BRIEF REPORT

Malignant Fibrous Histiocytoma Two Years after Autologous Stem Cell Transplant for Hodgkin Lymphoma: Evidence for Genomic Instability

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Secondary malignancies (SMs) in Hodgkin lymphoma (HL) are thought to be related to exposure to alkalating agents, topoisomerase II inhibitors and ionizing radiation, and tend to occur a decade after initial therapy. We report a 14 year old autistic male, who developed malignant fibrous histiocytoma (MFH) two years after autologous stem cell transplantation for advanced stage HL. The MFH and post-surgical reactive tissues exhibited multiple clonal abnormalities. In addition, PHA-stimulated peripheral blood lymphocytes showed increased frequency of non-clonal chromosomal aberrations. The potential role of genomic instability in early onset of SM in our patient is discussed. Pediatr Blood Cancer 2011; 56:1143–1145. © 2011 Wiley-Liss, Inc.

Key words: Autism; Autologous stem cell transplantation; Genomic instability; Hodgkin lymphoma; Malignant fibrous histiocytoma; Non-clonal chromosome aberration (NCCA)

INTRODUCTION

Hodgkin lymphoma (HL) constitutes 6% of all childhood cancers. With the use of effective chemotherapy, radiotherapy, and autologous stem cell transplant (ASCT) in recurrent cases, the prognosis has improved dramatically in HL [1]. The increase in survival rate has placed more emphasis on managing long-term morbidity and mortality among the survivors.

Secondary malignancy (SM) is one of the main contributors to long-term morbidity and mortality in survivors of HL. The cumulative incidence of SMs 20 years after completion of therapy has been reported as 10.6%, which increases to 26.3% at 30 years [2]. Acute leukemia, non-HL and solid tumors including soft tissue sarcomas (STS) are the three main categories of SM [2,3]. While the former two categories are seen often within the initial few years following completion of therapy, the latter predominates a decade following therapy. Depending on length of follow-up and primary treatment modality, STS constitute 8–19% of all SM cases in HL patients [3,4]. Alkylating chemotherapy, radiotherapy, and postulated inherent defects have been proposed as the risk factors for SM development in HL, of which radiotherapy is the major risk factor for STS.

Malignant fibrous histiocytoma (MFH), a form of STS is rare after HL therapy; very few cases have been reported in the adult literature [5–8]. Moreover, most of the post-radiation sarcomas develop more than 10 years following the initial therapy [5–8]. We report a 14 years old autistic male with HL who developed MFH within 3 years of initial HL treatment and 2 years of ASCT and discuss the potential role of genomic instability in early onset SM.

CASE REPORT

A 14 year old autistic male was diagnosed with nodular sclerosing, stage IV-B HL. At presentation, he had extensive tumor burden with bulky intra-thoracic lymphadenopathy, pulmonary nodules bilaterally and large left pleural effusion, enlarged lymph nodes within the periportal and peripancreatic region, and lesions in the anterior cortex of both kidneys. A positron emission tomography (PET) scan demonstrated numerous foci of abnormal FDG activity corresponding to the findings noted on the contrast enhanced CT scan. Cytogenetic evaluation of the involved lymph node tissue revealed multiple complex clonal abnormalities

(Table I). The bone marrow sample showed normal male karyotype without lymphoma involvement.

The patient received chemotherapy as per Pediatric Oncology Group 9425 protocol consisting of doxorubicin, bleomycin, vincristine, etoposide, prednisolone, and cyclophosphamide (ABVE-PC). He did not achieve complete remission after completing a total of seven courses of ABVE-PC chemotherapy. A follow-up PET scan performed after completion of chemotherapy revealed a variable response to treatment with increase in size and intensity of right and left upper lobe lung lesions. In view of primary refractory and progressive disease, he received two cycles of high dose ifosfamide, carboplatin, and etoposide chemotherapy followed by ASCT.

A year following his initial diagnosis, he received carmustine, etoposide, cytarabine, and melphalan, followed by ASCT with 3.20×10^6/kg CD 34 + cells. A follow-up PET scan revealed decreased FDG uptake in most of the tumor, but three foci of abnormal FDG uptake were still seen in the prevascular space in the mediastinum. He received 30 Gy of radiation to the involved chest fields, after which complete remission of HL was achieved and he had remained asymptomatic for 18 months.

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TABLE I. Karyotypes in Various Tissues

Site	Tissue diagnosis	Karyotype findings
Lymph node- at diagnosis	Hodgkin lymphoma	46,XY[cp18] 48,XY,+X,add(4)(q21),+5,+9,del(9)(p13), add(12)(q24.3), −13, t(14;15) (q10;q10),+17[cp2]
Bone marrow- at diagnosis	Normal	46, XY [20]
Soft tissue mass	MFH	46,XY,inv(6)(p21p25) [13] 46,XY,t(3;13)(q12;q34) [2] 46,XY [nonclonal abnormalities 5]
Soft tissue surrounding tumor resection site	Granulation tissue and foreign body giant cell reaction	45,X,Y,t(1;2)(p32;q37),inv(6)(p21q21),der (7)t(7;15)(p15;q21),del(11)(q22),add(12)(q13),t(12;12)(q13;p11.2), −15,del(20(q11.1) [8] 46,XY,add(2)(p25),t(3;6)(p21;p2,del(5)(q13),add(12q22) [6] 46,XY,add(1)(p32),del(2)(p13),t(3;10)(p21;p13),t(7;12)(q11.2;q13), add(9)(q22),add(14)(p13) [5]

Two years after ASCT, he presented with a 10 cm × 8 cm × 6 cm hard immobile subcutaneous lesion involving the left scapula. The lesion was in the field exposed to prior radiotherapy for HL. On evaluation increased FDG uptake was noted on PET scan. Complete local excision of the lesion was done, which showed inflammatory type of malignant fibrous histiocytoma with anaplasia. In view of malignant nature of the tumor a wide local re-excision was performed, it showed granulation tissue with foreign body reaction without any evidence of tumor. Metastatic work-up was negative. Surgical resection was followed by 60 Gy of electron beam therapy to the tumor bed. One year after the radiotherapy, the patient continues to be without evidence of HL or MFH.

Cytogenetic analysis on the tissue samples from the two surgical resections revealed two and three different unrelated abnormal clonal tumor cells, respectively (Table I). In view of marked chromosomal aberrations seen in HL, MFH, and granulation tissue, and short interval between initial therapy for HL and development of MFH, spectral karyotyping (SKY) analysis for genomic instability was performed using peripheral blood lymphocytes [9]. According to standard medical genetics practice, clonal chromosomal aberration (CCA) is reported to be present when the same chromosomal aberration is detected at least twice within 20–40 mitotic figures [10]. Based on this practice standard, CCAs refer to common aberrations with over 4–15% occurrence among the examined cell population. In agreement with this standard, non-clonal chromosome aberration (NCCA) is defined as aberrations with a frequency of less than 4%. In our patient, based on 48 SKY analyzed mitotic figures, there was no CCA detected. However, there was a high level of NCCAs observed pointing at genome instability (Fig. 1) [11–13]. In healthy individuals, cultured lymphocytes show a very low percentage of NCCA, ranging from 0 to 2% [14]. However, in our patient, the frequency of NCCA was 35% among examined mitotic figures, of these 15% were structural NCCA and 20% were the numerical NCCAs (mainly aneuploidy). Interestingly, there was also high frequency of defective mitotic figures (DMF), which are a type of structural NCCA that is also associated with genome instability [11–13]. Based on the examination of 189 Giemsa-stained mitotic figures, the DMF frequency was very high at 15% [12,13].

DISCUSSION

Malignant fibrous histiocytoma, a type of STS has been reported following radiation therapy in HL [5–8]. Though the absolute risk of developing MFH is not known, relative risk (RR) of developing STS is the highest among all SM (RR-135) [3,4]. Multiple unrelated clonal abnormalities are not uncommon

Fig. 1. Representative examples of NCCA. Upper image shows t(15;11;18) and three copies of chromosome 17 and 19. Lower image shows the translocation between chromosome 1 and 2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary. com.]

in STS, it has been documented to occur in three out of the ten cases of post radiation sarcomas reported by Mertens et al. [15]. Most cases of MFH have been reported to occur in adults (18–59 years) who have received more than 40 Gy (40–53 Gy) of radiotherapy and most of them developed MFH after a latent period of more than 10 years [5–8]. The shortest latency period reported in a series of post-radiation sarcoma cases in HL was four years [5]. In our patient, despite smaller radiation dose (30 Gy), MFH developed within 18 months of RT and 34 months of initial therapy, which is very unusual. High dose chemotherapy and ASCT are known to increase the risk of SM [5,8]. Presence of multiple unrelated clonal karyotype abnormalities in both MFH and granulation tissue and very short latency prompted us to investigate for underlying predisposition to malignancy in our case. Although there was no tumor tissue identified by microscopy, there is a possibility of contaminating malignant cells among the reactive tissue cells.

Multiple non-specific numerical and structural aberrations of chromosomes have been well documented in HL [16]. Heng et al. have recently proposed that genomic instability leading to NCCA aberrations might be the main factor in malignant transformation and progression in a majority of cancers [12,17]. NCCA is a newly identified marker of overall genome instability [11–13]. The frequencies of NCCA have been directly linked to tumorigenicity [18]. In normal individuals, the frequency of NCCA in their cultured blood lymphocytes is between 0 and 2% [14]. The elevated frequency of NCCA (35%) detected in our case suggests high level genome instability. However, it is not clear how much of this high-level of instability is caused by recent exposure to chemotherapy or from the individual's inherent chromosomal instability. Nevertheless, further radiation exposure to the local tissue with already known karyotype abnormalities can increase the risk of other SM in our case.

Multiple loci of chromosomal instability (16p11.2, 15q13, and 7q) and increased incidence of PTEN mutations have been identified in a small percentage of children with autism [19,20]. To date, there have been no studies to see whether the genomic instability noted in these patients are associated with increased NCCA, which if present, might predispose them to the development of malignancy. In our case, though the SKY results were very abnormal, the initial karyotype done at the time of diagnosis was normal by classical cytogenetics. Further investigation specifically looking for known loci of chromosomal instability in autism was not performed. In future more studies are needed to better understand the possible association.

In conclusion, the development of MFH as an SM much earlier than normally seen in survivors of HL is very unusual. The presence of multiple clonal cytogenetic abnormalities in tumor and reactive tissues, and further demonstration of high-level NCCA in peripheral blood lymphocytes suggest genome instability in our patient.

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