Acute myeloid leukemia and follicular lymphoma after very low dose radioiodine therapy for thyroid diseases

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Introduction

Radioiodine (^{131}I) has been used in the treatment of thyroid cancer in order to eliminate residual thyroid tissue after thyroidectomy and to treat metastatic disease. Leukemia is one of the most prominent late effects of exposure to ionising radiation, but is an uncommon complication of exposure to ^{131}I. We report here on two patients who were admitted to our clinic 12 and 17 years after very low-dose radioiodine exposure for thyroid diseases with acute myeloid leukaemia and follicular lymphoma, respectively.

Case reports

Case 1: A 55-years old female presented at our Division with pancytopenia in January 2007, 12 years after 90 mCi radioiodine treatment for Graves' disease. Molecular biology studies showed no AML1-ETO, BCR/ABL p190(e1a2), BCR/ABL p210 (b3a2), BCR/ABL p210 /b2a2), and TEL/AML1, gene translocations, and immunohistochemistry for nucleophosmin excluded mutations in this gene. Cytogenetics showed a normal female karyotype with isochromosome 7q.

Immunophenotyping was negative (< 5%) for sCD3, CD3, CD4, CD7, CD10, CD16, CD19, CD20, CD22, CD41a, CD56, CD61, CD117, MPO and TdT, but positive for CD14 (81%), CD15 (81%), CD33 (93%), CD34 (9%), CD11b (87%), and HLA-DR (51%) in the blast gate. The patient was diagnosed with acute myeloid leukaemia (FAB subtype M4) and underwent conventional chemotherapy with idarubicin and cytarabine, achieving complete remission without complications. She was then consolidated with etoposide, idarubicin and cytarabine, still maintaining complete remission and was scheduled for an allogeneic stem cell transplantation, which is pending at the time of our report.

Case 2: A 56-years old female presented with an enlarged righ axillary lymph node in November 2004 : a lymph node biopsy showed follicular lymphoma grade I, stage IV (lymphomatous B-cell infiltration detected in bone marrow smear and trephine biopsy and clonal IGHV and BCL2-IGHV gene rearrangements in bone marrow blood). She had been diagnosed 16 years before with papillary thyroid carcinoma and treated with partial thyroidectomy and immediate adjuvant radioiodine (30 mCi). Two years later she had been consolidated with an additional dose of radioiodine (130 mCi). Apart from therapeutic radioiodine, she had also performed 4 whole-body scintigraphies with ^{131}I, for a total dose of 11 mCi (cumulative dose: 171 mCi). She was treated with R-CHOP and achieved partial remission, which persisted after salvage chemotherapy according to the R-DHAP scheme. On partial remission, she was treated with 4 administrations of rituximab while awaiting high-dose chemotherapy (according to the BEAM protocol) and autologous hematopoietic stem cell support.

Discussion

Myelodysplastic syndrome has been previously reported in a 67-years old woman after 820 mCi of ^{131}I for thyroid cancer (and who ultimately evolved to leukaemia)[1] and in another patient who also received external beam radiation therapy.[2]

Leukemia after treatment for thyrotoxicosis has been previously reported,[3-5] even if the 36-yr follow-up of 116 patients under the age of 20 yr with Graves' disease who were treated with radioiodine between 1953 and 1973 did not disclose any leukaemia case.[6]

Leukemia as a second malignancy after treatment of thyroid cancer is rare and was first reported in 1955.[8] Most cases in the literature are represented by acute leukemia[8-13] and have occurred after cumulative doses higher than 800 mCi,[14] with a case of M6 AML occurring after as long as 8 years.[7] Despite this, 2 cases of acute myeloid leukaemia (AML) (one M2 and the other M3) have been reported after single dosage of only 150 mCi,[9] and a third case after 2 doses of 150 mCi.[15] The risk associated with microdoses has also been suggested by Laurenti et al, who reported a 45-years old female who developed M2 AML 14 months after a single dose of just 23 mCi.[7] At least 2 cases of acute promyelocytic leukaemia (AML M3, APL) have been reported : Kolade et al reported a 51-year-old woman who developed APL within 27 months of completing a cumulative dose of radioiodine of 22.1 mCi,[16] while Roldan et al reported APL after single dosage of only 150 mCi.[9]

Chronic leukaemia has also been reported after ^{131}I treatment. At least 10 cases of chronic myeloid leukemia (CML) have been reported after radioiodine treatment of thyroid cancer with a total dose less than 150 mCi,[17-20] one 13 years after a cumulative dose of 670 mCi[18] and another 14 years after.[19]

A general recommendation is that the bone marrow should not receive a total dose which exceeds 1000 mCi, and there should be an interval of at least one year between doses.[15] Almost all cases reported in the literature occurred after a total dose of more than 800 mCi and with an interval between doses of 2 and 6 months.[15,22] Total quantities up to 1 Ci or more may be used, with a limiting factor being a 200 rad acute exposure to the bone marrow.[21] ^{131}I at any dose could cause sublethal damage to the bone marrow, but individual susceptibility cannot be excluded in patients developing leukemia after ^{131}I treatment.

Since ^{131}I was introduced for hyperthyroidism, no apparent increase in the incidence of leukaemia has been detected,[14,23] although an increased (but not statistically significant) risk was observed for both chronic lymphocytic leukemia (CLL) and non-CLL in two large retrospective studies from Sweden;[10,14,24] leukemia has

also been reported in rare cases as a complication of ^{131}I treatment for metastatic thyroid cancer, although epidemiological analyses show conflicting results.[15,22,25] As a matter of fact, the incidence of leukemia after ^{131}I treatment for thyroid cancer is estimated at around 2% in large series,[2,12,13] while the incidence of leukemia after ^{131}I treatment for hyperthyroidism, which is a relatively benign condition, is still a matter of debate.[14,24]

On the other hand, lymphoma is an extremely rare occurrence after ^{131}I treatment. Wiseman et al reported two cases of lymphoma of the parotid gland 10 and 3 years after 675 mCi and 350 mCi radioiodine therapy for thyroid carcinoma, respectively.[26]

^{131}I is widely used in the treatment of hyperthyroidism and for remnant ablation in patients with differentiated thyroid cancers,[27] and it is considered an efficacious and safe approach, although recently some authors prudentially restrict its use to older patients after surgery or medical failure. In conclusion, since the benefits of radioactive iodine therapy in the treatment of hyperthyroidism and thyroid cancer are proven and the use of ^{131}I appears to be increasing for nonmalignant thyroid diseases,[6] a strict hematological follow-up of patients submitted to ^{131}I is warranted in order to accurately detect the incidence of leukemias and lymphomas. Although the development of these malignancies can be due to aging or other causes rather than exposure to ^{131}I treatment, its role could have been underestimated. Radioprotectants such as amifostine could eventually be used to reduce extrathyroid toxicity.

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