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BRIEF COMMUNICATION

Unbalanced 11;18 translocation in an acute erythroid leukemia after radioactive iodine therapy

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Therapy-related acute myeloid leukemia (t-AML) is well described after chemotherapy or radiotherapy for diverse malignancies. Radioisotope therapy is also recognized as a less-common cause of t-AML. We describe a patient with acute erythroid leukemia after radioactive iodine administration for papillary thyroid cancer, with an unbalanced 11;18 translocation resulting in three copies of 11q, including the *MLL* gene. Although an increased incidence of chronic myeloid leukemia has been documented after radioactive iodine exposure, acute leukemia in this setting has been less frequently seen. Moreover, to our knowledge, the chromosome abnormality present in our patient has not been previously reported. The literature on cytogenetic abnormalities in t-AML after radioactive iodine administration is reviewed.

Keywords Acute leukemia, therapy-related, radioactive iodine

Therapy-related acute myeloid leukemia (t-AML) that occurs after cytotoxic chemotherapy and/or radiation therapy has been frequently described as outcomes of therapies for other malignancies improve. Radioisotope therapy is also recognized as a less-common cause of t-AML.

Several subtypes of t-AML after cytotoxic chemotherapy have been defined (1). t-AML after alkylating agent therapy is most commonly associated with abnormalities of chromosomes 5 and 7 and complex karyotypes, and is associated with a low complete remission (CR) rate and short disease-free survival (DFS) and overall survival (OS). In contrast, t-AML after topoisomerase 2 inhibitor therapy is most commonly associated with diverse reciprocal translocations involving chromosome 11q23, which rearranges the *MLL* gene, and is characterized by a higher CR rate, but also with short DFS and OS.

We describe a patient with acute erythroid leukemia after radioactive iodine therapy for papillary thyroid cancer, with an unbalanced 11;18 translocation resulting in three copies of 11q, including the *MLL* gene. Although an increased incidence of chronic myeloid leukemia (CML) has been documented after radioactive iodine exposure (2–4), acute leukemia in this setting has been less frequently seen. Moreover, to our knowledge, the chromosome abnormality seen in our patient has not been reported previously.

Materials and methods

A 48-year-old man was found to have a white blood cell (WBC) count of 1,200/μL with absence of neutrophils, a hemoglobin level of 6.7 g/dL and a platelet count of 67,000/μL. He had been noted to have a slowly progressive downward trend in his WBC count over a period of several years before onset of pancytopenia. Papillary thyroid carcinoma had been diagnosed 10 years previously, and treatment had consisted of thyroidectomy and three doses of radioactive iodine. The patient worked as a molecular biologist and had also handled radioactive iodine under a hood.

The patient's initial bone marrow aspirate and biopsy were markedly hypocellular (<5% biopsy cellularity) with trilineage aplasia; however, one small cellular spicule was present in the clot section with erythroid cells, lymphocytes, and possibly increased immature precursors, suggesting a patchy distribution of marrow cellularity and prompting a second bone marrow aspirate and biopsy after referral to the University of Maryland Greenebaum Cancer Center.

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The second marrow aspirate was cellular, with >50% erythroid cells and 15–20% blasts (Figure 1A). Maturing granulocytes and megakaryocytes were extremely rare. The biopsy was small but appeared cellular (50%), with a predominance of erythroid precursors and a small number of immature precursors or blasts. Flow cytometric analysis identified a population of myeloblasts, representing 27% of the total events and expressing CD13, CD15, CD33, CD34, CD117, and HLA-DR, with terminal deoxytransferase (TdT) expression in a subset of cells.

A diagnosis of acute erythroid leukemia (i.e., erythroid/myeloid in the World Health Organization (WHO) classification or FAB M6b in French-American-British (FAB) classification) was established.

Cytogenetic analysis

Karyotype analysis was performed on metaphase cells from the bone marrow aspirate using a standard G-banding method. Twenty metaphase cells from two cultures were analyzed at the 400-band level. Fluorescence in situ hybridization (FISH) was performed using an *MLL* probe (Abbott Laboratories, Abbott Park, IL) at 11q23 to confirm the findings of the G-banding analysis.

Results

A total of 10 cells had a normal male karyotype (46,XY), and the other 10 cells had an abnormal karyotype (46,XY,der(18)t(11;18)(q13;q21.1)), with an unbalanced 11;18 translocation that led to a partial gain of 11q and partial loss of 18q (Figure 1B). The FISH probe detected three copies of *MLL* in 78 of 200 cells (39%) (Figure 1B). The diagnostic bone marrow aspirate and biopsy samples were scant, unfortunately precluding additional analyses to define the genes at the chromosomal breakpoints involved in the translocation. Isolation of DNA from the paraffin block was attempted for array comparative genomic hybridization (aCGH) analysis, but unfortunately did not yield adequate material. In addition, the limited number of cells obtained for cytogenetic analysis did not allow additional exploratory FISH analyses with candidate probes to further characterize the translocation breakpoints.

Discussion

We describe an acute erythroid leukemia that occurred after radioactive iodine therapy for papillary thyroid carcinoma, with an unbalanced translocation of chromosome 11, which resulted in a trisomy 11q and included three copies of the *MLL* gene. To our knowledge, this translocation was previously unreported.

Although t-AML most commonly occurs after chemotherapy, with or without radiation therapy, exposure to radioactive substances has also been implicated in leukemogenesis, with effects most evident in nuclear accident survivors (5). An increased incidence of myeloid malignancies has been reported after radioactive iodine (RAI) therapy, consisting mainly of CML (2–4). Accounts of AML date back as early as 1960 (6,7), with myelodysplastic syndromes

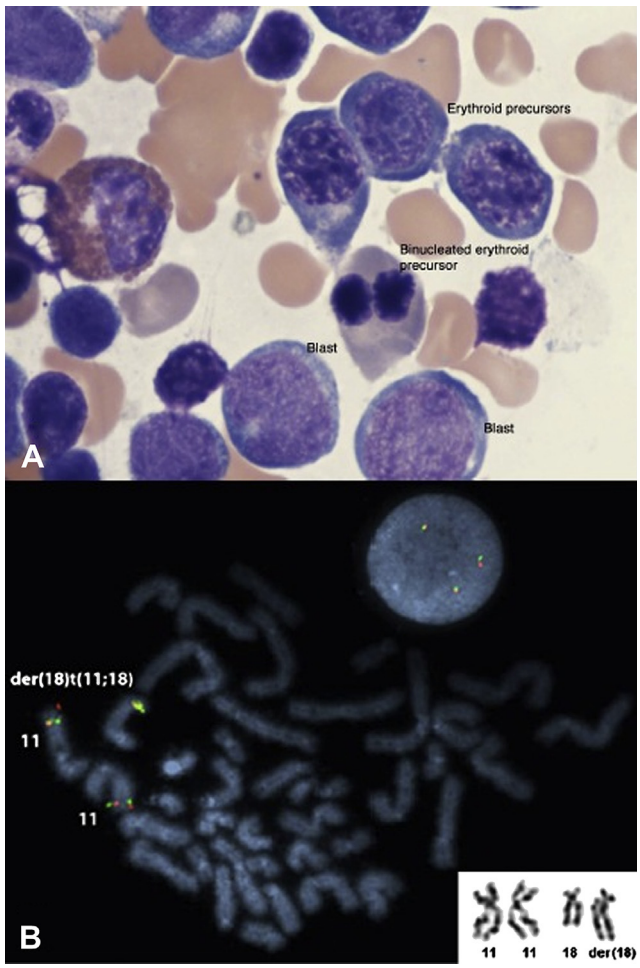

Figure 1 (A) Hematoxylin & eosin (H & E) stain of bone marrow aspirate. (B) A representative metaphase and an interphase with three copies of *MLL* detected by FISH. G-banded chromosomes 11, 18, and the der(18)t(11;18) are shown at lower right.

(MDS) sometimes preceding AML after RAI administration (8). The latency period can span a few decades (9). Reported cases of AML after therapeutic RAI exposure are summarized in Table 1 (8,10–18).

The dose of RAI may play a role in leukemogenesis risk, although this has not been extensively investigated. It has been suggested that doses >800 mCi might predispose to acute leukemia, whereas lower doses may be associated with development of CML after a long latency period (4,19), albeit with exceptions reported (10).

Read et al. followed 116 patients <20 years old, who were treated for Graves' disease and none of whom developed a hematologic malignancy (20). On the other hand, a recent meta-analysis estimated a 2.5-fold increase in leukemia risk for patients who were treated with RAI for thyroid cancer (21). This was confirmed by Iyer et al., who analyzed data from the Surveillance, Epidemiology and End Result (SEER) database on patients with low-risk thyroid cancer who were treated with RAI and were identified with an increased standard incidence ratio that was more pronounced in patients <45 years old (22).

Our patient had an unusual exposure history and clinical course. He was exposed to repeated iodine doses, possibly