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Secondary clonal hematologic neoplasia following successful therapy for acute promyelocytic leukemia (APL): A report of two cases and review of the literature

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ABSTRACT

Although rare, secondary clonal hematologic neoplasia may occur after successful therapy for acute promyelocytic leukemia (APL). These secondary clonal events may be considered therapy-related, but may also be due to an underlying background of clonal hematopoiesis from which both malignancies may develop. In this manuscript, we describe two patients with secondary clones after APL therapy characterized in one patient by deletion of chromosome 11q23 and, in the other, by monosomy of chromosome 7, and also provide a review of all secondary clonal disorders described after APL therapy. We suggest that since most reports identify karyotypic abnormalities not typically associated with chemotherapy, there may be another mechanism underlying secondary clonal development after complete response to initial APL therapy.

1. Introduction

Acute promyelocytic leukemia (APL) is a biologic and clinically well-defined subtype of acute myeloid leukemia typically characterized by the balanced translocation of chromosomes 15 and 17 resulting in fusion of the promyelocytic (PML) and retinoic acid receptor alpha (RARalpha) genes. The disease is also characterized by an unique response to the differentiating agent all-trans retinoic acid (ATRA). Combination therapy of ATRA with either chemotherapy or arsenic trioxide (ATO) has made APL a highly curable leukemia [1–3]. Nevertheless, relapses occurring after a complete remission (CR) of APL do occur and usually derive from their original APL [4]. Secondary myelodysplastic syndrome (MDS) or acute myelocytic leukemia (AML) developing in APL patients in complete remission (CR) is rare but has been documented. Here we describe two patients who initially were diagnosed with acute promyelocytic leukemia (APL) and later relapsed with a distinct neoplastic hematopoietic clone that was not, on simple cytogenetic findings, ancestrally related to the original APL.

2. Case reports

The first patient was a 76-year-old woman with a past medical history of hypertension, diabetes, hypothyroidism, berylliosis requiring corticosteroids, and renal insufficiency who originally presented in February of 2009 with dizziness and orthostatic hypotension. Laboratory studies revealed pancytopenia with blasts on the peripheral blood smear. Bone marrow biopsy showed acute promyelocytic leukemia and t(15:17) was detected with fluorescence in situ hybridization (FISH). Her disease was characterized as intermediate-risk with a white blood cell count of 1.5×10^3/uL and a platelet count of 34×10^3/uL [5]. She received induction chemotherapy with all-trans retinoic acid (ATRA) 45 mg/m^2/day and idarubicin 12 mg/m2 × 4 doses, achieving complete remission, followed by consolidation chemotherapy consisting of intermittent ATRA and idarubicin 5 mg/m2 × 4 doses. Following recovery of blood counts, idarubicin was discontinued due to cardiomyopathy (ejection fraction 39%) and consolidation continued with arensic trioxide (ATO) 45 mg daily for 5 days per week for an abbreviated course of 3 weeks. Maintenance therapy with methotrexate 15 mg weekly and ATRA 50 mg twice daily continued for 18 months. Two years following completion of maintenance therapy, she developed thrombocytopenia with bone marrow biopsy negative for recurrent leukemia. Seven years following her initial remission, she developed anemia as well. Bone marrow biopsy at this time revealed 20–25% myeloid blasts and cytogenetic testing identified deletion of

Abbreviations: AML, acute myelocytic leukemia; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; ATG, antithymyocyte globulin; CR, complete remission; FISH, fluorescence in situ hybridization; 6-MP, 6-mercaptopurine; MDS, myelodysplastic syndrome; PML-RARalpha, promyelocytic leukemia/Retinoic acid receptor alpha; t-AML, therapy-related acute myelocytic leukemia; t- MDS, therapy-related myelodysplastic syndrome

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chromosome 11q23 in 7 out of 20 metaphase cells examined, but FISH was negative for the t(15;17) translocation. Next-generation DNA sequencing was performed on the Illumina Miseq to identify somatic variants in 54 of the most commonly mutated genes in myeloid malignancies, and mutations in Additional Sex combs-like Transcriptional Regulator 1 (ASXL1), PHD finger protein 6 (PHF6), and TET methylcytosine dioxygenase 2 (TET2) were also detected. Reinduction with cytarabine 200 mg/m^2 × 7 days and idarubicin 12 mg/m^2 × 3 days was attempted without remission. Karyotype then revealed deletion of the long arm of chromosome 7 (del 7q22) in 19 or 20 metaphase cells analyzed. Decitabine therapy produced a modest response, and she died after further attempts at reinduction.

The second patient was a 65-year-old man who originally presented in December of 2014 with fevers, fatigue, thrombocytopenia, anemia, and leukocytosis. Peripheral blood smear revealed blasts with Auer rods, and bone marrow biopsy demonstrated acute promyelocytic leukemia with t(15;17) present. His disease was characterized as high-risk given a white blood cell count of 56.1 × 10^3/uL [5]. The patient initially received ATRA 45 mg/m^2/day and ATO 0.15 mg/kg daily but developed symptomatic QT prolongation and proceeded to treatment with idarubicin. His course was complicated by prolonged neutropenia with Pseudomonas bacteremia and Aspergillus pneumonia requiring filgrastim and granulocyte transfusions. Bone marrow biopsy following induction was negative for blast cells with normal molecular pathology and negative FISH testing for the t(15;17) translocation. He received three cycles of consolidation consisting of ATRA with idarubicin, mitoxantrone, and cytarabine followed by maintenance therapy with methotrexate 15 mg weekly, 6-mercaptopurine (6-MP) 50 mg daily, and intermittent ATRA 50 mg bid. One year into maintenance, the patient developed pancytopenia, and methotrexate and 6-MP were stopped. A short time later, he developed intermittent right facial paresthesia. MRI brain was concerning for hypointensity over the cerebellum, reflective of subarachnoid bleeding, and hyperintensity in some regions. Lumbar puncture revealed 78% promyelocytes with cytogenetics from cerebrospinal fluid positive for t(15;17). Bone marrow biopsy showed no evidence of blasts, but the karyotype disclosed a new set of anomalies with monosomy of chromosome 7 and an extra marker chromosome in 18 of 20 cells observed (+mar(18)). There were no marrow cells with t(15;17) by FISH or routine karyotype. Hematologic malignancy sequencing panel noted two mutations in the SET binding protein 1 (SETBP1) with allele frequency 36% and 12%. The patient was treated with intrathecal methotrexate 12 mg and intrathecal cytarabine 100 mg followed by whole brain radiation, 2 Gy x 9 fractions. Repeat bone marrow biopsy one month later revealed no excess blasts by flow cytometry, but the karyotype showed persistent monosomy 7 and an extra marker chromosome in all 20 cells observed (+mar(20)). The patient received systemic chemotherapy consisting of cytarabine 100 mg/m^2 × 7 days and daunorubicin 60 mg/m^2 followed by allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning of busulfan, fludarabine, and antithymocyte globulin (ATG). Post-bone marrow transplant bone marrow biopsy showed no evidence of disease and full donor chimerism. Repeat MRI brain/orbits showed resolution of previously seen enhancement. The patient is doing well 10 months post-bone marrow transplant.

3. Discussion

We describe two patients who developed distinct AML clones without t(15;17) following treatment for APL. Such secondary clonal hematologic neoplasia occurring after successful therapy for APL is rare but has been documented, and these cases are illustrated in Table 1 [6–34]. Frequencies ranging from 1–9.8% [18,20,29,33] have been reported with a median latency period of 35.6 months (range 1–158 months) after remission of APL. Two separate hypotheses can describe this observation of the secondary clonal hematologic neoplasia: (1) these diseases may be an outgrowth of an existing undetectable subclone or (2) they may be two independent clones evolved from separate hematopoietic stem cells, likely a result of toxicity from chemotherapy.

The well-described entities of therapy-related myelodysplasia (t-MDS) and acute myeloid leukemia (t-AML) are known to occur following therapy with either alkylating agents or topoisomerase II inhibitors [35,36]. They are characterized by distinct cytogenetic abnormalities: loss of chromosome 5 or 7 with alkylating agents [37,38] and 11q23 and 21q22 aberrations with topoisomerase II inhibitors [39,40]. The most common primary therapies for APL include anthracyclines, which are believed to work through topoisomerase II enzyme inhibition, in addition to 6-MP, methotrexate, and ATRA. It has been hypothesized that methotrexate, 6-MP, or ATRA might modify anthracycline leukemogenesis and contribute to the development of a secondary leukemia [7,10,16,21]. Alkylating agents, however, are not commonly used therapies for APL. Indeed, out of the cases reported of secondary clones following APL therapy, only 4 received an alkylating agent (cyclophosphamide). However, the karyotypes of the secondary clones, including those not treated with alkylating agents, most commonly had characteristics typically associated with prior therapy with an alkylating agent: 16 patients had deletion of all or part of chromosome 7 [6,10,11,13,14,16–19,21,26,29,31] and 15 patients had deletion of all or part of chromosome 5 [6,7,16–18,20,21,29,33]. Despite the fact that all patients were treated with topoisomerase II inhibitors (anthracyclines), only 4 patients, or 6 including our patients, presented with karyotypes typical of prior therapy with a topoisomerase II inhibitor [17,28,29]. Almost half of the patients (23) did not have karyotypic abnormalities at all associated with t-MDS/t-AML. This result suggests either that anthracycline therapy may induce such alkylating agent-type karotypic aberrations in APL patients [32] or that the secondary clones were not in fact therapy-induced. Another possibility to consider is induction of a selective advantage to pre-existing hematopoietic stem cell subclones carrying certain mutations, such as *TP53* or *SETD2*, that allowed them to expand preferentially after treatment [41,42].

Such secondary clones detected after APL therapy may have been derived from an ancestral pre-leukemia stem cell that developed into APL and thereafter contributed to the second disorder. Clonal evolution has been well-defined in AML [43,44] and has also been described in APL [45,46]. A similar theory has been proposed for secondary unrelated clones in CML patients that developed deletions of chromosome 5 and 7 after CML treatment with interferon alpha or imatinib mesylate in the absence of chemotherapy [47,48]. The fact that many patients presented with secondary myelodysplasia may yield support for this theory of clonal evolution. Of the 50 cases of secondary clonal neoplasia following APL treatment reported in the literature, more than half (28) developed myelodysplasia. Furthermore, selected cases of initial diagnosis of APL with concurrent myelodysplastic changes have been reported [8], though it is uncommon.

Going against the theory of clonal evolution and more in support of chemotherapy-induced secondary MDS/AML is the fact that no cases of secondary AML have been reported after arsenic/ATRA therapy for APL without exposure to chemotherapy. However, given that this therapeutic regimen has only recently become standard practice [49], there may not yet have been sufficient time to observe such secondary malignancies. Indeed, the majority of the patients in Table 1 were treated prior to this new therapy.

4. Conclusion

In conclusion, secondary clonal hematologic neoplasia following APL treatment is increasingly being reported. We have described an additional two patients with such a phenomenon. Further research is needed to determine the causality of such secondary clones in terms of relation to chemotherapy versus a common leukemic progenitor and to assess its clinical implications.

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