Acquired Acute Myelogenous Leukemia after Therapy for Acute Promyelocytic Leukemia with t(15;17): a Case Report and Review of the Literature

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Therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myelogenous leukemia (t-AML) in patients with acute promyelocytic leukemia (APL) are rare events. The cumulative exposure to chemotherapy with alkylating agents and topoisomerase II inhibitors is associated with t-AML that may develop any time after the completion of the treatment. We report the case of an acquired AML who previously received therapy for APL, after two years of being diagnosed. The diagnosis was established by morphologic findings, membrane markers, cytogenetic studies, and fluorescence in situ hybridization (FISH). To our knowledge this is the first documented case in Puerto Rico of a patient with APL that developed a t-AML without the characteristic chromosomal and morphologic findings of APL.

Key words: Acute myelogenous leukemia, Acute promyelocytic leukemia, Therapy-related myelodysplastic syndrome, Therapy-related acute myelogenous leukemia

Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML) by the French-American-British (FAB) classification characterized by the presence of malignant promyelocytes in the bone marrow and peripheral blood, t(15;17), a high incidence of disseminated intravascular coagulation (DIC), and a unique sensitivity to anthracyclines and all trans retinoic acid (ATRA) (1-2). The occurrence of t-AML after treatment for other malignant disorders is one of the late complications seen in cancer patients; however, the incidence of t-MDS/AML after APL ranges from 1% to 6.5% (3), but although rare, it has been considered by the World Health Organization as t-AML (4). It is important to differentiate t-AML from relapsing APL because their management is very different. Among the chemotherapeutic agents, alkylating agents and topoisomerase II inhibitors have been the most commonly associated with t-MDS/AML. Since APL is such a unique disorder and is sensitive to several less leukemogenic medications, including ATRA and arsenic trioxide. Consequently, there exists the possibility that in the future we could avoid leukemogenic drugs in the induction therapy of APL thus avoiding myelodysplasia and its resulting t-AML. The appearance of a t-AML with clonal chromosome changes unrelated to the abnormal initial APL clone is a rare event and only few cases have been reported in the literature.

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Case Report

A 32 year-old male presented with gum bleeding, pale conjunctiva, fever, and tachycardia. The CBC revealed pancytopenia: WBC 0.5 x 10^3/µL, Hgb 5.4 g/dL, and platelets 62 x 10^3/µL. Coagulation parameters were compatible with DIC: PT 13.9 sec (normal value (NV) 11-13 sec), PTT 22.9 sec (NV 25-33 sec), and fibrinogen level 88.3 mg/dL (NV 140-400 mg/dL). Bone marrow aspiration was compatible with AML M3, the hypergranular variant according to the FAB classification criteria (Figure 1). The cytochemistry studies showed a Sudan Black B (SBB) with 90% of strongly positive cells, periodic acid-Schiff (PAS) reaction with strong diffuse positivity, and a-naphtyl butyrate esterase (ANBE) with 12% weakly positive cells. Membrane markers revealed positivity for CD13, CD33, CD45, and negative HLA-DR as described in APL. Karyotype analysis reported 46, XY, t(15;17). The patient received induction chemotherapy with daunorubicin 45 mg/m^2/day intravenously (I.V.) for 3 days, and cytosine

arabinoside (Ara-C) 100 mg/m^2/day I.V. for 7 days in continuous infusion. He was also treated with ATRA 45 mg/m^2/day orally simultaneously during induction chemotherapy, achieving a complete response. He received three consolidation chemotherapies with daunorubicin 45 mg/m^2/day IV for 3 days. The maintenance therapy was given with 6-mercaptopurine (6-MP) 50 mg/m^2/day, methotrexate (MTX) 15 mg/m^2/day plus ATRA 45 mg/m^2 orally every other week for 24 months. The patient was followed-up in our clinics, and remained in clinical and hematologic remission for two years.

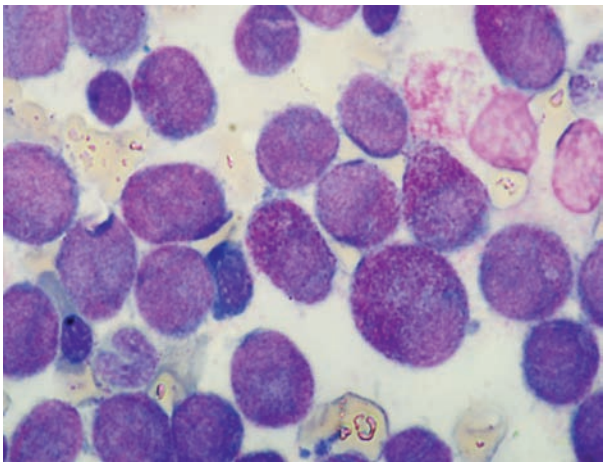

Figure 1. Bone marrow aspiration compatible with AML M3, the hypergranular variant, according to the FAB classification criteria.

After a year lost for follow-up, the patient came to the hospital with a marked pancytopenia that required hospitalization. On admission, the physical examination was essentially negative. The initial CBC showed: WBC 2.2 x 10^3/µL, Hgb 10.6 g/dL, and platelets 27 x 10^3/µL. Coagulation parameters were normal. The bone marrow examination was compatible with AML with the presence of some maturation and negative for malignant promyelocytes (Figure 2). Cytochemistry studies showed a SBB strongly positive, PAS weakly positive, and ANBE was negative, compatible with AML FAB M2. Membrane markers revealed positivity for CD13, CD33, CD34, CD38, CD45, CD117, and a HLA-DR 54. The karyotype disclosed: 45, XY, monosomy of 7, t(3;21)(q26;q22), but absence of t(15;17). FISH analysis was negative for PML RARa gene. The patient was started on Ara-C and mitoxantrone, and CR was attained. After four months of treatment, he developed pancytopenia again and the marrow examination was compatible with AML in relapse. Membrane markers and karyotype analysis were reported the same as when the t-AML was diagnosed. The patient was started on high-dose Ara-C and mitoxantrone, and CR was attained. He also received a second consolidation therapy with high-dose Ara-C. Unfortunately, a lumbar biopsy was compatible with osteomyelitis by Aspergillus requiring long-term antifungal treatment and unabling him to have a bone marrow transplantation which was being considered. The patient eventually died from his primary disease two years after diagnosed.

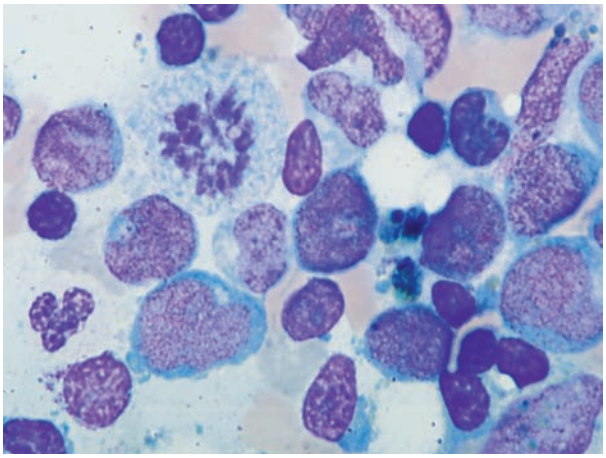

Figure 2. Bone marrow aspiration compatible with AML M2, according to the FAB classification criteria.

Discussion

Acute myelogenous leukemia (AML) develops as a consequence of a series of genetic changes in the hematopoietic precursor cells. These cells are susceptible to a variety of chemotherapeutic agents. Glutathione S-transferases (GSTs) are enzymes that detoxify potentially mutagenic and toxic DNA-reactive electrophiles, including metabolites of several chemotherapeutic agents, some of which are suspected human carcinogens (5). There is a hypothesis that suggests polymorphisms in genes that encode GSTs alter susceptibility to chemotherapy-induced carcinogenesis, specifically to t-AML. Therapy-related MDS (t-MDS) and therapy-related acute myelogenous leukemia (t-AML) can occur after chemotherapy and/or radiotherapy for malignant or nonmalignant disorders characterized by its devastating outcome. Although secondary leukemias and MDS are the most frequent secondary neoplasms following chemotherapy for acute leukemia, their development in patients with APL is uncommon, ranging from 1% to 6.5% (3, 6). The two main classes of cytostatic drugs associated with induction of t-MDS and t-AML are alkylating agents and topoisomerase II inhibitors. The induction of t-AML by alkylating agents usually occurs

between 3 to 10 years, and is frequently preceeded by a MDS phase. Cytogenetically, it is characterized by deletions of 5/5q and/or deletions of 7/7q and responds poorly to chemotherapy, while only a low percentage of the topoisomerase II inhibitors presents with an initial MDS (7), and the period for occurrence of t-AML varies between 12 to 36 months. The potential leukemogenic drugs that this patient received were anthracycline, 6-MP, and MTX. Nevertheless, the low dose of MTX and 6-MP used during maintenance therapy of APL have been reported to be safe (3). Also, it has been hypothesized that MTX and 6-MP might modify the leukemogenic effect of anthracyclines (8). Therapy-related MDS and t-AML are rare events after single drug treatment by 6-MP or MTX; however, these drugs may enhance the risk of developing a t-MDS and t-AML when are used after other drugs. Indeed, after DNA damage induced by other drugs, 6-MP metabolites can interfere with DNA repair, leading to the introduction of point mutations, and both 6-MP and MTX can predispose to non-homologous recombination.

Review of the literature revealed 30 such cases of t-AML after APL (Table 1), and all the cases were treated with anthracyclines. In only 8 cases the MDS phase was not present or documented. The karyotype of topoisomerase II inhibitors frequently discloses anomalies of the t(11;16)(11q23;p13) or the t(3;21)(q26;q22) as well as normal karyotype or cytogenetics rearrangements specific to de novo AML. The chromosomal abnormalities usually observed after alkylating agents may also occur after anthracycline therapy (8-10).

In a period of two years after treatment for APL, our patient developed a t-AML with a characteristic karyotype anomaly involving the monosomy 7 and t(3;21)(q26;q22) that most likely occurs with topoisomerase II inhibitors . The presence of the monosomy 7 suggests that this patient may have developed a t-MDS which progressed rapidly to a leukemic transformation.

The risk of t-MDS and t-AML after chemotherapy appears to be increased with age with a median age of 48 (29-57) years (10). Another risk factors are the duration of chemotherapy administered and the number of relapses. Our patient was younger than 40 years and had no relapses, so the only risk factor was chemotherapy itself.

Therapy-related MDS and t-AML are high risk diseases with poor prognosis. The low overall survival correlates with the poor response to chemotherapy. Allogeneic bone marrow transplantation has been reported as being effective in young patients (11).

Conclusions

The occurrence of t-AML after successful therapy for APL with t(15;17) is a rare event and only few cases have been reported in the literature. With this report, we want to stress the importance of performing conventional karyotyping on a regular basis in all treated APL patients for the early detection of chromosomal aberrations indicative

Table 1. Review of previously published cases of t-MDS/AML occurring during the course of APL after treatment with anthracyclines

Reference (number)	Number of patients	Progression to MDS (months)	Progression to AML (months)
Gunduz (3)	1	52	66
Lobe (6)	16	33, 43, 24, 49, 34, 51, 43, 25, 84, 34, 26, 29, 43, 46, 48, 24	44, 26, 35, 30, 61, 47, 50, 29 No progression in 5 pts
Au (8)	1	84	Unknown
Athanasiadou (9)	1	40	Unknown
Zompi (12)	2	30, 24	32, 39
Bseiso (13)	1	+	34
Felice (14)	1	-	26
Hatzis (15)	1	+	23
Jubashi (16)	1	+	37
Meloni (17)	1	Unknown	36
Myazaki (18)	1	-	23
Sawada (19)	1	-	43
Todisco (20)	1	-	49
Latagliata (21)	5	25, 44, 46, 19 (4 pts)	48, 43, 46, 48, 24
Panizo (22)	2	+	Unknown
Annunziata (23)	1	Unknown	29
Snijder (24)	1	+	20
Lee (25)	1	-	12
Pecci (26)	1	+	Unknown

of the development of t-MDS or t-AML. The review of the literature suggests the impression that therapy with anthracyclines is a risk factor for this unfavorable event that changes the prognosis of the disease from a possible curable one to a more aggressive one. To our knowledge the case presented is the first documented of t-AML without the t(15;17) and the characteristic morphology of APL at the Hematology-Medical Oncology service of the University District Hospital, which is the main referral center for acute leukemia in Puerto Rico.

Resumen

El síndrome mielodisplástico y la leucemia mielógena aguda relacionados a terapia (t-LMA) en pacientes con leucemia promielocítica aguda (LPA) son eventos raros. La exposición acumulativa de quimioterapia con agentes alkilantes e inhibidores de la topoisomerasa II está asociada con LMA relacionada a terapia, la cual puede desarrollarse en cualquier momento después del tratamiento. Nosotros estamos reportando un caso de t-LMA que recibió terapia para LPA, luego de dos años de ser diagnosticado. El diagnóstico se estableció mediante hallazgos morfológicos, marcadores de membrana, estudios de citogenética y moleculares. Para nuestro conocimiento éste es el primer caso documentado en Puerto Rico de un paciente con LPA que desarrolla t-LMA sin los hallazgos citogenéticos y morfológicos característicos de APL.

Abbreviations

AML = Acute myelogenous leukemia
APL = Acute promyelocytic leukemia
t-MDS = Therapy-related myelodysplastic syndrome
t-AML = Therapy-related acute myelogenous leukemia
DIC = disseminated intravascular coagulation
NV = normal value
t(15;17) = translocation 15;17
t(3;21) = translocation 3;21
CBC = cell blood counts
WBC = white blood count
Hgb = hemoglobin
PT = prothrombin time
PTT = partial thromboplastin time
FAB classification = French-American-British classification
SBB = Sudan Black B
PAS = periodic acid-Schiff
ANBE = α-naphtyl butyrate esterase
GSTs = glutathione S-transferases
6-MP = 6-mercaptopurine
MTX = Methotrexate
ATRA = all-trans retinoic acid
FISH = fluorescence in situ hybridization

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