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Case Report

Therapy-induced Acute Lymphocytic Leukemia with the 11q23 Translocation: 2 Cases and a Review of the Literature

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Abstract

We report two cases of therapy-induced ALL (t-ALL) with the 11q23 translocation (Mixed Lineage Leukemia or MLL rearrangement). Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are well known to occur in patients who had previously received topoisomerase II inhibitors or alkylating agents for the treatment of a prior malignancy. t- ALL, however, is a rare entity. Similar to therapy- induced AML (t-AML) or MDS; t-ALL can also be associated with the11q23 translocation. This translocation typically occurs in t-AML secondary to prior DNA topoisomerase II inhibitor therapy. We present two uniquecases of t-ALL along with the literature review of 30 previously reported t-ALL cases associated with the 11q23 translocation. A balanced translocation at the 11q23 region was observed in most cases as in our review. The MLL gene at locus 11q23 was observed to have a break point in the majority of analyzed cases at a site similar to t-AML. All the t-ALL cases reviewedwith the 11q23 translocation were secondary to prior topoisomerase II inhibitor therapy. The diagnosis of t-ALL was made at a median time point of 19 months from prior therapy. t-ALL, similar to t-AML with an 11q23 translocation, is associated with a poor prognosis. These patients should be considered for allogeneic stem cell transplantation in first complete remission. This therapeutic approach may improve the long term overall survival. However, given the dearth of clinical trials in this select population, further clinical studies need to be done to validate this approach.

Keywords: ALL; t-ALL; 11q23 Translocation; Bone marrow transplant; Secondary leukemia

Introduction

AML (acute myeloid leukemia) occurs at an increased frequency in patients previously treated with alkylating agents and topoisomerase II inhibitors [1]. Leukemia secondary to previous use of alkylating agents is most commonly associated with the rearrangements of chromosome 5 and/or chromosome 7 [1,2]. However, in the 1990s, a small subset of AML was reported by Pedersen-Bjergaard et al. [3,4] along with several other groups [5-10] that had a karyotype specific for *de novo* AML. Most of these patients were reported to have a balanced translocation between the 11q23 region and another chromosome and majority of them had received topoisomerase II directed agent (i.e., the epipodophillotoxins, VP 16 or VM 26 and, to a lesser extent, anthracyclines or their derivatives) for their previous cancers [3,4,9-11].

Interestingly, the occurrence of ALL (acute lymphoid leukemia) secondary to either prior chemotherapy or radiotherapy is very rare [11]. In a pediatric case series of secondary acute leukemias, only 6 % were found to be therapy related ALL (t-ALL) [12]. Andersan et al. [13] reviewed 23 cases of chemotherapy related ALL since 1992, all of which hada balanced 11q23 translocation. All of these patients had received prior topoisomerase II inhibitors [13]. Auxenfants et al. [11] and Pui et al. [9] reported similar associations in their reviews. DNA topoisomerase II therapy is recognized to be strongly associated with the occurrence of balanced translocations of 11q23 and chimeric rearrangements of the MLL gene in t-AML [14]. This is very likely to be the cause of similar genetic anomalies in t-ALL [13].

In this article, we report two observed cases of secondary ALL with t(4;11)(q21;q23) in our institution along with literature review of 30 previously published cases.

Case 1

A 68 year old gentleman presented with a left lung mass that had been incidentally picked up on a routine chest x-ray in March 2007. He was diagnosed with small cell lung cancer and was treated with cisplatin and etoposide for 4 cycles. He also received concurrent 45 Gy in 30 fractions to the mediastinum with a curative intent. He had a complete response to chemo-radiation and went on the receive prophylactic cranial radiation (36 Gy in 18 fractions). He was in complete remission until January 2009, when he presented with fever, malaise and had a marked leukocytosis on laboratory evaluation. His white blood cell count was 288.5 K/uL. He also had mild anemia with hemoglobin at 12.1g/dl and thrombocytopenia with platelets of 39 K/uL. Bone marrow biopsy showed a hyper cellular marrow with lymphoblastic predominance (80 % of bone marrow). The blasts expressed CD 19, HLA-DR, CD22 and TdT andCD10 was found to

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be negative. The morphological and phenotypic appearance of the marrow was consistent with precursor B cell ALL. Further genetic studies demonstrated stable translocation, t (4, 11) with the MLL gene re-arrangementin 91 % of nuclei. He was treated with multi-agent induction chemotherapy per Larsen protocol **(cyclophosphamide, daunorubicin, vincristine, prednisone, l-asparginase)** and an allogeneic hematopoietic transplant was being considered. He achieved a complete morphologic and molecular remission without any evidence of t (4, 11) translocation on FISH analysis after Phase 1. Unfortunately, he relapsed shortly thereafter and decided to pursue comfort measures only.

Case 2

A 31 year old gentleman presented in August of 2007 with a right medial thigh mass which he had noticed while playing soft ball. Subsequently, he was diagnosed to have a high grade soft tissue sarcoma on excisional biopsy**.** The specimen had mixed features of an undifferentiated high grade pleomorphic sarcoma and myxoidliposarcoma**.** He received neoadjuvant chemotherapy with MAI (doxorubicin, total dose was 200 mg per meter squared) and one cycle of cisplatin. He later underwent a limb preserving surgery post chemotherapy. Surgical pathology revealed microscopic evidence of disease at the surgical margins and hence he received adjuvant external beam radiation of 60 Gy to the tumor bed with a boost to the scar of a total of 66 Gy. He had a delayed bone marrow recovery and by fall of 2008, he had developed persistent cytopenias raising the concern for MDS and therapy related leukemia. A bone marrow was performed in November of 2008 which showed marked hypoplasia. Circulating blasts were present in peripheral blood and further testing revealed morphological and phenotypical features consistent with pre-B lymphoblastic leukemia. The lymphoblasts expressed CD19, CD34, TdT, HLA-DR, but they did not express CD10. Cytogenetic studies performed at that time showed the presence of a balanced translocation t(4,11) in 12.6 % of nuclei**.** The break point on chromosome 11 was at band q23-MLL gene. He received mulitagent induction chemotherapy in November of 2008 per Larsen protocol **(cyclophosphamide, daunorubicin, vincristine, prednisone, l-asparginase).** A bone marrow biopsy performed on 1/9/2009 showed no morphologic evidence of leukemia consistent with complete hematologic remission with a negative FISH for MLL rearrangement. He received some additional chemotherapy and CNS prophylactic chemotherapy to maintain remission while awaiting a potential allogeneic stem cell donor. He underwent a non-myeloablative allogeneic stem cell transplant from a matched unrelated donor in June 2009 and he continues to be in remission to date with excellent quality of life (Table 1).

Discussion

We presented two cases of t-ALL with the 11q23 translocation. We also reviewed the published literature and found several more published cases of t-ALL dating back to 1988. In addition to our 2 cases, we reviewed 30 previously reported cases by Auxenfants et al. [11] and Andersen et al. [13] in their separate prior reviews. In our combined analysis of 32 cases of t-ALL, we found a 1:1 male to female ratio. Breast cancer was found to be the most common primary cancer in females (9 out of 17 reported cases), whereas no clear predominance of a single cancer type was seen in males. Twenty five out of 32 patients (78%) had cytogentic abnormalities involving the 11q23 locus of their cells where MLL gene is located. In addition, 22 of the 32 patients (68.7%) had t(4,11) translocations and 10 of the latter had known MLL gene rearrangement. All patients had previously been treated with a topoisomerase II inhibitor alone or in combination with a platinum derivative or a vinka alkaloid. Three patients had received topoisomerase II inhibitors as the only chemotherapeutic agent and one of them had received radiation therapy as well. All three had 11q23 rearrangements involving the MLL gene. One had t(11,16) translocation and the other two (including one who had received radiation) had t (4,11).

The MLL gene, is located on chromosome 11 band q23, and normally functions as a transcription regulator of the HOX genes [15], is essential for normal mammalian development and hematopoiesis [16]. MLL gene rearrangement is seen in 5-6% of patients with AML, 7-10% with ALL and 60-70% of all acute leukemias in infants. It is a rearrangement that is increasingly being recognized in individuals with t-AML/t-ALL who had previously received chemotherapy with topoisomerase II inhibitors.

In a case series reported by Auxenfants et al. [11], 9 cases of t-ALL were reported with translocation t (4,11) and thereafter 23 cases were reported with balanced translocation involving chromosome 11q23,and interestingly all had received topoisomerase II inhibitor therapy [11]. This supports a causal relationship between chemotherapy with topoisomerase II inhibitors and subsequent development of t-ALL [13]. In our analysis, we found that the median latency period for development of t-ALL was 19 months, which is similar to that observed in t-AML after exposure to topoisomerase II inhibitor therapy [17]. In addition, as reported by Andersen et al. [13], break points in 3 out of 6 cases analyzed were seen at the telomeric part of the gene, characteristic for t-AML following chemotherapy with topoisomerase II inhibitors.As suggested by Andersen et al. [13], it is prudent to add t-ALL with the 11q23 translocation to the risk calculations along with the present cohort of high risk acute leukemias, t-AML in patients who had previously received DNA topoisomerase II therapy when deciding about their therapeutic options.

In spite of the clinical importance of the phenomenon of secondary mixed lineage leukemia related to prior topoisomerase II inhibitors, the precise molecular mechanisms are not well understood. *In vitro* experiments with cell lines have shown that epipodophyllotoxins can induce the characteristic translocations reproducibly. Interestingly, Nakada et al. [18] demonstrated that the mechanism for the induction of the MLL translocations involves early G2/M checkpoint failure. This failure appears to be induced by an inherent genetic risk factor resulting in this checkpoint failure [18]. A defective tumor suppressor gene such as ataxia telangiectasia (AT) may be a germ line defect that confers the propensity to get the first malignancy as well as the sensitivity to the etoposide as a carcinogen used in its treatment [18]. Some of the infant leukemia are also associated with the MLL translocation and have been linked to maternal exposure to exogenous topoisomerase II inhibitors in foods and the environment [19]. These infants may also have an inherited germ line defect resulting in early G2/M checkpoint failure resulting in the MLL leukemia [17]. It is speculated that the development of both the AML and ALL forms of secondary MLL leukemia may

Table 1: Summary of the reviewed cases (1, 10, current).

Reference	Age/sex	Primary malignancy	Previous treatment	Latent period in months	Cytogenetics/ MLL status
[21]	7/Female	Neuroblastoma	VCR+Cy+Dox+Cisplatin+VM 26	54	t(4,11)
[22]	15/Male	Osteosarcoma	MTX+VCR+DOX+IFOS+VP 16+Carboplatin	18	t(4,11)
[23, 24]	51/Female	Breast carcinoma	DOX+MTX +5FU+ RT	18	t(4,11)
[24]	43/Female	Breast cancer	DOx+Cy+5FU+RT	24	t(4,11)
[25]	33/Male	Hodgkin	MOPP+DOX+,Bleomyin+VLB+ Dacarbazine+RT	144	t(4,11)
[26]	39/Female	Hodgkin	MOPP+CLB+,VP16+CCNU+MTX+ RT	34	t(4,11)
[27]	16/Female	Hodgkin	MOPP+CLB+VP16+CCNU+,MTX+RT	24	t(4,11)
[11]	56/Female	Breast cancer	Cy + Mit + 5FU + RT	9	t(4;11)
[11]	60/Male	Small cell lung cancer	DOX + Cy + VCR+ VP16 + RT	21	t(4;11)
[28]	44/Female	Breast cancer	Flu + Pirub.	19	B-cell /t(11;19)/ MLL rearr.
[29]	35/Male	AML M5 t(6;11) MLL rearr. intron 7	DNR + AraC + Mit + M-Amsa	12	B-cell/t(4;11)/ MLL rearr. intron 9
[30]	36/Female	Hodgkin	Clb + VLB + Pro+ Pred 1 DOX+ VP16+ + VCR + RT	24	PreB ALL/t(4;11)
[30]	28/Male	Hodgkin	Me + VLB + Pro + Pred +Clb + DOX+ VP16	36	Pre B/t(4;11)
[31]	9/Female	Non-Hodgkin	CY + DNR + VCR + Pred + l-Asp+ MTX	20	T-ALL/ del(6q), 18,del(11)(q23)/ 2MLL rearr.
[31]	10/Male	Osteogenic sarcoma	DOX + Carbo + IFOS + Mtx + VP16 + VCR	16	L1/t(4;11)/ MLL rearr.
[32]	5/Male	Neuroblastoma	Cis + Etop+ DOX+ CY	18	L1/t(4;11)/ MLL rearr. intron 8
[33]	64/Female	Breast cancer	Epi	19	Pre B-ALL/1X, t(4;11),i(17q)/ MLL rearr.
[34]	2/Male	Neuroblastoma	CY + VCR + DOX + VP 16 + Cis	22	L1/t(5;11)(q35;q23)/ MLL rearr.
[35]	36/Female	Breast cancer	DOX+ 5FU + CY+ Ellip + VP 16 + Tax + RT	?	Pre B-ALL/t(4;11)/ MLL rearr.
[36]	NS/Male	T-ALL	VM26 + DOX	21	B-ALL/t(5;8)(q33;q12) t(11;16)(q23;p13)/ (normal karyotype) MLL rearr.
[37]	33/Female	Rhabdomyo-sarcoma	Vp 16+ Cy +IFOS + Dact + VCR + RT	15	t(4;11)/ MLL rearr. intron 6
[38]	45/Female	Breast cancer	MTZ+ Alkyl + Pred + RT	12	Pre B-ALL/t(4;11), del(17)(p11)
[38]	31/Male	Testicular cancer	VP 16 +Cis + Bleo	24	ALL/t(4;11)
[38]	41/Male	Testicular cancer	VP 16 + Cis	16	Pre B-ALL/t(4;11)
[39]	35/Female	Breast cancer	DOX + 5FU+ MTX + Cy + Cis + BCNU + ABMT	13	t(1;11)(p32;q23)
[40]	13/Female	Osteogenic sarcoma	Cis + DOX	22	t(1;11)(p32;q23)
[41]	42/Female	Uterine cancer	VP 16 + Epi + Carbo+ RT	12	Pre B-ALL L2/t(3;6)(p21:q21),del(3)(p24), t(4;11), del(6)(q15), iso(7)(q10),add(9)(p22), del(17)(p11)/ MLL rearr. intron 6
[42]	10/Male	Hepatocellular carcinoma	DOX + Cis + VP 16 + Carbo +IFOS	48	lymphobl. lymphoma/t(1;13)(q4;q13),t(11;19) 1X, 15, 18, 113, 114/MLL rearr.
[13]	64/Female	Breast cancer	Epi + RT	10	Pre B-ALL/t(4;11)/ MLL rearr. intron 8
[13]	27/Male	Testicular cancer	VP 16 +Cis+ Bleo + RT	18	Pre B-ALL/t(4;11)/MLL rearr. intron 6
Present	68/Male	Lung cancer	Cis + Etop + RT	16	Pre B-ALL/t(4;11)/MLL rearr.
Present	31/Male	Soft tissue sarcoma	MAI + DOX + cis	11	Pre B-ALL/t(4;11)/MLL rearr.

NA, not available; VM 26, teniposide; VP 16, etoposide; Cy, cyclophosphamide; DOX, doxorubicin; VCR, vincristine; IFOS, ifosfamide;MTX, methotrexate, VLB, vinblastine; CLB, chlorambucil; 5 FU, fluorouracil; MTZ, mitoxantrone; MOPP: mechlorethamine, vincristine,;procarbazin, prednisone, Mit, mitoxantrone ,RT, radiotherapy; VCR, vincristine; Flu, fludarabine; Pirub, pirarubicin; DNR, daunorubicin; AraC, cytosine arabinoside; M-Amsa, amsacrine; Clb, chlorambucil;Pro, procarbazine; Pred, prednisone; Me, mechlorethamine; l-Asp, l-asparaginase; Carbo, carboplatin; Epi, 4-epi-doxorubicin; Ellip, ellipticin; Tax, taxol; Cis, cisplatin; Bleo, bleomycin; BCNU, carmustine; MAI (mesna, doxorubicin, ifosfamide) ;ABMT, autologous bone marrow transplantation; Dact, dactinomycin; Alkyl, alkylating agent not otherwise specified.

require an inherited genetic susceptibility in addition to exposure to a toposiomerase II inhibitor for disease expression to occur.

In conclusion, DNA topoisomerase II therapy may result in a similar 11q23 re-arrangement in t-ALL as in t-AML. Both entities are associated with a poor prognosis. They are incurable with chemotherapy alone, with a median overall survival reported as six months [20] and warrant allogeneic stem cell transplantation in first remission. Allogenic stem cell transplant can produce long term remission in some, as seen in one of our patients and should be considered for this select group of secondary leukemias. However, transplant may not be an option for some patients due to factors like old age, medical comorbidities, poor performance status, lack of an idea donor etc. There is paucity of data on optimal choice of treatment for these patients and patients should be encouraged to participate in clinical trials when eligible.

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