INTERNAL MEDICINE

□ CASE REPORT □

Transformation of p53-Positive Papillary Thyroid Carcinoma to Anaplastic Carcinoma of the Liver following Postoperative Radioactive Iodine-131 Therapy

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Abstract

Multiple liver metastases were incidentally detected in the lobe of the liver of an 81-year-old woman following total thyroidectomy and ablative radioactive iodine administration for the treatment of papillary thyroid carcinoma. A biopsy specimen taken from the metastatic liver tumor was histologically diagnosed as anaplastic carcinoma. Immunohistochemical staining for p53 was positive in both the primary tumor and liver biopsy specimens. We considered this to have been caused by anaplastic transformation from papillary thyroid carcinoma during treatment. We report a rare case of multiple liver metastases from a papillary thyroid carcinoma, which we believe to be the result of anaplastic transformation during postoperative radioactive iodine-131 therapy.

Key words: anaplastic transformation, differentiated thyroid carcinoma, iodine-131 therapy, p53 mutations, liver

(Inter Med 47: 1709-1712, 2008)
(DOI: 10.2169/internalmedicine.47.1190)

Differentiated thyroid carcinoma is considered to have a comparatively favorable prognosis, but 10-20% of patients are known to die of distant metastases (1). Hepatic metastasis from differentiated thyroid carcinoma is found in 3% to 25% of these patients, and is usually secondary to other distant metastatic sites (1, 2). Liver metastasis from papillary thyroid carcinoma without other organ metastasis has been reported in only one case (3). Here, we describe a rare case of multiple liver metastases from papillary thyroid carcinoma, which we believe to be the result of anaplastic transformation during postoperative radioactive iodine-131 (^{131}I) therapy.

An 81-year-old woman was referred and admitted to our hospital in May 2003; multiple liver metastases had been incidentally detected in the lobe of her liver by computed tomography (CT). The patient had undergone a total thyroidectomy for thyroid carcinoma in July 2000, and she had no organ metastasis when surveyed with ^{131}I scintigraphy following surgery. Histologically, the tumor was diagnosed as well differentiated papillary carcinoma without components of poorly differentiated carcinoma. She had a dry cough, bloody sputum, and dyspnea in May 2001. Bronchoscopic examination revealed a polypoid tumor that almost completely obstructed the airway. Since the polypoid obstructive tumor was progressive during the postoperative course, we tentatively diagnosed it as an intrathoracic thyroid carcinoma infiltrating to the trachea. The obstructing tumor was treated with a neodymium-yttrium-aluminum-garnet (Nd: YAG) laser for 0.5 s at 30 to 40 Watts through a flexible bronchoscope under local anesthesia. Unfortunately, the biopsy specimen was obtained after Nd: YAG laser treatment and was diagnosed histologically as “active inflammation and definite malignant squamous metaplasia.” We cannot rule out the possibility that the Nd: YAG laser treatment modified the histology. Since her untreated lesion was positive based on ^{131}I scintigraphy, ^{131}I therapy was begun in August

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Received for publication April 3, 2008; Accepted for publication June 23, 2008

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Table 1. Laboratory Data upon Admission

WBC	3700	/μL	CRP	5.9	mg/dL	CEA	2.1	ng/mL
RBC	3.70×10^6	/μL	BUN	11	mg/dL	CA19-9	6	U/mL
Hb	10.5	g/dL	Cr	0.46	mg/dL	AFP	<10	ng/mL
Ht	33.7	%	Ca	8.3	mg/dL	PIVKAII	13	mAU/mL
Plts	230×10^3	/μL	ALP	193	IU/L	FT4	1.46	ng/dL
			GTP	59	IU/L	FT3	1.68	pg/dL
			AST	23	IU/L	TSH	1.67	mIU/mL
			ALT	18	IU/L	Thyroglobulin	<5.0	ng/mL
			LDH	175	IU/L	Anti-TPOAb	2.4	IU/mL
			Amy	33	IU/L	Anti-TgAb	25.4	IU/mL
			T-Bil	0.5	mg/dL	PTH	19.6	pg/mL
			TP	6.1	g/dL	Fe	74	μg/dL
			Alb	3.3	g/dL	Ferritin	384	ng/mL
			T-Chol	188	mg/dL	HBsAg	Negative	
						HCVAb	Negative	

CA19-9, carbohydrate antigen 19-9; HBsAg, hepatitis B virus surface antigen; HCV, antibody to hepatitis C virus; PIVKA-II, protein induced by vitamin K absence-II;TSH, thyroid-stimulating hormone

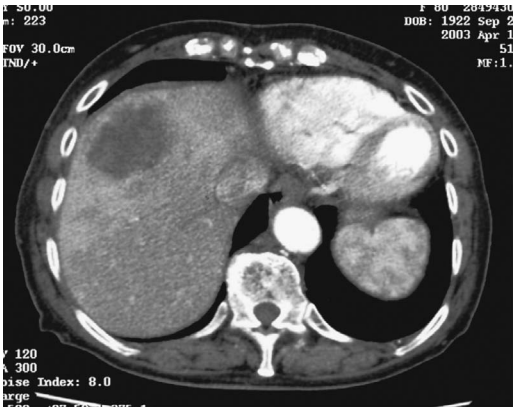

Figure 1. Computed tomography of the abdomen on admission.

2001, at a dose of 150 mCi to prevent re-obstruction. ^{131}I therapy was followed by a 200 Gy dose of external-beam radiation. The patient was discharged in May 2002 and remained stable as an outpatient until the current readmission.

On admission, no abnormalities were noted in the physical and laboratory examinations: no masses were palpable in either the abdominal cavity or remnant thyroid gland. In addition, no swelling was observed in the lymph nodes. The routine laboratory data obtained on admission are shown in Table 1. Thyroid hormone serum levels were all within normal limits. Tumor markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), the precursor of protein induced by vitamin K absence-II (PIVKA-II), and thyroglobulin (Tg) were not elevated (Table 1).

Abdominal CT showed a hypodense, ring-enhanced mass in the left lobe of the liver (Fig. 1). CT did not provide any evidence of a malignant lesion in the lung, gastrointestinal tract, pancreas, or lymph nodes. A biopsy specimen from the liver tumor was diagnosed histologically as anaplastic spindle cell carcinoma. Immunohistochemically, the atypically large spindle cells were positive for cytokeratin 7 and vimentin, while these cells were negative for cytokeratin 20, CEA, Tg, and thyroid transcription factor 1 (TTF-1). Radiofrequency ablation (RFA) was administered to the liver tumors and was followed by chemotherapy with paclitaxel (4) at 140 mg/m^2 per 96 hours as a continuous intravenous infusion. Despite this treatment regimen, the disease progressed. The tumor increased in size and multiple lung metastases were also detected. No tumor markers, including AFP, CEA, CA 19-9, PIVKA-II, and Tg, were elevated, even at the end stage, probably due to the anaplastic transformation of the papillary thyroid carcinoma during treatment with total thyroidectomy and ablative radioactive iodine. The patient died of respiratory insufficiency due to progressive lung metastases on August 5, 2003.

Autopsy findings showed metastatic tumors in the liver, lung, and pancreas. No tumors were detected in the neck. Histologically, the tumors stained positively for cytokeratin CAM 5.2, cytokeratin 7, vimentin, and focally for Tg, while the spindle cells did not express TTF-1 or CEA. Based on the clinical, histopathological, and immunohistochemical findings, we diagnosed the tumor as anaplastic carcinoma transformed from papillary thyroid carcinoma.

The clinical course of the patient was characterized by a rapid progression to multiple liver metastases soon after the second round of ^{131}I therapy. These observations prompted us to investigate additional molecular and biochemical factors present in the tumor tissues. The primary tumor, liver needle biopsy specimen, and tumor tissues sampled at autopsy were all positive for the p53 antibody (Fig. 2).

This case represents a rare case of liver metastases without other metastases. Liver metastasis from differentiated thyroid carcinoma usually occurs as a terminal stage of thyroid carcinoma and is generally accompanied by bone, lung, or cervical lymph node metastases (5). Specifically, the liver is thought to be a secondary site of other distant metastases, while direct liver metastases from a primary lesion are very

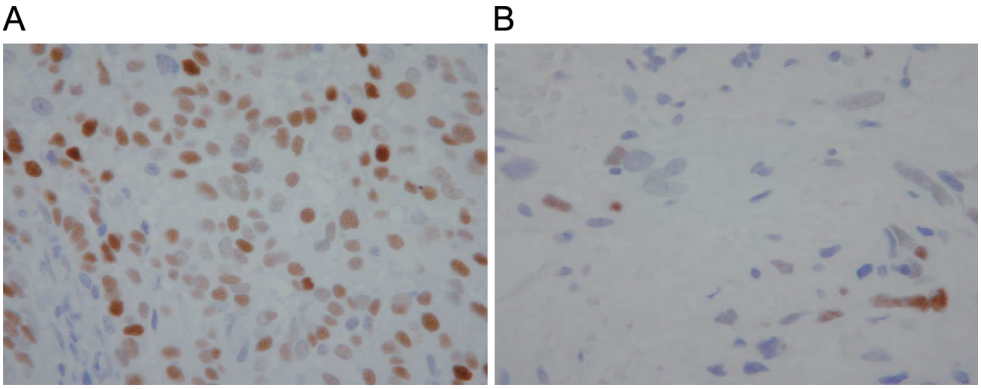

Figure 2. **p53 immunohistochemical staining of the primary tumor (A) and liver needle biopsy specimen (B).**

rare (3). Whether the solitary metastasis in the liver, as observed in the present case, is associated with anaplastic transformation of papillary thyroid carcinoma should be examined in the future by accumulating similar cases.

The metastatic lesions of malignant diseases tend to present histological findings similar to those of the primary tumor. However, thyroid carcinoma is one malignancy that may be an exception to this rule. The histology of the primary tumor and metastases is usually divergent (6), and in the present case, the histological divergence in the primary thyroid tumor and liver metastases were thought to be the result of anaplastic transformation from papillary thyroid carcinoma during treatment with total thyroidectomy and ablative radioactive iodine. Surgical resection of distant metastases in differentiated thyroid carcinoma has been reported to offer the best chance for prolonged survival (3, 7). Although anaplastic carcinoma is associated with a bleak prognosis, combined multimodality therapy may offer hope of long-term survival (8).

Among patients with recurrent papillary thyroid carcinoma, invasive cancers are not likely to concentrate radioactive iodine. Alternatively, patients with abnormalities confined to the lymph nodes are more likely to have radioactive iodine-avid tumors and to benefit from active iodine therapy (9). In addition, radioactive iodine has been suggested to increase the rate of anaplastic transformation in differentiated thyroid cancer (10). ^{131}I therapy may cause early anaplastic changes, such as the p53 gene mutation, in patients who do not accumulate sufficient ^{131}I and therefore are less responsive to this therapy (11). The relationship between the p53 gene mutation and tumor progression has been supported in studies on brain tumors (12). Thyroid carcinomas possess p 53 mutations at a relatively low frequency (10-17%). The patients with these mutations tend to be older, and have more aggressive, therapy-resistant disease (13, 14). Therefore, the p53 mutation is an excellent predictor of lymph node metastasis and capsular invasion of the tumor, and is a significant prognosticator of the survival outcome in patients with thyroid cancer (14).

It has been suggested that the presence of p53 mutations is not associated with tumor stage or histological type, but is instead involved in thyroid carcinogenesis, thereby playing an important role in the malignant transformation of thyroid cells, as well as thyroid tumor progression (15). Nishida et al (16) reported that both positive staining for the p53 protein and DNA ploidy are independent prognostic factors that may predict the overall survival of patients with differentiated thyroid carcinoma. Accumulation of the p53 protein has been demonstrated to be correlated with p53 mutations (17). The wild-type p53 protein has a short half-life and is virtually undetectable by immunohistochemical staining; however, mutations in the p53 gene often result in stabilization of the protein. Our patient's tumor stained for p53, suggesting that she had the mutated p53 gene at the time of her initial operation, before ^{131}I therapy. We speculate that some DNA damage in the tumor cells was induced by the first course of ^{131}I therapy; however, neither DNA repair nor cell apoptosis occurred because the p53 gene had already mutated. Further DNA damage was induced by the second course of ^{131}I therapy, leading to anaplastic transformation.

We report a rare case of multiple liver metastases from a papillary thyroid carcinoma with the p53 mutation, which we believe to be the result of anaplastic transformation during postoperative radioactive ^{131}I therapy. Lessons from our experience and that of others (11, 18, 19) regarding the management of differentiated thyroid carcinoma are as follows: the biopsy or surgical specimens should be immunostained with p53 antibody in order to detect a possible p53 mutation, and if the tumor specimen is positive for p53, which suggests the p53 mutation, ^{131}I therapy should be considered only for a patient who shows sufficient accumulation of ^{131}I tracer to avoid further p53 mutation and anaplastic transformation.

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