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Case Report

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Extremely Late Extramedullary Relapse of Acute Promyelocytic Leukemia, Case Report and Review of the Literature

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Abstract

With the use of all-trans retinoic acid (ATRA) as frontline treatment for acute promyelocytic leukemia (APL), there has been an increase in overall remission rates and extended survival, but relapses still occur. While most cases of relapse are limited to the bone marrow and/or blood, APL can relapse in extramedullary sites as well. These relapses may develop several years after remission. While different reasons for extramedullary relapse have been presented in the literature, the exact mechanism and reason for late relapse still needs to be defined. Our case documents the longest interval from diagnosis to relapse of APL described in the literature to date.

Keywords: Acute promyelocytic leukemia; Atra; Extramedullary relapse

Introduction

Myeloid leukemias are caused by neoplastic hematopoietic cells that have already committed to the myeloid lineage. Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML), with a translocation involving the PML-RARA fusion gene t(15:17). APL accounts for between 5-20% of all AML cases, with approximately 600-800 new cases of APL diagnosed yearly in the United States [1]. The incidence of APL is unique in that APL occurs across most age groups, with a decreased incidence seen in early childhood and in people over 70 years old [2].

Due to the presence of an abundance of immature promyelocytes, patients who present with APL are at high risk of developing coagulopathies [3]. Hemorrhage and infection are the main causes of early mortality in APL. Primary drug-resistance occurs only rarely in APL. Currently, over 90% of patients will obtain a complete remission with primary treatment [4]. However, the relapse rate for APL is 10-15%, with a 20-30% relapse rate for high-risk forms of the disease. Late recurrence, defined as a recurrence after 4 years or more, occurs in approximately 3% of all cases [5].

While most cases of relapse are limited to the bone marrow and/or blood, APL can relapse in extramedullary sites as well. Such presentation is often referred to as a chloroma or myeloid sarcoma. While such relapse might occur as frequently as 3-5% of the time, there is little information about the pathogenesis and treatment of such disease [6]. Myeloid sarcomas often occur in the central nervous system, but can be found in any organ. Once diagnosed with myeloid sarcoma, and according to the newest version of the WHO classification of myeloid neoplasm and acute leukemia, a patient is considered to have had a full relapse, and is treated systemically, even if bone marrow biopsy is negative for malignancy [7-9]. Radiation therapy is used occasionally for localized disease [10].

Case Report

In 1994, a 23-year-old female was diagnosed with APL. She received induction therapy with cytarabine, daunorubicin, and all-trans retinoic acid (ATRA). Consolidation was done with two cycles of daunorubicin and all-trans retinoid acid, followed by ATRA maintenance for one year. Repeat bone marrow biopsy showed complete remission, and she was followed for several years without evidence of relapse.

In May 2009, 180 months after the patient's first presentation, she began to develop upper respiratory symptoms, including sinus congestion, ear fullness, and left sided hearing loss. She completed a course of ciprofloxacin, but failed to show improvement. The patient was seen by an otolaryn-

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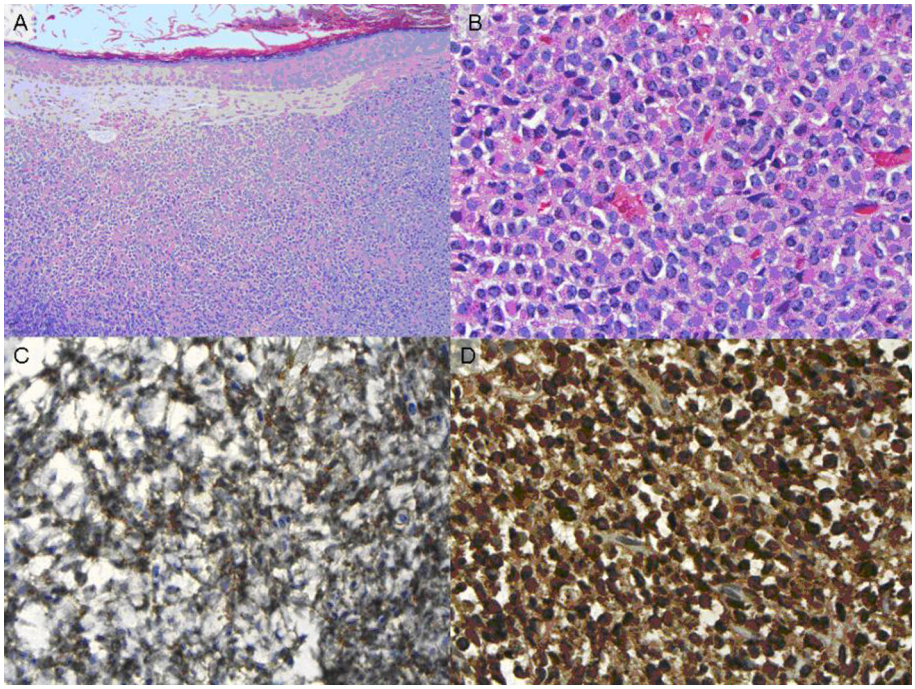

Figure 1. (A) H&E stain, low power (B) H&E stain, high power (C) CD-33 staining (D) Myeloperoxidase staining.

gologist who found a mass in her left ear canal; CT imaging revealed a soft tissue mass in the left external auditory canal abutting the tympanic membrane. The mass was biopsied and pathology was consistent with a granulocytic sarcoma, consisting of immature myeloid cells that stained positive for both anti CD-33 and myeloperoxidase (Fig. 1). Florescence in-situ hybridization (FISH) analysis of the tumor was positive for t(15;17) in 91.5% of the cells (Fig. 2).

Complete blood count at the time was unremarkable, with a white blood cell count of 8.3×10^9 cells per liter, normal white blood cell differential, hemoglobin 13.3 grams per liter, and platelet count of 399×10^9 per liter. A bone marrow biopsy at the time was normocellular and showed no increase in myeloblasts or promyelocytes. Chromosomal analysis revealed a normal female karyotype (46XX). FISH of the bone marrow was borderline positive, with 0.4% of cells showing a PML/RARA fusion signal. Polymerase chain reaction (PCR) for PML/RARA transcripts was positive at 0.074. PCR from peripheral blood for PML/RARA was negative.

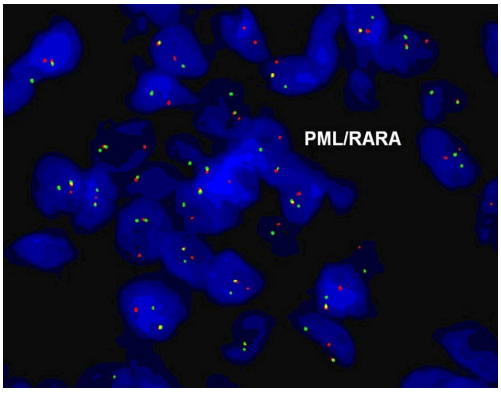

Figure 2. FISH analysis for PML/RARA t(15;17).

The patient underwent radiation therapy of the ear mass in July 2009, with an initial treatment of 1800 cGy at 6 mV followed by a cone-down of 600 cGy at 6mV. She also underwent systemic therapy with arsenic trioxide for 14 weeks, starting in August 2009. Bone marrow biopsy in December 2009 confirmed that she was in a second complete molecular remission. She subsequently underwent successful peripheral stem cell mobilization and received an autologous transplant in August 2010. She tolerated the transplant well, fully recovered her counts and remained in complete molecular remission.

Discussion

This case is an example of an extremely late relapse of APL with extramedullary involvement. At 180 months, it is the longest interval from diagnosis to relapse of APL described in the literature to date. In general, with current treatments of APL, relapse occurs in 10-15% of all patients [11]. Late relapse in APL (> 4 years) is a rare event, occurring in approximately 3% of all cases, and 12% of all relapse cases [5]. In the literature, late relapses have been well described for 28

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Author	Sex / age	Front Line therapy	Time Since Diagnosis	Extramedullary disease	Therapy at Relapse	Follow-up therapy	Follow-up
Latagliata et al[12]	M / 22	IDA + ARAC	60	No	ATRA	allogenic transplant	2nd CR
Latagliata et al[12]	F / 16	IDA + ARAC	155	Right mastoid	ATRA + mitoxantrone + ARAC	Not reported	2nd CR
Latagliata et al[12]	F / 16	AIDA 0493	71	Left mastoid	ATRA + mitoxantrone + ARAC	Not reported	2nd CR
Latagliata et al[12]	M / 16	AIDA 0493	61	Left mastoid	ATRA + mitoxantrone + ARAC + RT	Not reported	3rd CR
Latagliata et al[12]	F / 30	AIDA 0493	101	No	ATRA + mitoxantrone + ARAC	Not reported	2nd CR
Zhan et al[13]	F / 52	ATRA + ARAC + daunorubicin	136	No	ATRA + ATO	Not reported	2nd CR
Ferrara et al[14]	M / 21	ATRA + ARAC	111	No	ATRA + IDA	ATRA	2nd CR
Ferrara et al[14]	M / 18	AIDA	84	No	ATRA + IDA	ATRA	2nd CR
Kelaidi et al[5]	7 males, 12 females Mean age: 45 (range 20-68)	ATRA + ARAC + daunorubicin	median 72 (50-120)	No	ATRA+anthracycline (14) ATRA (2) anthra (1) ATO (1) ATRA+ATO (1)	allogenic transplant (3) autologous transplant (5) nonspecified chemo (7) ATRA (2)	17/19 CR 2 died
This Report	F / 23	ATRA + ARAC + daunorubicin	180	Left mastoid	ATO + RT	autologous transplant	2nd CR

Figure 3. Late relapse of acute promyelocytic leukemia. ARAC, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CR, complete remission; IDA, idarubicin; RT, radiotherapy.

cases (Fig. 3) [12, 13] Most cases of late relapsing disease occur within the first 7 years, with the previously longest recorded time to relapse occurring at 155 months. In two cases, the immunophenotypic, cytogenetic, and molecular pattern at relapse were the same as those at diagnosis, which confirmed that the late relapse was indeed a relapse of the original disease, not a new malignancy [14]. In almost all cases of late relapse described, patients were initially treated with ATRA and chemotherapy, but the treatment given after relapse differed. Many patients either received a second round of ATRA and chemotherapy, while others received arsenic trioxide. There were also several cases where patients received a transplant post-treatment, either allogenic or autologous. All patients who survived the initiation of treatment entered a second complete remission.

Our patient is also unique in that her relapse presented as extramedullary involvement of the ear canal. Extramedullay relapse can occur in various parts of the body, including (but not limited to) skin, central nervous system, testes, and ear [15]. While some studies have found a correlation between increased incidence of CNS disease and the use of ATRA [16], other studies have not found an increased incidence of extramedullary disease with ATRA administration [15]. Of note is that all reported cases of extramedually relapse in late-recurring disease occurred in the head and neck region (Fig. 3). A recent review of external auditory canal and middle ear relapse found 23 similar cases previously described, with most cases occurring within the first 2 years after diagnosis [17]. While the reason for extramedullary relapse is not certain, several theories exist. One theory is that certain adhesion molecules are disturbed with ATRA administration, due to ATRA's differentiating activity. This disturbance permits leukemia cells to migrate into sanctuary sites and survive for a long period of time. Potential molecules include CD56 [18], intercellular adhesion molecule-1 and CD18 [19]. Treatment of extramedullary relapse has not been thoroughly studied, but it appears that arsenic trioxide is useful not only in medullary relapse, but in extramedullary relapse as well. This may be due to arsenic's ability to deposit well in epidermal tissues [17].

Declaration

Each author certifies that he has participated sufficiently in the intellectual content and the analysis of data. Each author has reviewed the final version of the manuscript and approves it for publication. Each author denies any conflict of interest related to this manuscript.

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