

Case Report

A Case of Thyroid Papillary Carcinoma: Remarkable Decrease in Multiple Lung Metastases within 40 Years after a Single Administration of Radioiodine without Thyroidectomy and with Later Anaplastic Transformation

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Keywords

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Abstract

Differentiated thyroid carcinoma is an uncommon malignancy of childhood and adolescence that is unique because it has an overall favorable prognosis despite its relatively high rate of nodal and distant metastases. Total thyroidectomy and positive ¹³¹I therapy are recommended for cases with pulmonary metastases. In contrast, anaplastic thyroid cancer is one of the

most aggressive malignancies that have an unfavorable and miserable prognosis. We report a case with an impressively long history. The patient had multiple pulmonary metastases that had been diagnosed by ^{131}I administration when he was 14 years old, about 45 years before he underwent thyroidectomy. He had been kept unaware of his disease by his family and received no treatment for most of his life. Pulmonary nodules were noted at several medical checkups and showed a remarkable decrease in size during the untreated 44-year period after the ^{131}I administration. At age 58, his thyroid cancer was first detected and total thyroidectomy was performed, with subsequent radioiodine therapy for pulmonary metastases. Unfortunately, anaplastic carcinoma developed and he died of disseminated tumors later.

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Introduction

Differentiated thyroid carcinoma in childhood and adolescence is an uncommon malignancy and unique as to its overall favorable prognosis despite its relatively high rate of nodal and distant metastases [1–3]. Total thyroidectomy and positive ^{131}I therapy are recommended for cases with pulmonary metastases. In contrast, anaplastic thyroid cancer is one of the most aggressive malignancies with a poor prognosis. It is thought that anaplastic cancer arises from transformation of differentiated thyroid cancer; however, the mechanism of dedifferentiation remains unclear [4, 5].

We experienced a case of differentiated thyroid carcinoma with pulmonary metastases that remarkably decreased in size over a 40-year period after early administration of ^{131}I for diagnosis without thyroidectomy. At age 58, the patient's cervical nodules were incidentally detected, and total thyroidectomy was performed along with subsequent administration of radioiodine therapy (RIT). Although very intense accumulations were observed in both lungs, some of the nodules developed in anaplastic transformation over the next several years. We report the long history of this case and discuss the relevant literature.

Case Report

History from the Patient's Adolescent Period

In 1960, a 12-year-old male was hospitalized in Shimane because a chest X-ray revealed multiple nodules in both lungs. Although he had no apparent symptoms, such as cough, high fever, or lethargy, he was assumed to have pulmonary miliary tuberculosis and received anti-tuberculosis therapy. Despite 2 years of therapy, the lung nodules continued growing, but he was doing well in general and developed no symptoms.

His family doctor doubted the clinical diagnosis of tuberculosis and consulted a specialist. The specialist recommended performing a ^{131}I scintiscan to rule out the presence of metastatic lung tumors from thyroid cancer. In the 1960s, ^{131}I scintiscans were not common and were only performed at one institution in Japan. The patient traveled to Tokyo to undergo the examination in 1962. After the examination, he returned to Shimane, and his medical treatment for tuberculosis was stopped because the ^{131}I scintiscan had revealed that his

pulmonary nodules were associated with thyroid cancer. Though his family doctor prescribed some medication, he quit taking the medicine, which caused him palpitation. In Japan patients were seldom informed that they had malignant tumors at that point of time; therefore, his father kept his son from being informed about his own disease. The patient grew up several decades without receiving any medication and led a typical life before his thyroid nodules were noted at a medical checkup. His thyroid carcinoma was resected at age 59 in 2006. Before that, multiple pulmonary nodules showed up many times in medical checkups including chest X-rays. However, further investigations were not performed because he knew that he had a history of multiple asymptomatic pulmonary nodules over a long time. Only one bronchoscopic examination that he underwent when he was 35 years old failed to confirm the diagnosis.

Since the first diagnosis had been made in the early 1960s, the medical records were no longer available. However, old letters from his doctor passed to the patient's father and an old chest X-ray retained by his father that were kept in his old house were found incidentally in his father's room in 2008 and revealed the details about the patient's past history.

History of the Patient's Present Illness

At age 58, in 2006, the patient's thyroid tumor and cervical lymphadenopathy were detected using ultrasonography at a health check screening. Total thyroidectomy and radical left neck dissection were performed, and the cancer was diagnosed as papillary carcinoma. X-ray and computed tomography (CT) of the chest revealed multiple fine nodules in both lungs (Fig. 1b). His serum thyroglobulin (Tg) level was 586 ng/mL even after the thyroidectomy; therefore, multiple pulmonary metastases from thyroid cancer were strongly suspected. However, it was necessary to clarify whether the miliary lung nodules were the metastatic disease from thyroid cancer or postinflammatory scars, because at that time he believed that he had a past history of miliary tuberculosis. A diagnostic ^{131}I whole body scan (^{131}I -WBS) was performed at Kyoto Prefectural University Hospital.

At the ^{131}I -WBS, he was asymptomatic, and no pulmonary nodule was audible on careful examination. After 2 weeks of L-thyroxine withdrawal and an iodine-free diet, ^{131}I scintigraphy was performed 2 days following the administration of capsules totaling 111 MBq of ^{131}I -NaI. Very intense accumulation was seen in both lungs, and small hot spots indicating metastatic lesions in the left supraclavicular region and in the thyroid bed remnant were found (Fig. 2). Subsequently, 3,700 MBq of ^{131}I was administered for treatment.

After the patient had received RIT at age 58, the fine nodular pulmonary lesions showed only slight decrease, and his serum Tg level had dropped to between 150 and 250 ng/mL. Since the Tg level remained still quite high, additional ^{131}I therapy was recommended, which the patient refused because he knew that he had carried the multiple pulmonary nodules for more than 45 years without suffering any symptoms, as he had discovered his father's secret letters that described the illness as having originated in the 1960s. He was convinced that the past detail-uncovered radioiodine administration in Tokyo had provided a dramatic decrease of his pulmonary nodules during several decades and expected a similar efficacy.

In 2008, his serum Tg was still high, and diagnostic ^{131}I -WBS and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT were performed. ^{131}I -WBS showed that the uptake in both of his lungs had markedly decreased and that the cervical lymph node lesions had disappeared. ^{18}F -FDG accumulation was not seen in the lungs except for

small hot spots in the relatively large nodules in his right lung base (Fig. 3), which had not increased in size for 2 years. The follow-up did not include any aggressive treatment other than thyroid-stimulating hormone suppression.

However, in 2011, the patient started developing shortness of breath, and X-ray radiography revealed right pleural effusion. CT revealed a pleural mass of about 5 cm in diameter in the right diaphragm. Aspiration examination of the effusion confirmed a diagnosis of anaplastic carcinoma. The right pleura was thickened and the nodules of the right lung base had increased, while the other fine nodules were unchanged compared with their sizes from his 2006 records. Systemic chemotherapy and drainage of the effusion with adhesion therapy were started. However, the pleural mass continued growing, and moreover bladder, multiple bone, and brain metastases developed. He eventually died 5 months after the diagnosis of anaplastic carcinoma. The time course of his disease is summarized in Table 1.

Discussion

Anaplastic thyroid carcinoma has been reported to arise from preexisting differentiated thyroid cancer [4, 5]. Although some reports have indicated that it may be related to mutation of the *p53* gene [4, 6], the exact mechanism of anaplastic transformation has not been clarified. There are also some reported cases of anaplastic carcinomas with DNA damage that might have been induced by RIT [5]. However, there are considerably more patients with differentiated carcinomas receiving RIT compared with those who come to have anaplastic carcinoma, so the causal relationship is not widely accepted currently.

In contrast to anaplastic carcinoma, it is universally agreed that differentiated thyroid carcinoma in children and adolescents has a very favorable prognosis. The long-term survival rates are >95%, despite the relatively high rate of nodal and distant metastases [1, 7]. Total thyroidectomy and RIT are also recommended for pediatric patients as well as for adult patients with pulmonary metastases [1, 2, 8].

In our case, disseminated pulmonary nodules had been detected in the 1960s when he was very young, and later they were diagnosed as metastatic tumor from differentiated thyroid cancer by ¹³¹I scintiscan. The patient grew up without having been informed about the exact diagnosis, undergoing thyroidectomy, or receiving medication. At age 58, a medical checkup led him to know his thyroid cancer and pulmonary metastases. Unfortunately, 5 years after thyroidectomy, RIT, and subsequent thyroid-stimulating hormone suppression with L-thyroxine had started for his thyroid cancer, some nodules came to be anaplastically transformed.

The clinical course of this patient has some interesting and meaningful aspects. After ¹³¹I administration in 1962, the dosage of which is unknown, multiple pulmonary metastases showed a marked decrease in size during a period of over 40 years without treatment. There are few reports of cases with multiple pulmonary metastases that were followed over long periods without resection of thyroid tumors. Okada et al. [8] reported the long-term follow-up of childhood and adolescent thyroid cancers, and in their 5 cases of pulmonary metastases, 2 patients who had not undergone total thyroidectomy died, while the other 3 cases who underwent total thyroidectomy were alive.

A total or at least subtotal thyroidectomy is thought to be indispensable before RIT for distant metastases, since normal thyroid tissue has a much higher affinity for iodine compared with other metastatic tissues. So, the improvement of one's metastatic nodules by RIT without undergoing thyroidectomy is not usually expected.

Some functioning metastatic lesions of thyroid cancer with thyroid function, which occasionally caused thyrotoxicosis, have been reported [9]. In our case, it is supposed that the thyroid hormone was prescribed after the ^{131}I scintiscan in 1962. However, the patient experienced some symptoms of hyperthyroidism and quit taking the medicine. At the histopathological confirmation at the total thyroidectomy in 2006, normal thyroid tissue surrounding the cancer tissue was observed. This may suggest that his metastatic pulmonary lesions had such considerably high iodine affinity equivalent to normal thyroid tissue that a sufficient amount of radioiodine might have accumulated in the lungs without him undergoing thyroidectomy, and the long-lasting irradiation effect had contributed to marked improvement of the lesions.

Another important aspect of this case was that after the RIT in 2006, the ^{131}I accumulation in both lungs decreased, despite the persistently high serum Tg level, and later anaplastic transformation occurred.

Dottorini et al. [7] reviewed 85 cases of differentiated thyroid carcinoma who were younger than 18 years of age at the time of diagnosis, and noted that a high percentage of pulmonary metastases disappeared by ^{131}I -WBS after RIT, while a completely undetectable serum Tg level was achieved in only a minority of patients. In some of their cases with persisting high serum Tg levels after RIT despite negative scintigraphic findings, the pulmonary metastases continued to decrease spontaneously even without further therapy. Some other reports have described patients with persistently positive Tg levels that declined or even disappeared over time without treatment [3].

There is no maximum dose limit for cumulative ^{131}I given to patients with persistent iodine-avid disease before intolerable toxicity develops or the patient refuses treatment [10]. The guidelines for RIT by the European Association of Nuclear Medicine Therapy Committee state that RIT may be halted in favor of "watchful waiting" for patients with iodine-avid tumors who do not achieve complete response to several radioiodine courses.

In our case, the second diagnostic scan showed that the ^{131}I accumulation had apparently decreased despite the persistently high Tg level. Detectability is influenced by the administered dose of ^{131}I [11], and higher therapeutic dose images frequently reveal more tumors than diagnostic low-dose images. Even if accumulation cannot be seen by the treatment dose, disappearance of small lung metastases is often observed [12]. Nobody knows whether another repeated high-dose RIT could have achieved a favorable response.

Unfortunately, our patient developed anaplastic cancer 5 years after RIT at age 58. While metastatic pleural tumors and pleural effusion were observed, most of the pulmonary fine nodules had not changed compared with those observed 5 years before. Only some relatively large nodules of the lung base with FDG avidity in 2008 had showed remarkably rapid growth.

The affinity of FDG-PET in thyroid cancer is thought to have an inverse relationship with the ability of the tumor to concentrate radioiodine [13]. This "flip-flop" phenomenon is recognized depending on the differentiation of the thyroid cancer. When it becomes dedifferentiated, thyroid cancer loses the ability to trap radioiodine [14], and compared with FDG-

negative lesions, FDG-avid metastatic lesions show significantly higher resistance to high-dose RIT [15]. Therefore, lesions with FDG accumulation often indicate relatively aggressive behavior, but this does not always mean anaplastic carcinoma. In our case, after the RIT in 2006, most of the pulmonary nodules had lost their affinity for iodine, but most did not concentrate FDG either. The findings that (1) the anaplastic carcinoma had developed from the right lung base and (2) only some nodules in which FDG had accumulated in 2006 had grown while other nodules remained unchanged are notable.

No one is sure whether the patients could have escaped from the anaplastic transformation if he had undergone total thyroidectomy and subsequent RIT in his childhood, whether the RIT had “woken a sleeping lion” or not, or whether we should have “let sleeping dogs lie” or not. However, this case proposes that the management of asymptomatic thyroid cancers in children and adolescents, who are usually expected to have good long-term prognoses even if they have disseminated disease, may be worth of careful consideration.

Statement of Ethics

On behalf of all the authors, the first author was given written informed consent to publish the disease history by the patient when he was alive.

Disclosure Statement

No potential conflict of interest relevant to this article is reported.

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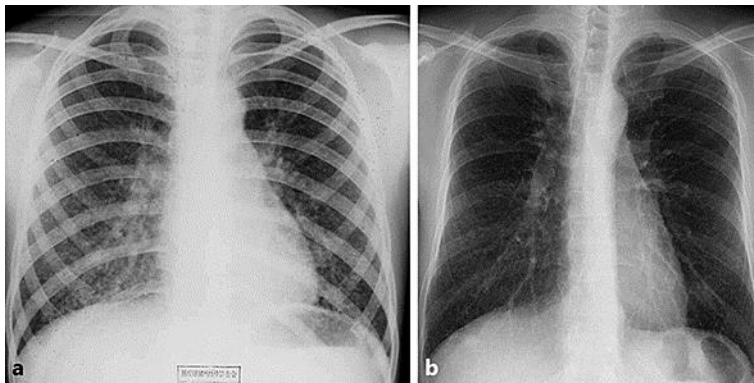


Fig. 1. Chest X-rays taken at the age of 12 years (**a**) and 58 years (**b**). **a** At 12 years, multiple pulmonary nodules were noted, which were diagnosed as miliary tuberculosis. **b** At 58 years, fine pulmonary nodules were observed; however, they were smaller than those observed in 1962.

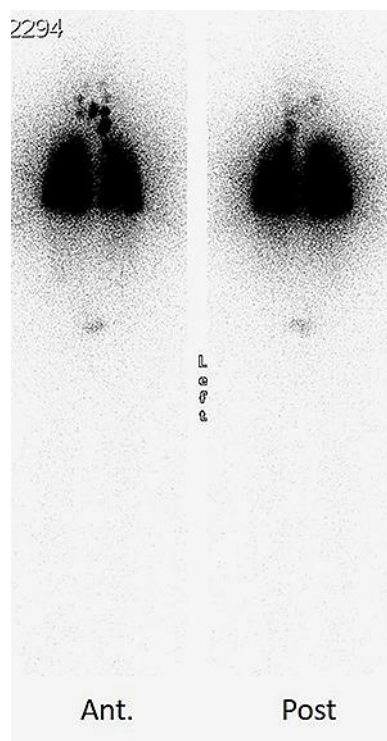


Fig. 2. ^{131}I scintigrams after administration of the diagnostic dose after total thyroidectomy at 59 years. Both lungs had intense accumulation of radioiodine, which suggested that there were multiple metastatic lesions of differentiated thyroid cancer. Thyroid bed and left supraclavicular lymph node lesion were also visualized.

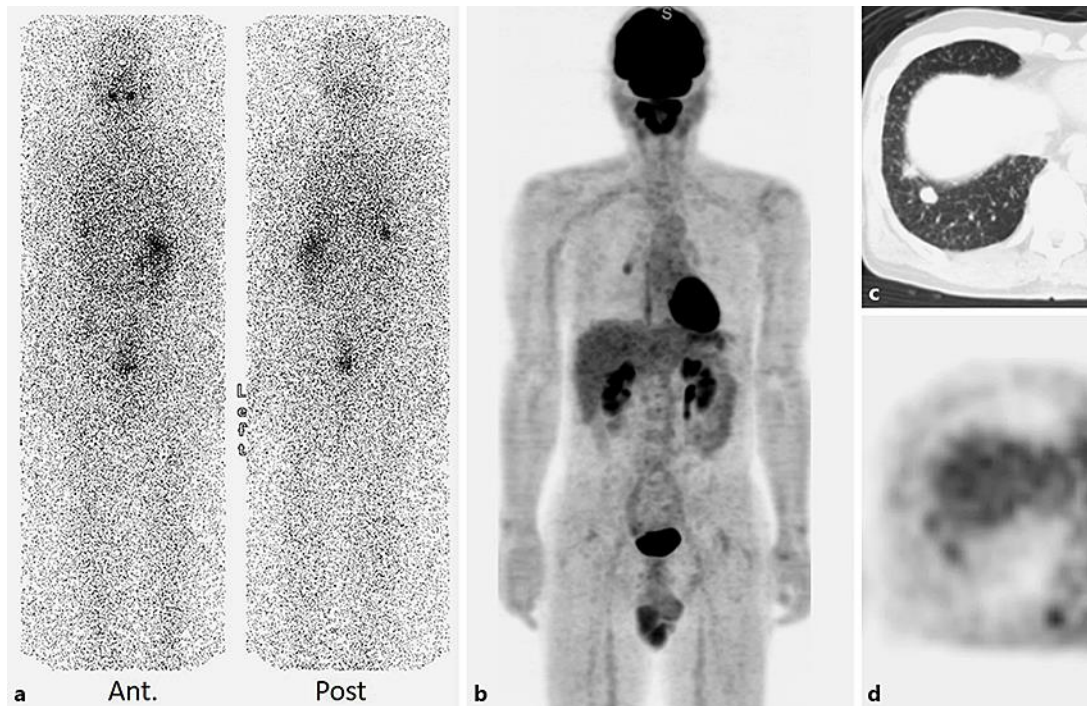


Fig. 3. ^{131}I whole body scan (^{131}I -WBS) and ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) performed in 2008. **a** ^{131}I -WBS. **b** Maximum intensity projection image of FDG-PET. **c** CT of the lung base. **d** FDG-PET of the lung base. The affinity to FDG appeared to be low in most of the lung nodules. Only mild accumulations were observed in the relatively large nodules in the right lung base.

Table 1. Time course of the patient's disease history

Year	Age	Examination findings and diagnosis	Treatment
1960	12	multiple pulmonary nodules ⇒Dx: miliary tuberculosis	anti-tuberculosis therapy
1962	14	radioiodine administration ⇒Dx: pulmonary mets from thyroid cancer (the patient was not told the diagnosis)	no medication ¹
1983	35	bronchoscopic examination ⇒it failed to confirm the diagnosis of the multiple lung nodules	
2006	58	medical checkup found the cervical tumors ⇒Dx: papillary thyroid carcinoma ¹³¹ I scintigraphy ⇒Dx: pulmonary and lymph node mets	total thyroidectomy radical neck dissection ¹³¹ I therapy (3,700 MBq)
2008	60	¹³¹ I diagnostic scan ⇒only little accumulation in the lungs FDG-PET ⇒mild accumulation in only the lung base high serum thyroglobulin value	thyroid-stimulating hormone suppression therapy
2011 (May) (July) (August) (October)	63	pleural effusion and large pleural mass ⇒Dx: anaplastic carcinoma bladder tumor ⇒Dx: metastatic anaplastic carcinoma multiple brain tumors bone tumor (Th1) death	chemotherapy (CDDP + DOC) transurethral resection; chemotherapy (DOC) radiation therapy radiation therapy

¹ After the radioiodine administration, the patient was maybe given thyroid hormone for a while. FDG, fluorodeoxyglucose; mets, metastases; PET, positron emission tomography.