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CASE REPORT

A case of therapy-related acute myeloid leukemia with inv(16)(p13.1q22) after single low-dose iodine-131 treatment for thyroid cancer

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Radioiodine is regularly used in the treatment of thyroid cancer to eliminate residual malignant tissue after thyroidectomy and to treat metastasis. Because of the low dose of radioiodine used to treat thyroid cancer patients, leukemia is an uncommon complication of exposure to radioiodine. Here, we present a patient who developed therapy-related acute myeloid leukemia with inv(16)(p13.1q22);*CBFβ-MYH11*, eosinophilia, and *K-ras* mutation and who had been treated with very low-dose radioiodine following total thyroidectomy.

Key Words Radioiodine, Thyroid cancer, Acute myeloid leukemia, *CBFβ-MYH11*, Eosinophilia, *K-ras*

INTRODUCTION

Therapy-related acute myeloid leukemia (t-AML) caused by radioactive iodine (RAI) occurs in less than 2% of thyroid cancer patients and is associated with a poor therapeutic response and prognosis [1-3]. Many cases of t-AML have occurred in >50-year-old patients after they received a cumulative radioiodine dose of more than 800 mCi, with intervals of less than 12 months between ^{131}I therapies [1-3]. Over 90% patients with t-AML or therapy-related myelodysplastic syndrome (t-MDS) exhibit an abnormal karyotype with approximately 70% patients having an unbalanced chromosomal aberration and the remaining 30% having a balanced chromosomal translocation [4]. Inv(16)(p13.1q22) is found in approximately 5-8% of patients with *de novo* acute myeloid leukemia (AML), but it is rarely reported in patients with t-AML. In 20-30% of t-AML patients, the first manifestation is AML without a preceding myelodysplastic phase [4].

Here, we report the case of a 38-year-old woman who developed t-AML with inv(16)(p13.1q22). *CBFB-MYH11*, markedly increased eosinophils, and *K-ras* mutation were noted after treating her for thyroid cancer with a single low intensity dose of ^{131}I.

CASE REPORT

A 38-year-old woman was admitted to our hematology clinic with a 10-day history of dyspnea and dizziness. She was diagnosed with papillary thyroid cancer 15 months prior to the admission, and had received a single dose of 150 mCi ^{131}I. The patient's condition remained stable thereafter on a suppressive dose of thyroid hormone. On physical examination, the patient appeared pale without other abnormalities. Peripheral blood analysis revealed hemoglobin level of 7.2 g/dL; platelet counts of 7,000×10^9/L; and a white blood cell count of 47.39×10^9/L with 60% blasts, 23% monocytes, and 4% eosinophils (Fig. 1A). The bone marrow (BM) aspiration revealed 10% myeloblasts, 20.4% monoblasts/promonocytes, and 53.4% eosinophils (Fig. 1B).

Immunophenotyping using flow cytometry revealed 2 populations of blast cells. One population showed positivity

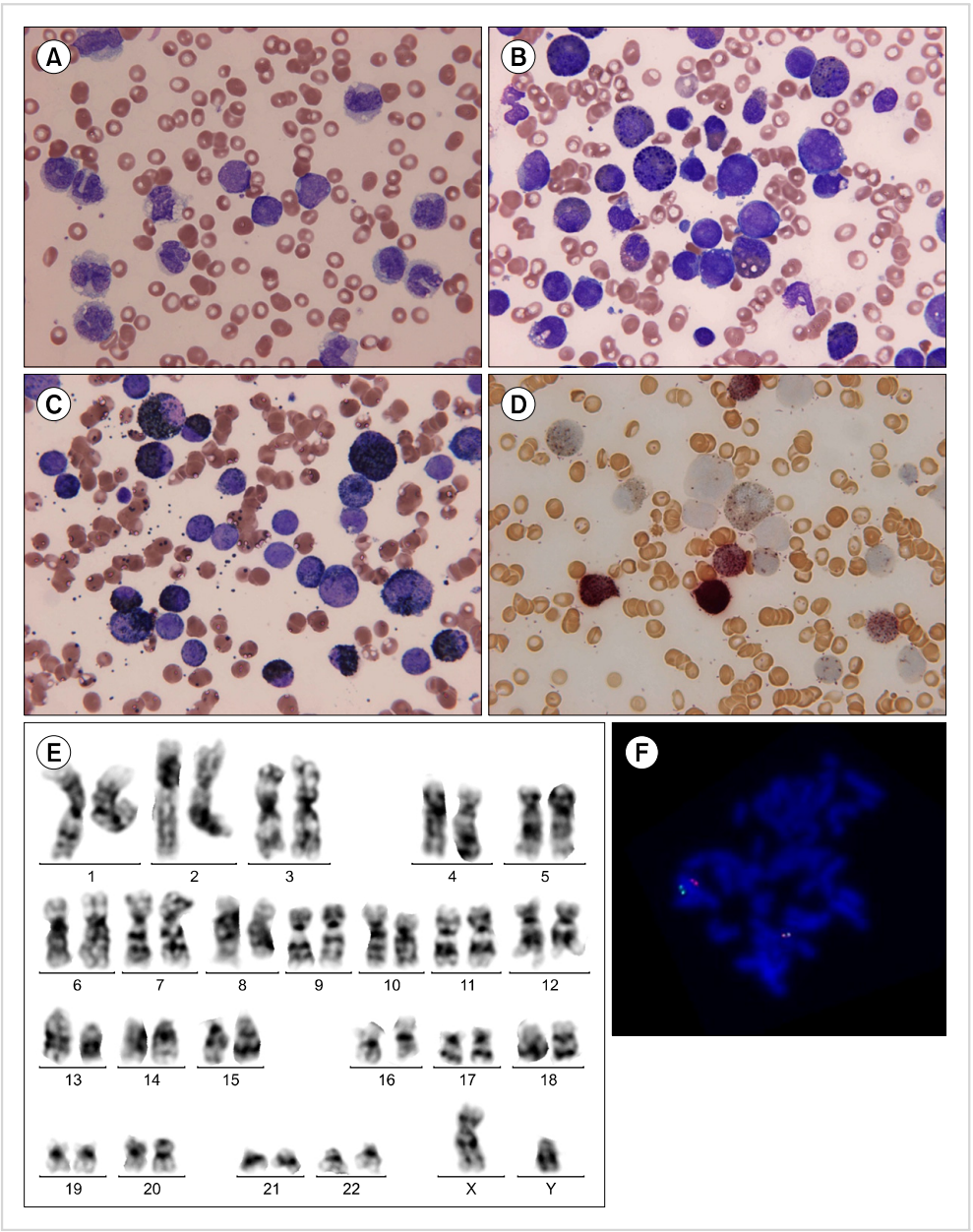

Fig. 1. Morphologic and cytogenetic study. **(A)** Peripheral blood smear and **(B)** bone marrow aspirates show myeloblasts, immature monocyte precursors, and abnormal eosinophils. The eosinophil count is markedly increased (53.4%), and some eosinophils have basophilic granules (Wright Giemsa stain ×1,000). **(C)** Blasts are positive for myeloperoxidase (MPO). **(D)** The marrow monocytic component is stained by α-naphthyl-butyrate esterase. **(E)** The karyotype reveals 46,XX,inv (16)(p13.1q22)[20] (GTL banding, ×1,000). **(F)** FISH using a LSI CBFB Dual Color Break Apart Rearrangement Probe reveals separate red (5′ *CBFB* gene) and green (3′ *CBFB* gene) signals, resulting in distinct hybridization signals on the arm of the inverted chromosome 16, and these signals were expressed in more than 89% of the cells. The normal *CBFB* allele is seen as one fused red-green (yellow) signal.

for CD45, CD34, myeloperoxidase (MPO), CD13, CD33, CD117, CD14, and HLA-DR, while the other population showed positivity for CD45, MPO, CD13, CD33, CD14, and HLA-DR. Blast cells were stained for MPO and α-naphthyl-butyrate esterase (Fig. 1C and 1D). BM cytogenetic analysis showed inv(16)(p13.1q22) in 20 analyzed metaphases (Fig. 1E). The result of fluorescence *in situ* hybridization (FISH) revealed that 89% of the nucleated cells had an abnormal break-apart signal pattern, that is, nuc ish(CBFBx2) (5'CBFB-sep3'CBFBx1)[356/400] (Vysis Inc., IL, USA; Fig. 1F). In the molecular study, gene rearrangements such as *PML/RARa*, *AML1/ETO*, and *BCR/ABL*, and a mutation in the *FLT3* gene (ITD or D835Y) were negative. The *K-ras* mutation in codon 12 (G>A transition, GGT→GAT) was detected by the pyrosequencing method, and this mutation induced an amino acid change of wild-type glycine (G) to aspartic acid (D) (TheraScreen NRAS/KRAS Pyro kit, QIAGEN, Hamburg, Germany). The mutant allele burden in BM mononuclear cells was 42% (Fig. 2A). Based on the World Health Organization's (WHO) 2008 criteria, the condition was diagnosed as t-AML with inv(16)(p13.1q22); *CBFB-MYH11*.

Blasts in peripheral blood and BM decreased rapidly after induction chemotherapy with cytarabine (100 mg/m^2 for 7 days) and idarubicin (12 mg/m^2 for 3 days), and the *K-ras* mutation, and the inv(16) rearrangement disappeared (Fig. 2B). The first consolidation therapy with cytarabine (100 mg/m^2 twice a day (b.i.d.) for 4 days) and daunorubicin (45 mg/m^2 for 3 days), and the second consolidation therapy with cytarabine (100 mg/m^2 b.i.d. for 4 days) and idarubicin (12 mg/m^2 for 3 days) were performed without serious complications. After the third consolidation therapy using high-dose cytarabine (3,000 mg/m^2 b.i.d. for 3 days), the

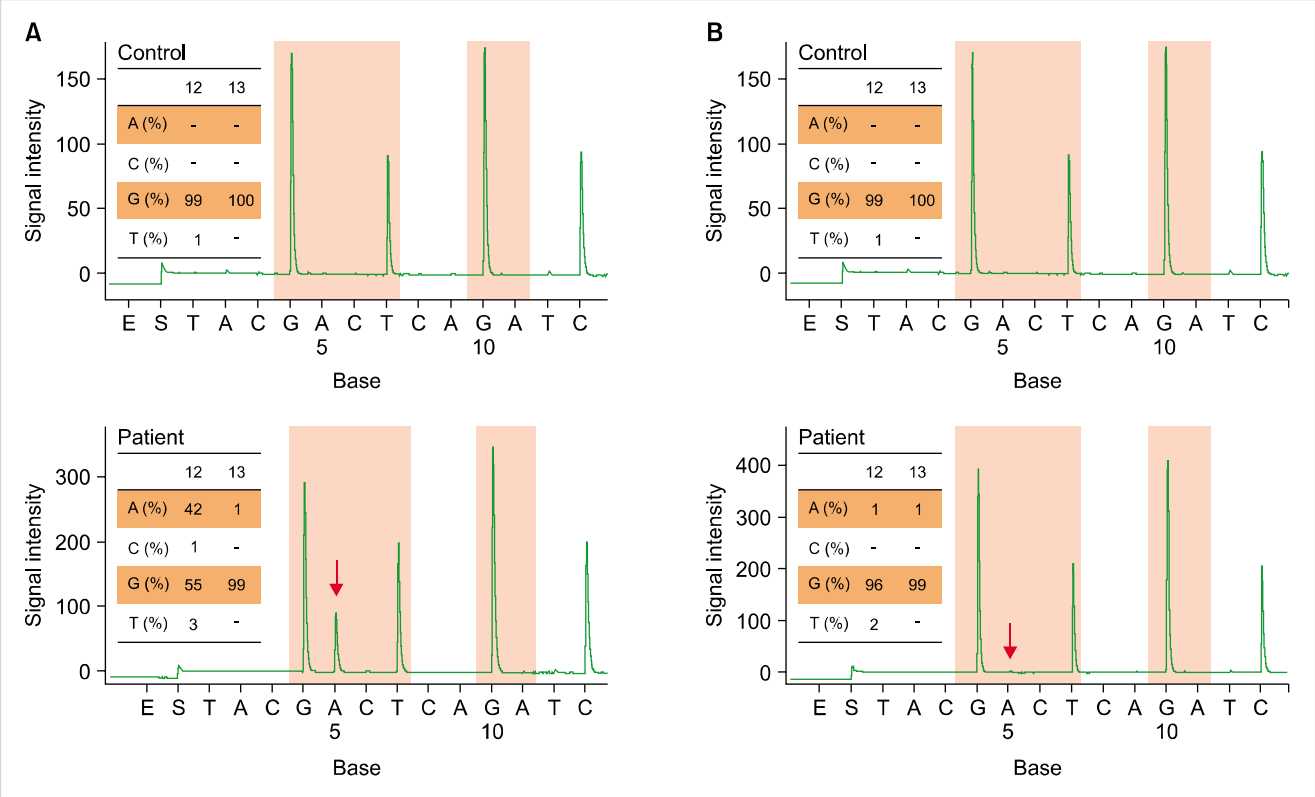

Fig. 2. *K-ras* mutation by pyrosequencing. Pyrogram shows the mutation and mutated clones. The X axis means the base and the Y axis represents the intensity of fluorescent signal. Shaded regions represent *K-ras* codons 12 and 13. **(A)** Arrow shows the analytic results of substitutions in the second base of *K-ras* codon 12. The mutation GGT (Gly) to GAT (Asp) in codon 12 was detected by pyrosequencing. **(B)** After induction of chemotherapy, the *K-ras* mutation disappeared.

patient has continued to have thrombocytopenia without blast increase.

DISCUSSION

RAI therapy has been the treatment of choice for toxic nodular goiter, Grave disease, and metastatic thyroid cancer. The National Thyroid Cancer Treatment Co-operative Group recently reported that RAI treatment in thyroid carcinoma had been administered in 62-75% of individuals in a cohort study [5]. Meta-analysis using 16,502 patients showed that the relative risk (RR) of second primary malignancy was increased in thyroid cancer patients treated with ^{131}I (RR= 1.19), and that the RR for the development of leukemia was increased by 2.5-fold in thyroid cancer patients treated with RAI [1].

Even though leukemia is a rare complication of ^{131}I therapy in these patients, the possible carcinogenic effect of ^{131}I is still a concern. Pochin described 4 cases of acute leukemia in 175 patients treated with ^{131}I for thyroid cancer, observing a leukemia incidence of 2.3% [2]. One group reported a case that the latency period from exposure to the occurrence of acute leukemia was 14 months [6]. The patient described here had received only a single dose of 150 mCi, and she developed AML in a shorter latency period than that seen in other t-AML cases. Moreover, Roldán reported 2 cases of AML, that is, AML with maturation (M_2, French-American-British (FAB) classification) and acute promyelocytic leukemia, after a single dose of 150 mCi in patients who were diagnosed with papillary thyroid carcinoma. The latency periods of these 2 patients were 2 and 5 years, respectively [7].

Another report by Anderson *et al.* focused on 48 patients who had a history of other primary disease such as breast cancer, lymphoma, or various other solid tumor and non-malignant disease, and were diagnosed with t-MDS/t-AML with inv(16). Ten of these patients (20.8%) received radiation therapy only, and inv(16) is more frequent in patients treated with only radiotherapy [8]. Patients with inv(16) exhibited a shorter latency period from the start of treatment for the primary tumor to the development of t-MDS/t-AML than did patients with other therapy-related diseases (median, 22 months; range, 8-533 months). Within the inv(16) subgroup, patients younger than 55 years of age had a longer survival period compared with patients older than 55 years of age [8]. However, Schroeder *et al.* had suggested that t-MDS/t-AML after RAI treatment was usually associated with an advanced disease stage, adverse chromosomal changes, a low response to induction chemotherapy, and a short overall survival even with the numerous treatment options [9].

Based on these findings, the patient presented here may be expected to have a poor outcome despite the presence of less severe risk factors such as inv(16) and young age. However, in the previous study, the t-AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) was morphologically identical to its *de novo* counterpart [4], while in the current case, the patient revealed strikingly increased eosinophils (53.4%) compared with eosinophilia in *de novo* AML with inv(16) that ranged from 1% to 33% [10]. The eosinophils had characteristically coarse, purple-violet colored granules that were larger than those of normal eosinophils (Fig. 1B). Importantly, Pulsoni *et al.* previously demonstrated that eosinophilia is a favorable prognostic factor and that the concomitant presence of both inv(16) and eosinophilia is associated with a significantly improved prognosis [11].

The common *Ras* gene mutation is a one base substitution in codon 12, 13, or 61 leading to constant activity of the Ras protein, which is caused by the guanosine triphosphate-bound status and can induce uncontrolled cell proliferation and escape from apoptosis [12]. The frequency of *K-ras* mutations at codon 12, 13, or 61 in AML patients has been reported to range from 3.5% to 13.3%. In a study by Valk *et al.*, *K-ras* mutations in codon 12 were found in 7% of the patients with AML and inv(16) [13]. The *in vitro* data suggest that mutant *Ras* promotes a myeloid maturation defect with relative sparing of the monocyte-macrophage lineage. This may be consistent with the overrepresentation of *Ras* mutations in the acute myelomonocytic leukemia (M4)/acute monoblastic and monocytic leukemia (M5) FAB types [14].

Based on these observations, Gilliland proposes a two-hit theory for leukemogenesis in which AML arises from the collaboration between 2 classes of mutations [15]. Class I mutations confer a proliferative and/or survival advantage to cells (*BCR-ABL* fusion gene and oncogenic *Ras*), while Class II mutations impair hematopoietic differentiation and apoptosis (*CBFβ-MYH11* and *PML-RARα* fusion gene) [15]. The patient described here had both a *K-ras* mutation and inv(16) at the time of t-AML diagnosis, and these abnormalities were not detected after achieving complete remission. It can be presumed that these findings support the two-hit model of leukemogenesis, and that *K-ras* mutation and inv(16) correlate with leukemogenesis in this patient.

In conclusion, only a small proportion of thyroid cancer patients treated with radioiodine have developed leukemia, and different dose ranges and latent periods have been reported in various trials. The case presented here is a rare case of inv(16) in t-AML that developed after a single low-dose iodine therapy. Although the risk of leukemia after ^{131}I exposure is hardly considered a contraindication to ^{131}I therapy, hematological follow-up of patients admitted for ^{131}I treatment is recommended.

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