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CASE REPORT

Therapy-related acute promyelocytic leukemia after treatment with radioiodine for thyroid cancer: case report with literature review

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Summary

Therapy-related acute promyelocytic leukemia (t-APL) is a rare but known complication of chemotherapy and/or radiation therapy. Approximately 200 cases of t-APL have been reported in the literature up until now. The development of t-APL after radioiodine therapy is very rare, keeping in mind the very low doses of radiation exposure of the patient. We present a case of a 47-year-old woman with t-APL t15;17(q22;q21) developed after radioiodine treatment for thyroid carcinoma. The patient was treated with chemotherapy and achieved complete response lasting for 3+ years. The patient's excellent response to treatment supports the data of the relevant literature that t-APL is associated with a better therapeutic result than the other subtypes of secondary acute myeloid leukemia (AML).

Key words: acute promyelocytic leukemia, radiotherapy, secondary malignancy, thyroid cancer

Introduction

Thyroid carcinoma is the most common malignant endocrine tumor (92%) and represents 0.8% of all malignant diseases [1]. The mortality rate is equal to that of all other endocrine carcinomas combined. It displays a wide range of histological types and subtypes, with different frequency, morphology and prognosis [2]. There are two gross histological categories: differentiated carcinoma (papillary and follicular), with over 90% of the cases and with very good prognosis, and the most aggressive forms of non-differentiated carcinoma [1,3]. There are rather broad geographical and ethnic variations of distribution [2,4].

The incidence of secondary malignancies (SM) after treatment of primary hematological malignancies or solid tumors increases. For effective prophylaxis and timely diagnosis of possible SM it is important to know the potential risk factors which could trigger SM [5].

The development of t-APL after radioiodine therapy is rare, keeping in mind the very low doses of radiation exposure of such patients [6-8].

Case presentation

We present the case of a 47-year-old white female with t-APL developed after treatment for pre-existing thyroid carcinoma. The initial thyroid neoplasia had been diagnosed in 2001 after scintigraphy confirming a thyroid cold nodule. There was no positive cancer family history. The treatment involved complete thyroidectomy (histology showed papillary carcinoma), followed by a single-dose of 118 mCi radioactive ^{131}I (04.2002). Treatment was without side effects. The follow-up period was uneventful.

In August 2003 she developed systematic symptoms including fever, bleeding, weight loss and signs of disseminated intravascular coagulation. She was admitted to the hospital for diagnosis.

The patient was in poor general condition. No

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peripheral lymphadenopathy or splenomegaly were present. Full blood count showed Hb 8.6 g/dL; white blood cells 1.9×10^9/l; platelets 34×10^9/l; differential blood count showed 85% hypergranular promyelocytes. Total serum protein, urea, creatinine, uric acid, transaminases, electrolytes, alkaline phosphatase and iron were within normal limits. Lactate dehydrogenase was 1258 U/l (normal up to 460); C-reactive protein 34 mg/l (normal up to 10); prothrombin time 45% (normal 70-110%); fibrinogen 0.90 g/l (normal 2.0-4.5); fibrin degradation products 40 μg/ml (normal up to 10); fibrin monomers positive.

Morphologically bone marrow aspirate revealed a predominance of promyelocytes and an estimated median cellularity of 68% (Figure 1). The numerous hypergranular promyelocytes displayed bilobed and reniform nuclei, finely granular chromatin, conspicuous nucleoli, and a moderate to abundant amount of cytoplasm. Auer rods were present in all cases (Figure 2). Blasts and promyelocytes in all cases were uniformly and strongly positive for myeloperoxidase, as shown by cytochemical analysis. Erythroid elements were markedly decreased; dyserythropoiesis was identified-the dysplastic features included nuclear irregularities, nuclear budding, megaloblastoid changes, cytoplasmic vacuolization, and the presence of Pappenheimer bodies. Megakaryocytes were absent. Dysplasia in granulocytes could not be evaluated reliably because most of the cells were promyelocytes. Only rare (1% to < 5%) maturing neutrophils were identified.

Conventional cytogenetics and fluorescence *in situ* hybridization (FISH) showed t15;17(q22;q21).

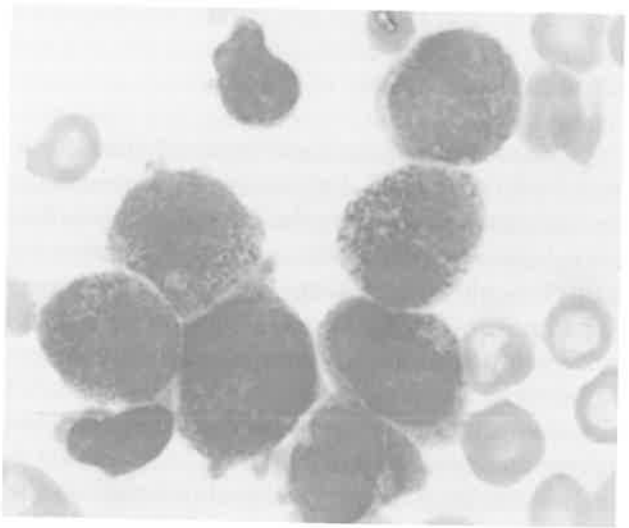


Figure 1. Bone marrow aspirate smear shows neoplastic promyelocytes with reniform nuclei, finely granular chromatin, and a moderate amount of cytoplasm with numerous granules (Wright-Giemsa ×1,000).

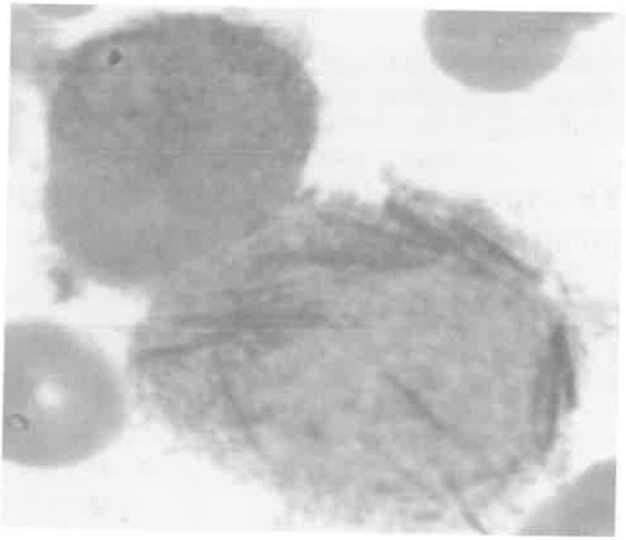


Figure 2. A promyelocyte with numerous Auer rods (Wright-Giemsa ×1,000).

Immunophenotypic analysis by flow cytometry demonstrated the presence of a distinct promyelocytic population: the promyelocytes were positive for CD13, CD33 and myeloperoxidase, and negative for CD3, CD10, CD19, CD20. Other antigens expressed in a subset of cases included CD117, CD9, CD38, CD2, CD64 and CD34.

The patient was characterized as low risk and received induction chemotherapy (AIDA) as follows: oral all-*trans* retinoic acid (ATRA) 45 mg/m^2 divided into 2 daily doses, continuously from the first day of treatment until complete remission; idarubicin 12 mg/m^2 i.v. bolus on days 2, 4, 6 and 8. Chemotherapy was given every 3 weeks for 3 courses. Complete remission was achieved 10 weeks after initiation of therapy, verified by normalization of peripheral blood counts and bone marrow biopsy.

Three monthly cycles of anthracycline-based consolidation chemotherapy were administered: 1st month: idarubicin 5 mg/m^2 i.v. daily for 4 days; 2nd month: mitoxantrone 10 mg/m^2 i.v. daily for 2 days; 3rd month: idarubicin 12 mg/m^2 i.v. daily on day 1.

Upon completion of the consolidation chemotherapy PCR (PML-RARα fusion protein) confirmed the presence of molecular remission.

The maintenance treatment included ATRA 45 mg/m^2 p.o. daily, days 1-15 every 3 months plus oral 6 mercaptopurine (6MP) 100 mg/m^2 daily plus i.m. methotrexate 15 mg/m^2 weekly [9]. Doses of 6MP and methotrexate were decreased by 50% if the white blood cell count was less than 3.5×10^9/l and discontinued if it was less than 2.5×10^9/l. Maintenance therapy continued for 2 years.

Discussion

The term "secondary malignancies" was introduced in 1927 because of the development of secondary malignant diseases related to the longer life expectancy of patients and is considered a late complication of the anticancer treatment for a preceding malignancy. We presented the clinical, cytogenetic and molecular characteristics of a case of t-APL after radioiodine treatment for thyroid carcinoma. Even though rare, the pathology of t-APL becomes more common in recent years according to data by Beaumont et al. [10]. Although approximately 200 cases of t-APL have been described in the literature, these cases have been reported in clinical studies comparing *de novo* APL with t-APL [7]. Morphologic evidence of dysplasia may be identified in all types of AML but usually it is present to a lesser degree in *de novo* AML compared with t-AML. In these cases granulocytes can not be assessed reliably due to the marked left shift in maturation with only rare maturing forms. However, the larger number of cases now reported and the presence of dysplastic features in erythroid precursors and megakaryocytes suggest that these tumors are therapy-related [7,8,10].

It has been shown that the frequency of complex karyotypes is higher in t-AML than in *de novo* AML [11-13]. No recurrent pattern of secondary abnormalities was observed. The study of 91 t-AML/MDS (myelodysplastic syndrome) cases identified del(7) and del(5) in 48 (53%) and 21 (23%) cases, respectively, with various other abnormalities and revealed that the number of chromosome aberrations was a significant and independent prognostic factor [13]. In the largest series of 83 patients with t-APL [10,13], 62 (75%) had an isolated t(15;17) and 21 (25%) had additional chromosomal rearrangements with complete or partial deletion of chromosomes 5 or 7, trisomy 8, and rearrangements of chromosome 17. Our case was classical for the disease diagnosis [t15;17(q22;q21)].

Studies on leukemogenesis suggest a multistep pathogenesis for AML [12,14]. Class I mutations, such as point mutations in receptor tyrosine kinases (e.g., *flt3* and c-*kit)*, result in gain of function and provide a proliferative and/or survival signal to hematopoietic progenitors. Class II mutations are loss-of-function mutations, usually involving transcription factors, and are due to chromosomal translocations or inversions [e.g., t(15;17), t(8;21), inv(16)], resulting in impaired myeloid differentiation. In keeping with this hypothesis, in this group of t-APL cases, *PML/RARα* would be class II mutation, resulting in a block of differentiation. The *flt3* gene mutations and additional abnormalities of unknown genes disrupted by secondary cytogenetic aberrations would be class I mutations that confer a proliferative advantage.

Various possibilities for the etiology of SM can be discussed [15-17]:

1. *Treatment*

Chemotherapy:

a) Alkylating agents cause cytogenetic anomalies in 5q7q with a latent period of development of 4-7 years.

b) DNA topoisomerase II inhibitors can cause 11q23 cytogenetic anomalies with a latent period of about 2 years.

Both a and b can lead to SMs-type MDS and AML.

Radiotherapy:

a) A British study with 5519 cases with Hodgkin's disease, covering a 30-year period (1963-1993) reported results on SM and mortality [15]. Three hundred and twenty-two SMs occurred. Relative risks (RRs) of gastrointestinal, lung, breast, bone and soft tissue cancers, and of leukemia increased significantly with first treatment at younger age. Absolute excess risks and cumulative risks of solid cancers and leukemia, however, were greater at older age than at younger age. Gastrointestinal cancer risk was greatest after mixed-modality treatment (RR=3.3); lung cancer risk was significantly increased after chemotherapy (RR=3.3), mixed-modality treatment (RR=4.3), and radiotherapy (RR=2.9); breast cancer risk was increased only after radiotherapy without chemotherapy (RR=2.5); and leukemia risk was significantly increased after chemotherapy (RR=31.6) and mixed-modality treatment (RR=38.1). Age at treatment had a major effect on risk of SM after Hodgkin's disease. The roles of specific chemotherapeutic agents in the etiology of solid cancers after Hodgkin's disease require detailed investigation.

b) The American Late Effects Study Group monitored 1380 children treated for Hodgkin's disease to determine the incidence of SM and the risk factors associated with them for the period 1955-1986. The average time of observation was 17 years; the average time until the appearance of a SM was 18.1 years. Results in this cohort: there were 88 SM as compared to 4.4 expected in the general population; the estimated actuarial incidence of any SM 15 years after the diagnosis of Hodgkin's disease was 7.0%. Breast cancer was the most common solid tumor with a median estimated actuarial incidence in women approaching 35% (95% CI 17.4-52.6) by 40 years of age. Forty-

two breast cancer cases were diagnosed in 30 patients and 12 of those were with bilateral localization. Older age (10-16 vs. < 10 years) at the time of radiation treatment (RR=1.9) and a higher dose (2000-4000 vs. <2000 cGy) of radiation (RR=5.9) were associated with significantly increased risk of breast cancer. Treatment with alkylating agents, older age (10-16 vs. < 10 years) at the diagnosis of Hodgkin's disease, recurrent Hodgkin's disease, and a late stage of disease at diagnosis were risk factors for leukemia [16].

2. *Factors influencing the risk of drug and radiation-induced defects [16-19]:*

a) Young age of the patient and tissues with incomplete growth

b) Mutagenic agent dose

c) Hormonal status (estrogens)

d) Positive family history for malignant diseases that justifies a genetic predisposition of the patient

e) Small nucleoproteins (SNPs) in DNA regeneration and SNPs genes for estrogen synthesis

f) Enzyme polymorphism, which influences the metabolism of cytotoxic drugs.

Conclusion

We assume that the t-APL in our patient could be attributed to the radiotherapy given for thyroid carcinoma, irrespective of the very low doses of radiation exposure. Her follow up supports the published data that the t-APL is associated with better therapeutic response compared to other subtypes (FAB) of secondary AML (after radiotherapy/chemotherapy or after transformation of MDS).

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