malignancy in three patients treated for acute leukemia in childhood, all of whom had had hematopoietic cell transplantation including total body

irradiation. First, we describe the unusual case of a young man who developed two different histological subtypes of malignant sarcoma in two different sites 10 years after curative therapy for a bi-phenotypic AL, including unrelated cord blood transplantation. We complete the report with two other cases of STS after curative therapy for acute leukemia.

Case Presentation

A 29-year-old man was addressed to the oncology department of Timone Hospital (Marseille) in October 2011 for a spermatic cord lesion. He had a medical history of bi-phenotypic AL diagnosed at 17 years of age in September 2005. White blood cell count did not reveal any hyper-leukocytosis and there was no sign of central nervous system infiltration. Karyotype was normal. The patient underwent an induction chemotherapy in the FRALLE 2000 group T protocol with prednisone, vincristine, daunorubicin, L-asparaginase and cyclophosphamide. Then, he received consolidation therapy with three cycles of chemotherapy: cycles 1 and 3 with Vincristine, Etoposide, Cytarabine and Dexamethasone (VEDA); and Cycle 2 With Vincristine, Methotrexate, Cyclophosphamide, Doxorubicin and Prednisone (COPADM). Because of the high risk of relapse associated with biphenotypic leukemia, an HCT was proposed.

His reduced-intensity conditioning regimen included chemotherapy with cyclophosphamide and fludarabine, and total body irradiation (2 grays). Since no donor could be found in the international registries, a double cord blood transplantation was performed in February 2006 with an HLA A and DR mismatch (HLA compatibility 4/6). The patient developed acute cutaneous and chronic digestive GVHD needing long-term immunosuppression (ciclosporin and corticosteroids) up to 16 months' post-transplant. He was free of leukemia 10 years after the HCT. In September 2012, patient self-examination revealed a left spermatic cord nodule. Histopathological examination of the resected tissue revealed a sharply demarcated mass composed of a spindle-to-ovoid proliferation of monomorphic cells embedded in an abundant myxoid stroma with a "chicken wire" capillary vasculature (Figure 1). In some areas, monovacuolar lipoblasts were visible.

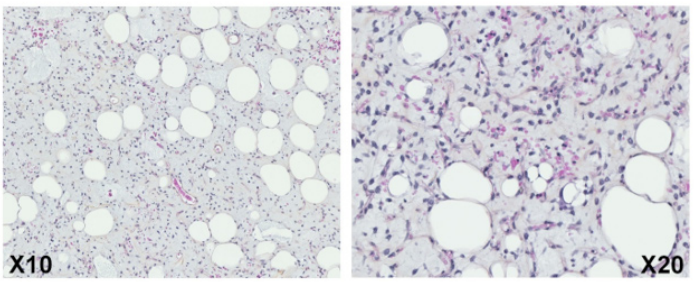

Figure 1: Histology of myxoid liposarcoma Proliferation of oval-shaped non-lipogenic cells and signet ring lipoblasts in a myxoid stroma (X10). Delicate arborizing vasculature is visible at higher magnification (X20).

There was no necrosis. The mitotic index was lower than 10 mitotic figures per 10 high-power fields. FISH analysis showed a rearrangement involving DDIT3 (CHOP) and FUS genes. The diagnosis of myxoid liposarcoma grade I according to FNCLCC grading system was made. Thoracic, abdominal and pelvic computed tomography showed no evidence of metastatic spread. No further treatment was given after the revision surgery and the patient is considered today to be in complete remission. However, in September 2017, an abdominal wall nodule was discovered. The abdominal MRI showed an 8.5 x 6.5 cm gadolinium-enhanced lesion. An incisional biopsy was performed in October 2017, which revealed a diffuse infiltration of the dermis and sub-cutis by a dense but low-mitotic proliferation of monotonous spindle cells, arranged focally in a storiform architecture with a characteristic non-destructive infiltration of the subcutaneous fat (Figure 2).

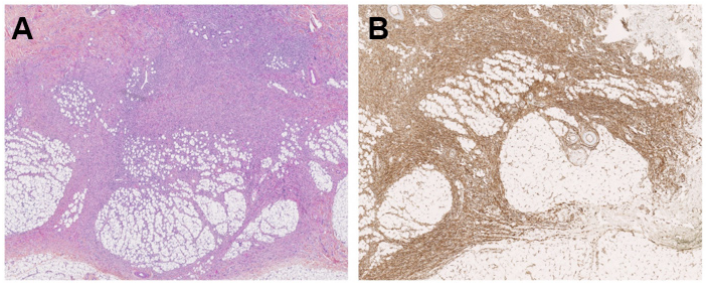

Figure 2: Histology of dermatofibrosarcoma protuberans **(A)** Proliferation of spindle cells with infiltration of subcutis with honeycomb appearance. **(B)** Diffuse and intense expression of CD34 protein by IHC.

Immunohistochemical (IHC) study showed diffuse and intense CD34 expression (without expression of S100 protein or factor XIII), which was highly suggestive of a Dermatofibrosarcoma Protuberans (DFSP). Of note, the DFSP did not display any areas of transformation into a fibro sarcoma. FISH analysis detected a COL1A1-PDGFB gene fusion which confirmed the diagnosis. Revision surgery was performed in November 2017. Testing for the germline p53 mutation (Li-Fraumeni syndrome) was indicated and the result ruled out the presence of any predisposing factor. Therefore, the tumorigenesis was attributed to the prior therapy alone. There are two other cases of STS that developed after successful AL treatment in the Timone Hospital registry, which includes more than 600 acute leukemia patients treated over a 20-year period. The first case was an 18-year-old man who developed a synovial sarcoma of the chest wall 14 years after his leukemia treatment.

He was treated for Acute Lymphoblastic Leukemia (ALL) in 1987 and was in complete remission. CNS relapse was diagnosed in 1998 and was successfully treated by chemotherapy and autologous HCT. In 2001, he developed an 80 x 90mm synovial sarcoma of the 11th left rib, grade III (FNCLCC grading system). Curative surgical resection was performed, completed by adjuvant

chemotherapy with vincristine and ifosfamide. The second case was a 22-year-old woman who developed a Malignant sPeripheral Nerve Sheath Tumor (MPNST) after she received treatment for an ALL1 in accordance with the FRALLE 92 protocol, followed by an autologous HCT. Twelve years after her complete remission, she developed a 63mm high-grade MPNST of the right psoas. Both patients received Total Body Irradiation (TBI), 12 grays, for their HCT conditioning regimen associated with aracytin and melphalan-based chemotherapy. The median time from initial cancer to secondary sarcoma was 11 years (6 to 14).

Discussion and Conclusion

Around 1-2% of all childhood cancer survivors develop secondary sarcomas with a median time from the initial cancer of 12 years [12,13]. In the report from the Childhood Cancer Survivor Study, in a cohort of 14 372 childhood cancer survivors, only 108 developed sarcomas (0.8%). Most of the secondary sarcomas were osteosarcoma (31) and MPNST (19). The other types of sarcoma were rarer. The association of acute leukemia and sarcoma was rare: out of 4833 patients included with acute leukemia, only 10 developed STS (0.2%). The co-existence in the same patient of two different STS in two different sites is exceptional. We hypothesize that the AL treatment was involved in the pathogenesis of this uncommon co-occurrence. Notably, the role of radiotherapy, HCT and chemotherapy regimens in the development of a secondary malignancy is well described in the literature, with a latency period after HCT of 3 to 5 years [3, 14].

This risk continues to rise with prolonged survival, and 10 years after HCT, the cumulative incidence of second cancer rises to 2.2% [14]. Osteosarcoma as a secondary malignancy after an HCT is rare, and is mostly related to relapsed or resistant acute leukemia [15, 16]. Many studies suggest that second malignancies including STS may develop in the setting of a chronic cutaneous GVHD [7, 17, 18]. It is thought that persistent skin inflammation creates a favourable micro-environment and leads to the emergence of neoplastic cells, while stimulating epithelia regeneration and angiogenesis [17, 19]. However, in our cases, the sarcomas occurred outside of the skin areas affected by chronic GVHD, and for two of them, in a context lacking allogeneic HCT. Our three patients received TBI in their HCT conditioning. Radiotherapy is the most significant risk factor even in survivors exposed to very low-dose radiation, such as patients with myelodysplastic syndrome or acute leukemia [20]. However, osteogenic or soft tissue sarcomas are also usually described but with higher doses than those used for TBI [21].

The role of Immunosuppressive Therapy (IT) used after HCT also deserves attention. Chronic immunosuppression secondary to IT induces a decreased immune supervision and is therefore associated with an increased incidence of malignancy [22]. Of note, chronic GVHD often needs a durable increase in immunosuppressive therapy and may explain the elevated risk of cancer. In the absence of genetic predisposition, the development of two STS was certainly favoured by the antitumoral treatment received in childhood. Furthermore, the increased risk is probably multifactorial, following the combination and interaction of the effects of the chemotherapy regimen, irradiation, HCT, immunosuppressive therapy and the patients' individual susceptibility. The improvement in the management of hematologic neoplasms has dramatically prolonged survival and oncologists must deal with these new specific complications that may occur during a follow-up that is longer. These cases highlight the need to biopsy any unusual soft tissue mass and to undertake prolonged clinical follow-up.

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Authors' Contributions

Conception and design: SS; Manuscript writing: SS and EB; Final approval: SS, EB, JLD, TC, NM, CB, CF; Pathological explorations: TC, NM, CB; Patient's management: SS, CF, NM, CB.

Competing Interests

We have read and understood Annals of Case reports' policy on disclosing conflicts of interest and declare that we have none.

Patient Consent for Publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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