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Case Report

Late isolated extramedullary relapse of acute promyelocytic leukemia present as chronic otitis media: case report and literature review

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Abstract: With employment of all-trans retinoic acid (ATRA) in treatment regimens of Acute Promyelocytic Leukemia (APL), vast majority of patients achieved complete remissions (CRs). While extramedullary relapse following therapy with ATRA have been reported more frequently. The most commonly reported involved sites are CNS, skin and lymph nodes. In this case, we reported a particularly rare APL patient who suffered extramedullary relapse in auditory canal after a very long completed remission for nearly 10 years. A 20-year-old male was diagnosed as APL and accepted induction therapy with daunorubicin (DNR) and ATRA. The completed remission was achieved and last for 10 years. Then he complained of hypoacusia and intermittent tinnitus on the right ear. He was misdiagnosed and mistreated as otitis media for about 3 years. After confirming as the extramedullary relapse with biopsy fragment of the mass and immunohistochemistry, this patient was treated with chemotherapy combined with ATO and achieved a complete molecular remission again. Unfortunately, the patient finally died of severe bone marrow suppression. Moreover, we reviewed the previous reported cases and hypothesized mechanisms of ear involvement in APL relapse, and discussed the importance of prompt diagnosis and relative reasonable treatment for these patients present with auditory symptoms with history of APL. This case provide information for rare extramedullary relapse and may remind clinicians recognizing the possibility of unusual APL relapses, especially in those acquired a long time complete remission.

Keywords: Late isolated auditory relapse, acute promyelocytic leukemia, case report, review

Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of leukemia. Introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) have improved the clinical outcome of refractory or relapsed and newly diagnosed APL as well [1]. Though APL have a much lower incidence of extramedullary disease (EMD) at time of diagnosis [2], the numbers of reported EMD in patients with APL relapse are increasing [3]. The affected sites include the central nerve system (CNS), skin, ear, nasopharynx, testis, lymph node, thymus, mediastinum, lung, pleura, heart, pericardium, breast, pelvis, spine, mandible, gingiva, muscle and the vascular access sites [3]. The CNS and skin were reported as the most common extramedullary relapse sites [3-5], while infiltration of the ear is exceedingly infrequent and only rare cases were reported [6-14]. Although the time intervals from the achievement of first hematologic remission to identified ear involvement were extremely variable, most reported cases were diagnosed in 3 years after completed remission (CR) when auditory symptoms present [6-14]. Here, we reported a case of late isolated auditory relapse that was diagnosed after nearly 13 years of primary APL and was misdiagnosed as otitis media for 3 years from the ear symptoms arisen.

Case report

In 2000, a 20-year-old male was diagnosed as APL. Induction therapy was started with daunorubicin (DNR) and ATRA, and then a completed remission was achieved. As maintenance schedule, the patient received ATRA (20 mg twice per day) for about 1 year. After that, the

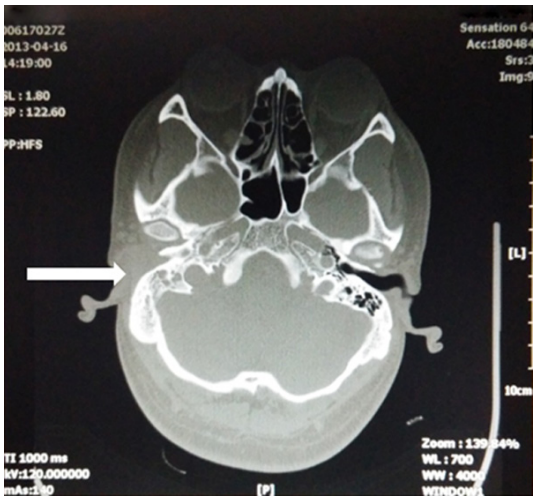

Figure 1. Computed tomography (CT) revealed the complete obstruction of right external auditory canal and absence of the normal mastoid air cells.

patient discontinued therapy by himself and lost to follow-up. In 2010, the patient complained of hypoacusia and intermittent tinnitus on the right ear. A diagnosis of otitis media was made and several antibiotics were given by local hospital, but the symptoms persisted. In the next year, hypoacusia was getting worse and tinnitus became continuous. To treat emergent earache, the patient received another course of antibiotic therapy. Interestingly, earache disappeared while hypoacusia and tinnitus remained. In October 2012, the patient was diagnosed as chronic otitis media and was suggested to receive surgical therapy. In April 2013, the patient was transferred to the otolaryngological department of our hospital to receive operation. Otoscopy examination showed a mass that blocked the right external auditory canal completely. Computed tomography (CT) and magnetic resonance imaging (MRI) scan revealed an obstructive mass in the right auditory canal, partial opacification of the mastoid air cells and tympanic cavity (**Figures 1** and **2**). The biopsy fragment of the tumor showed the partial loss of squamous epithelium, the infiltration of abundant plasmocyte and lymphocyte, and visibility of fibrinous exudate. Immunohistochemistry exhibited MPO (+), CD68 (+), lysozyme (+) and CD1a (-) (**Figure 3**). Thus, myeloid sarcoma was defined.

In May 2013, this patient was transferred to the hematology department for appropriate therapy. Although the blood smear, complete blood cell count, coagulation tests, smear of bone marrow aspiration and cerebral spinal fluid (CSF) analysis were negative, molecular analysis of bone marrow aspiration with RT-PCR showed positive fused PML-RARα mRNA of 2.5E4 copies per ML. The patient was treated with chemotherapy (DNR 60 mg/m^2/d × 3 d, Ara-C 150 mg/m^2/d × 7 d) combined with ATO (10 mg/d × 28 d) as induction. After recovery from severe pancytopenia and infection, the patient was proved to achieve a complete molecular remission again. Unfortunately, without suitable donor, the patient died of severe bone marrow suppression caused by consolidation chemotherapy with DNR and ATO, which resulted in lethal infection and septic shock two months later.

Discussion

Although reported cases are accumulating in the ATRA era [1], EMD is still be considered as the rare complication in APL [3]. The majority of reported cases are related to the central nervous system and skin [3-5, 15, 16]. Ear involvement in APL relapse is anecdotal [3]. To the best of our knowledge, there are only 22cases (including ours) of ear involved APL relapse have been reported [6-14, 17-20]. The clinic feature, treatment regimen and outcome of these similar cases was summarized in **Table 1**.

In the previous reports, time intervals from proved remission to diagnosis of ear involvement in APL were extremely variable and most of them were in 3 years [6-13]. Though regular consolidation and maintenance therapy were absent in this patient, the time interval from CR to presentation of auditory symptoms was up to nearly 10 years. To the criterion of therapeutic effect, this patient should have been *cured*. Moreover, it took nearly 3 years to make the right diagnosis. And the absent leukemia cells in bone marrow until diagnosis indicated a relatively chronic course of auditory relapsed promyelocytic sarcoma in this patient.

The reported local symptoms of auditory recurrent APL include hypoacusia [6-9], headache [7, 8], earache [7, 8], otorrhea [8, 13], mass in the auditory canal [10-12] and facial paralysis [9, 13]. As we know, these symptoms are nonspecific and usually indicate infection in ear. In fact, two patients including ours had been mis-

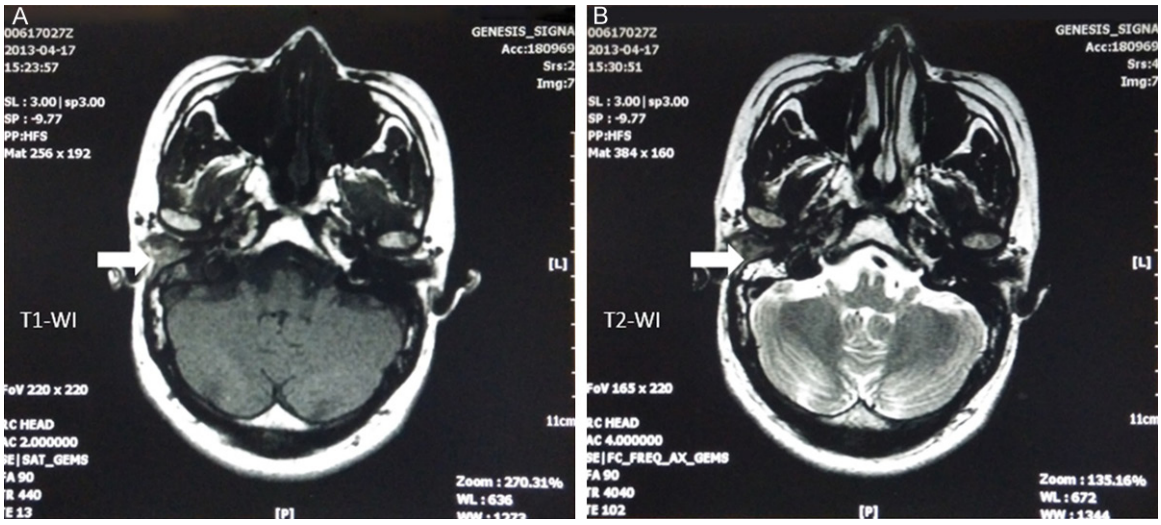

Figure 2. Axial unenhanced MRI scanning show the mean signal intensities on T1-WI and T2-WI in right external auditory canal and mean signal intensity on T1-WI (A) but high signal intensity on T2-WI in right mastoid (B).

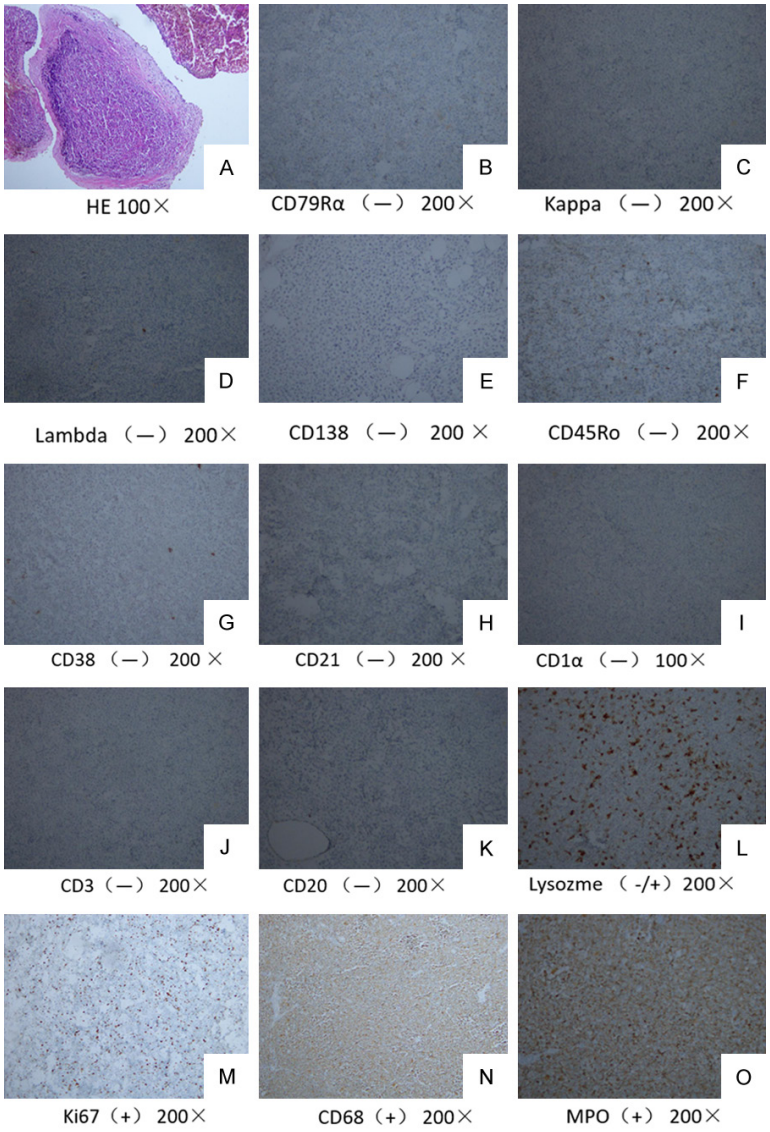

Figure 3. Histology and Immnohistochemistry of the biopsied tumor. Hematoxylin eosin (HE) showed immature granulocytes infiltration (A). Immunohistochemical staining shows expression of CD79Rα, Kappa, Lambda, CD138, CD45Ro, CD38, CD21, CD1α, CD3, CD29 was negative (B-K). Expression of lysozyme, Ki67, CD68, MPO was positive (L-O).

diagnosed as otitis media and had achieved partial relief of the symptoms by anti-infectious therapy [13]. Moreover, the frequent hearing disturbance in patients with leukemia might cause the underestimate and misdiagnosis of ear infiltration in APL [8]. Thus, otological recurrence of APL can apparently occur very late or casually. For these reasons, we consider that any auditory symptom in patients with history of APL should be recognized as the indication of prompt detection and re-evaluation of extramedullary relapse of the disease.

No clinical trial ever studied the preferred treatment for EMD relapse of APL, let alone the ear involved cases [3].

Table 1. EM relapse of acute promyelocytic leukemia in the ear

Case	Age (y)/Sex	Front line Threapy	Time to present EMD	Site of EMD	Therapy	Outcome of Treatment for EMD	Reference
1	9/F	IDA and MIT	22 months	Left external auditory canal	As_2O_3	CR	[9]
2	37/F	ATRA and ATO	NS	Left external auditory canal	NS	APL progression	[14]
3	22/F	NS	24 months	external auditory canal	NS	NS	[7]
4	49/M	AIDA	5 months	Left auricular canal mastoid	Mastoidectomy	NS	[8]
5	16/F	AIDA	69 months	Left mastoid	Mastoidectomy	NS	[8]
6	16/M	AIDA	58 months	Left mastoid	Mastoidectomy	NS	[8]
7	37/M	AIDA	9 months	Right mastoid	Mastoidectomy	NS	[8]
8	51/F	AIDA	12 months	Left auricular canal	NS	NS	[8]
9	21/F	IDA+ARA-C	64 months	Right auricular canal	NS	NS	[8]
10	36/F	AIDA	6 months	Right mastoid	NS	NS	[8]
11	40/M	ATRA	24 months	NS	NS	NS	[10]
13	41/M	BHAC-DMP	24 months	Left external auditory cana	NS	NS	[11]
14	42/M	ATRA	7 months	Bilateral external ear	ATRA and Irradiation	Death	[20]
15	36/M	BHAC-DMP/BHACAMP	14 months	Left middle ear	HD-ARAC+Irradiation	Death	[13]
16	24/F	BHAC-DMP	15 months	Middle ear	HD-ARAC+Irradiatio	CR	[13]
17	54/F	ATRA BHAC DNR	12 months	Left external auditory canal	ATRA+Irradiation+Chemotherapy	CR	[17]
18	16/F	IDA ± Cytarabina	155 months	Right mastoid	MIT+ID-ARAC+ATRA	CR	[18]
19	16/F	AIDA	71 months	Left mastoid	MIT+ID-ARAC+ATRA	CR	[18]
20	16/M	AIDA	61 months	Left mastoid	MIT+ID-ARAC+ATRA+Irradiation	CR	[18]
21	35/M	ATRA+Daunorubicin	5 months	Right ear	As_2O_3+Irradiation+Triple intrathecal chemotherapy	CR	[19]
22	1/F	VP-16, Ara-C, MIT, IDA	49 months	Right external auditory canal	VP-16, Ara-C, MIT, IDA+CBT	CR	[21]

ARA-C indicates cytarabine; As_2O_3 , arsenic trioxide; ATRA, all-trans retinoic acid; BHAC, behenoyl cytarabine; BHAC-DMP, behenoyl-ara-C; BHAC-AMP, behenoyl-ara-C aclarubicin; CBT, Cord Blood Transplantation; CR, complete remission; EM, extramedullary; VP-16, etoposide; HD-ARAC, high dose Cytarabin; IDA, idarubicin; LAP, GIMEMA protocols; MIT, Mitoxantrone; NS, not stated.

Therapy to otological relapse of APL for four patients have been described in three reports, that were high dose Ara-C plus irradiation of the temporal bone [13], irradiation only [6] and monotherapy with ATO [9]. Three patients died of disease progression eventually [6, 13] and a girl with isolated ear relapse who had been treated with ATO achieved CR and long-term survival [9]. In our settings, considering the molecular relapse in bone marrow, intensive chemotherapy with DA regimen and ATO was given. Unfortunately, in spite of the achievement of second molecular CR, the patient died of severe bone marrow suppression and septic shock after the first consolidation chemotherapy. In consideration of the relatively slow-advancing course and previous exposure to intensive chemotherapy, the regimen with less marrow toxicity containing just ATRA and ATO plus local irradiation might be more reasonable.

The mechanisms of auditory relapse of APL have not been illustrated [8]. Firstly, although increasing frequency of extramedullary relapse in APL is thought to correspond with the ATRA using [3, 8, 14], APL relapse in ear was also observed in patients with chemotherapy alone before the advent of ATRA [8]. Secondly, in spite of the presumption that mastoid might is the origin of leukemia cells in ear, some patients did relapse with mere isolated ear involvement [6-8, 10-13]. So the rare case and confusing phenomenon make the illustration of the mechanism difficult.

In summary, APL has become a "curable cancer" even without chemotherapy since ATRA and ATO were used [3]. However, cases of the extramedullary recurrence of APL with ear involvement are accumulating [6-14]. The mechanisms of this phenomenon have not been well illustrated and more inspection and research are needed. The case that we report here suggest that it is important for clinicians to recognize the possibility of disease relapse even in cured APL patients who complain of any auditory symptoms, and to execute prompt re-evaluation for the disease. Considering potential organ injury caused by pre-chemotherapy and the relative indolent disease course, treatment for these patient with less toxicity combined with local irradiation should be the more reasonable choice.

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Disclosure of conflict of interest

None.

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