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Case Report

Treatment-related acute myeloid leukemia with type D *CBFB-MYH11* after chemotherapy and radiotherapy in non-hodgkin lymphoma: a rare case report

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Abstract: Treatment-related Acute Myeloid Leukemia (t-AML) is among complications which occur after treatment of primary malignancies due to exposure to chemotherapeutic drugs and/or radiation. These malignancies include solid tumors and hematological neoplasms. T-AML accounts for approximately 10%-20% of total AML. Patients with t-AML are of special concern, because generally they have poor response to treatment and thus median survival is short. *CBFB-MYH11* is a fusion gene which generally occurs in AML, but only a few t-AML cases have been reported with *CBFB-MYH11*, and none of them aroused after non-Hodgkin lymphoma (NHL) treatment. Here, we report a rare case with t-AML with *CBFB-MYH11* (type D subtype) occurred four years after 9-month chemotherapy and radiotherapy for NHL. Lab findings are mainly discussed especially molecular genetic abnormality, which is considered as a reference for individualized treatment and prognosis. Through this report, we hope to remind the clinics and lab staff, that in order to be aware of t-AML, during treatment of NHL, dose of chemotherapy and radiotherapy should be weighed and follow up is necessary.

Keywords: Treatment-related acute myeloid leukemia, *CBFβ-MYH11*, acute myeloid leukemia

Introduction

According to The World Health Organization (WHO) classification system, AML is classified into different subtypes, and treatment-related myeloid neoplasms (t-MN) are one of them. Treatment-related acute myeloid leukemia (t-AML) is grouped along with Treatment-related myelodysplastic syndrome (t-MDS) and treatment-related myelodysplastic syndrome/myeloproliferative neoplasms (t-MDS/MPN) as t-MNs according to the WHO classification of tumors of hematopoietic and lymphoid tissues [1]. T-MN is a complication of primary malignancies including solid tumors and hematological neoplasms after exposure to chemotherapeutic drugs and/or radiation, or exposure to alkylating agents, topoisomerase II inhibitors, radiation [1-3]. T-AML arises from these reasons is an increasing risk to successfully cured patients, and t-AML accounts for approximately 10%-20% of total AML cases [1].

CBFB-MYH11 is a fusion gene which results from the abnormality of chromosome 16, for example inv (16) or t (16; 16). More than 10 different sized *CB*FB-MYH11 fusion transcript variants have been reported, among which 87% are type A, 3%-9% are each type D and type E fusion [4-6], other types of the fusion are mostly reported in single case. Generally speaking, CBFB-MYH11 fusion gene exists in AML, but only a few cases of t-AML have been reported with CBFB-MYH11, and none of them aroused from NHL. The clinical history and laboratory features of t-AML with CBFB-MYH11 especially after chemotherapy and radiotherapy in NHL are unknown. In this report, we describe a case of t-AML with CBFB-MYH11 that developed after exposure to chemotherapy and radiotherapy four years after 9-month treatment for NHL.

Case report

Male patient, 42 years old, was hospitalized because of 15-day fever and finding pancytopenia 3 days. He was diagnosed with allergic pur-

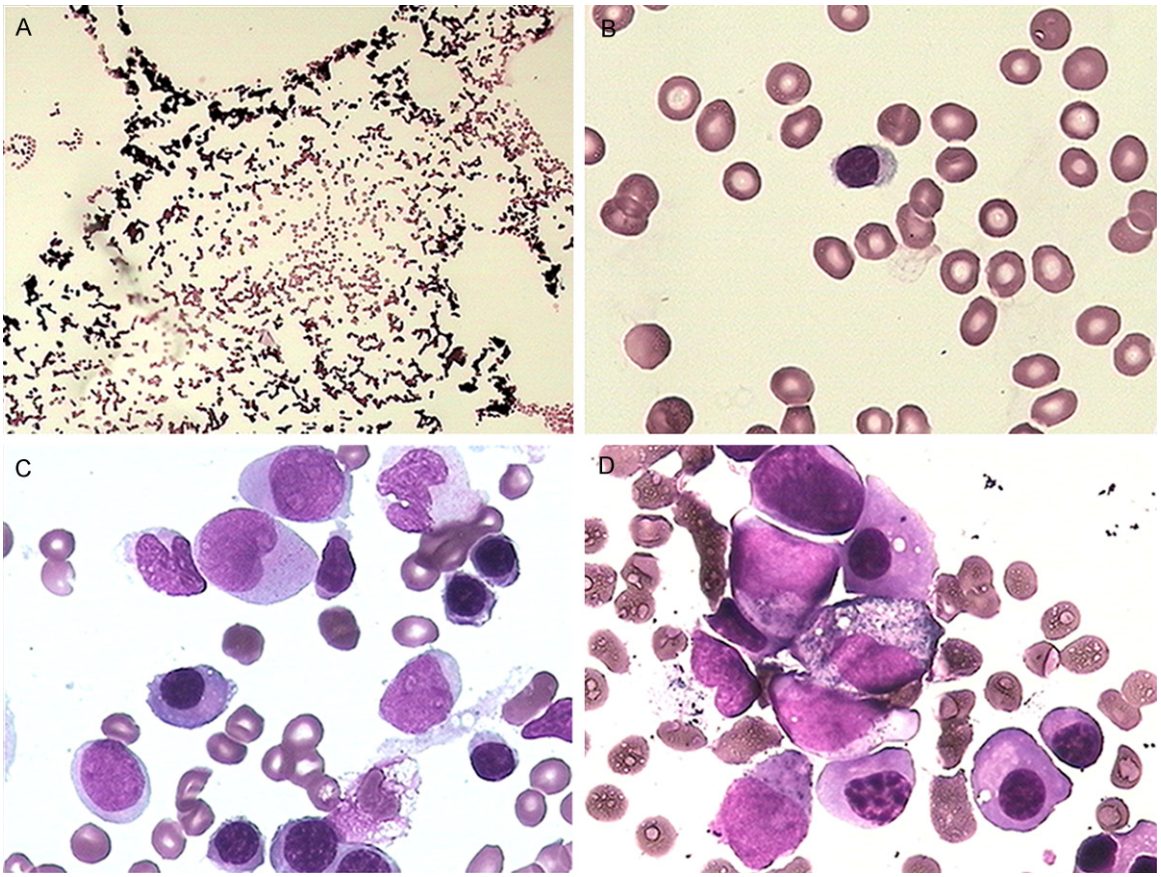

Figure 1. Morphological analysis of bone marrow cells. (A) (Wright staining, ×100) and (B) (Wright staining, ×1,000) The bone marrow (BM) aspiration of posterior superior iliac spine showing severe marrow hypocellularit. (C) The BM aspiration of sternum showing large monoblasts/promonocytes (Wright staining, ×1,000). (D) Myeloperoxidase stain of blastic cells of BM aspiration of sternum showing the abnormal cells weakly positive (×1,000).

pura 10 years ago. After treated with hormone he got better, but there is left femoral head necrosis. Four years ago, he was diagnosed with stage IIA NHL, extranodal NK/T-cell lymphoma, nasal type according to WHO classification. The patient remained complete remission after 9-month regular chemotherapy and radiotherapy (detailed therapeutic schedule was unknown). On physical examination, the patient appeared pale and pharyngeal hyperemia without other abnormalities.

Peripheral blood analysis revealed low hemoglobin (Hb) level of 68 g/L, low platelet (PLT) counts of 26×10^9/L as well as white blood cell (WBC) count of 1.50×10^9/L with 30% monoblasts/promonocytes under microscopic blood smear examination. Bone marrow (BM) aspiration at posterior superior iliac spine revealed severe marrow hypo-cellularity (**Figure 1A** and **1B**). But BM aspiration of sternum revealed 49% monoblasts/promonocytes with variably irregular nuclei, dispersed chromatin, variably prominent nucleoli, but with no eosinophilia (**Figure 1C**). A percentage of 74% abnormal cells were weakly positive and 26% were negative in myeloperoxidase staining of bone marrow (**Figure 1D**). Based on the above lab findings, the patients were initially diagnosed as AML, classified morphologically as M5 according to French-American-British (FAB) classification systems. Other abnormal lab results include: IgA 6.92 g/L (↑), C4 0.52 g/L (↑), hypersensitive c-reactive protein (hs-CRP) 85.30 mg/L (↑).

Immunophenotype using flow cytometry reported immature cells. Abnormal cells accounted for 34.8% of BM cells, mainly expressing CD34, CD117, HLA-DR, CD38, CD33, CD13, and lymphoid markers such as CD7, CD2, CD4, CD5, cCD3, CD10, CD79a were negative. Cytogenetic

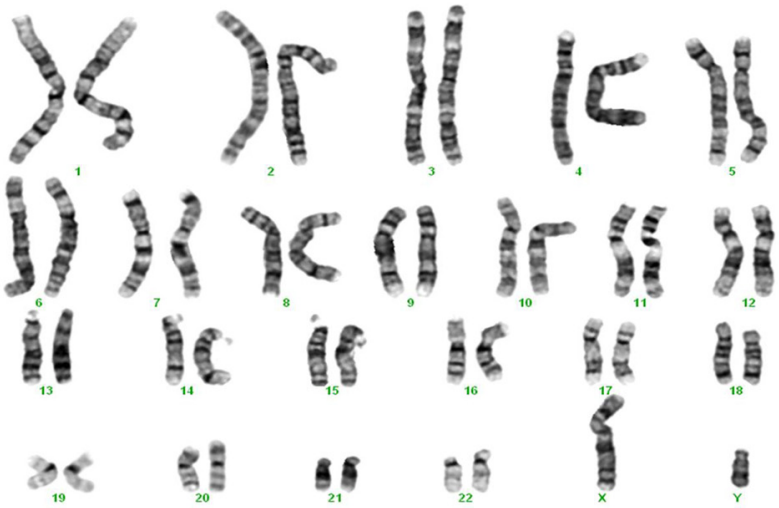

Figure 2. G-banded karyogram of the bone marrow cells obtained at diagnosis showing 46, XY.

analysis by G-banding showed 46, XY in all 6 metaphases at a resolution level of 300-400 bands (**Figure 2**). The patient didn't have fluorescence in situ hybridization (FISH) result. In the molecular study, *CBFB-MYH11* fusion gene was detected in BM cells, but other AML fusion genes such as *PML-RARa*, *AML1-ETO*, and *BCR-ABL*1 were negative. RT-PCR for *CBFB-MYH11* revealed that the fusion was type D subtype.

These findings suggest that the patient was an AML with the features of monocytes differentiation but with no evidence of eosinophilia. Based on the World Health Organization's (WHO) 2008 criteria, a diagnosis of t-AML with *CBFB-MYH11* was made. The patient was given DA (daunorubicin and arabinoside) treatment by comprehensive consideration.

Discussion

With the development of comprehensive treatment for malignant tumors, more patients were cured. Treatments such as chemotherapy, radiotherapy or autologous stem cell transplantation (ASCT) improve patients' survival and suppress tumor recurrence rate. However t-AML turn to be the serious late stage complication for primary cancers, which is of increased concern. Radiation and chemotherapy also disturb normal hematopoietic cells and cause molecular genetic or cytogenetic abnormalities. However, treatment also produces delayed toxicities which would proceed to t-MDS and t-AML [1]. Chemotherapy agents, such as alkylating drugs or topoisomerase-inhibitors, and radiotherapy are risk factors for the development of secondary cancers, particularly t-AML [1-3]. In the world, t-AML accounts for approximately 10%-20% of AML cases [1]. Generally, t-AML respond poorly to treatment and median survival after diagnosis is short. Smith [7] et al. reported that median survival time after diagnosis of t-MDS/t-AML was 8 months; 5-year survival was less than 10%.

T-AML secondary to chemotherapy and/or radiotherapy in NHL has been reported; however the incidence of t-AML secondary to NHL is different. Mudie [8] et al. reported that from 1973 to 2000 in Britain, there were only 17 cases (0.7%) were t-AML out of 2456 cases NHL patient. A large multicenter study [9] on 2739 patients collected 1784 NHL patients, finding that the cumulative incidences of t-AML/MDS developing from 1784 NHL patients after 7 years was 3.9%. According to Czuczman's study [10] on the incidence of t-MDS and t-AML, from the year 1996 to 2002, among 746 NHL patients who were treated with the ibritumomab tiuxetan, there were 19 patients (2.5%) developed t-MDS or t-AML at a median follow-up of 4.4 years. The patient in this case developed t-AML four years after 9-month chemotherapy and radiotherapy for NHL. The finding suggests that during NHL treatment, although curative effect of chemotherapy may work shortly after drug use, the side effects of chemotherapy drugs may have long-term toxicity which should take special attention after whole course of treatment. So follow-up of these patients is of crucial necessary to monitor onset of t-AML/MDS.

Since MICM classification may provide cytogenetic and molecular abnormalities as well as morphological and immunological disorders, apart from BM morphology and flow cytometry, t-AML/MDS patients should also take chromo-

some examination and molecular diagnosis to check chromosome and fusion gene abnormalities. Chromosome abnormalities include numerical chromosome changes, recurring balanced rearrangements, and other clonal abnormalities. Fusion gene abnormalities include *PML-RARA*, *AML1-ETO*, *BCR-ABL*, *CBFB-MYH11* et al.

Among abnormal karyotypes in AML, inv (16) or t (16; 16) is relatively common, as inversion or translocation of 16 chromosomes can result in *CBFB-MYH11* fusion gene. *CBFB-MYH11* fusion transcripts have 10 different types, respectively named type A to type J, which can be identified using RT-PCR [4-6]. Type A transcript appears most common among these types, and type D is relatively rare. However, in t-AML CBFB-MYH11 transcripts have showed that type A was less common than other types [5]. CBFB-MYH11 fusion gene is common in AML, but rare in t-AML. In 2015, Akiyama [11] reported a case of t-AML with inv (16) (p13.1q22) and Type D CBFB-MYH11 after exposure to Irinotecan-containing chemoradiotherapy. In this case report, CBFB-MYH11 fusion transcript of t-AML after treatment for NHL is detected and subtype is type D, but conventional cytogenetic analysis (CCA) has not detect abnormality in 16 chromosome. Considering BM chromosome karyotyping has resolution level of 300-400 G bands, there might be resolution level limitations to detect micro abnormalities in chromosomes. This also consists with several reports that CBFB-MYH11 transcripts are positive without inv (16) or t (16; 16) chromosome [12, 13]. Fujieda [12] reported that cytogenetic analysis by G-banding of a patient showed 46, XY, inv (9), but FISH analysis revealed the inv (16) signal. The karyotype of the patient is normal, and CBFB-MYH11 fusion gene is positive. We may infer that chromosome 16 of the patient may exist abnormality, only is not checked out due to the limitation of CCA. To this point, diagnosis of fusion gene transcripts exhibits more efficient and accurate results than G-banding.

The patient reported here was hospitalized for fever and pancytopenia, BM aspiration of iliac spine was severe hypo-cellularity, but sternum was AML. There was unbalanced proliferation in different sites of bone marrow. And the patient had a normal karyotypes but with *CBFB-MYH11* fusion transcript. In conclusion, BM morphology for those patients should be taken in multiple sites to have comprehensive information of the disease state. Our study suggests after NHL treatment, close follow-up is required to identify t-AML in time; once t-AML is highly suspected or initially diagnosed, detection of fusion gene is necessary, whether a chromosomal abnormality is found or not. This would benefit individualized treatment as well as prognosis.

T-AML secondary to chemotherapy and radiation is an increasing problem, and patients with t-AML have poor response to treatment and median survival is short. During treatment of NHL, doctors should make cautious consideration on dose of chemotherapy and radiotherapy. Besides, follow-up is necessary to identify t-AML using morphological and immunological techniques and cytogenetic and molecular diagnosis as well, accompanied by chemotherapy and radiotherapy treatment history.

Disclosure of conflict of interest

None.

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