CASE REPORT
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Importance of Regular Follow-Up Examination during Active Surveillance: a Case of Anaplastic Transformation of Papillary Thyroid Microcarcinoma

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Because papillary thyroid carcinoma (PTC) is indolent and has an excellent prognosis, active surveillance, without immediate surgery, can be considered for small PTC. However, rarely, PTC can transform to anaplastic thyroid carcinoma (ATC), over a period of 5-20 years. We report 73-year-old man with rapid anaplastic transformation of a PTC. He was diagnosed with colorectal cancer, and a 1-cm-sized thyroid nodule was found incidentally and confirmed as PTC on fine-needle aspiration. He underwent transanal excision and chemotherapy for colorectal cancer. However, he was not concerned about the PTC, and no follow-up examination was performed. After 37 months, he suddenly noticed an enlarging neck mass, which was diagnosed as an ATC. Despite total thyroidectomy, locally advanced recurrence with lung metastasis developed, and he eventually died. Although PTC is indolent and progresses slowly in elderly people, it can transform to ATC. Therefore, during active surveillance in the elderly, follow-up examinations should be performed regularly.

Key Words: Anaplastic thyroid carcinoma, Papillary thyroid carcinoma, Thyroid neoplasm

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer and accounts for 95% of all thyroid cancers in Korea. PTC has a favorable prognosis, with a 10-year survival rate of more than 90%.[1] Papillary thyroid microcarcinoma (PTMC), defined as a tumor of 1 cm or less in size, has a better outcome. Therefore, some investigators insist on active surveillance without immediate surgery for PTMC. Observational studies for PTMC showed no distant metastasis or cancer-specific death,[2-4] supporting active surveillance management. However, tumor enlargement and clinically apparent lymph node (LN) metastasis developed in 8% and 3.8% of patients without surgery, respectively, after 10 years of observation.[4] Moreover, LN metastasis in PTMC has been reported to range from 24% to 64% on the surgical pathology, and more than half of them are clinically unapparent preoperatively.[5-8] Therefore, active surveillance implies a lack of action, other than regular follow-up examination, in order to detect any significant progression.

On the other hand, anaplastic thyroid carcinoma (ATC) accounts for only 1-2% of all thyroid cancers.[9] ATC is very aggressive and shows a poor prognosis, with a 5-year survival rate of 1-7%,[10,11] in contrast to differentiated thyroid cancer (DTC). Anaplastic

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transformation of DTC is a well-known process and seems to account for a large proportion of ATC cases. The coexistence of ATC and DTC supports the hypothesis that ATC arises from pre-existing DTCs.[10] During surgery for ATC, 14-90% of ATC cases have been found to coexist with DTC.[12] Conversely, ATC has been detected incidentally on pathological examination after surgery for DTC.[13-15] Several mutations such as *BRAF* and *RAS*, that occur in DTC, have also been reported in ATC.[16]

We here report a rare case of rapid anaplastic transformation of PTMC 3 years after the initial diagnosis. This case suggests that regular follow-up examination is important, even in elderly people with PTMC, during active surveillance.

Case Report

A 73-year-old man presented with a neck mass. He had been diagnosed with colorectal cancer 37 months earlier at another hospital. On preoperative positron emission tomography-computed tomography (PET-CT), a hypermetabolic lesion was incidentally found in the thyroid gland (Fig. 1A). Neck ultrasonography (US) revealed a 1.0-cm rim-calcified nodule in the right thyroid gland and a 0.8-cm calcified nodule in the left thyroid gland (Fig. 1B). The results of the US-guided core-needle biopsy revealed PTC in the right thyroid gland (Fig. 1C). Because colorectal cancer has priority over thyroid cancer and the patient was elderly, it was decided to observe the PTC without performing surgery at the time. After neoadjuvant concurrent chemo-radiotherapy with capecitabine, the patient underwent transanal excision, followed by adjuvant chemotherapy with a combination of 5-fluorouracil and leucovorin. No further evidence of colorectal cancer was evident thereafter.

Unfortunately, the patient was not concerned about his thyroid cancer at the time and underwent no follow-up examinations. After 37 months, he eventually visited our hospital because of an enlarging neck mass. During neck US, it was found that the right thyroid nodule had increased from 1.0 cm to 4.8 cm (Fig. 2A). An ATC was suspected based on the results of the fine-needle aspiration cytology. A hypermetabolic mass in the right thyroid gland was observed on PET-CT (Fig. 2B). Total thyroidectomy with central LN dissection was performed. The surgical specimen

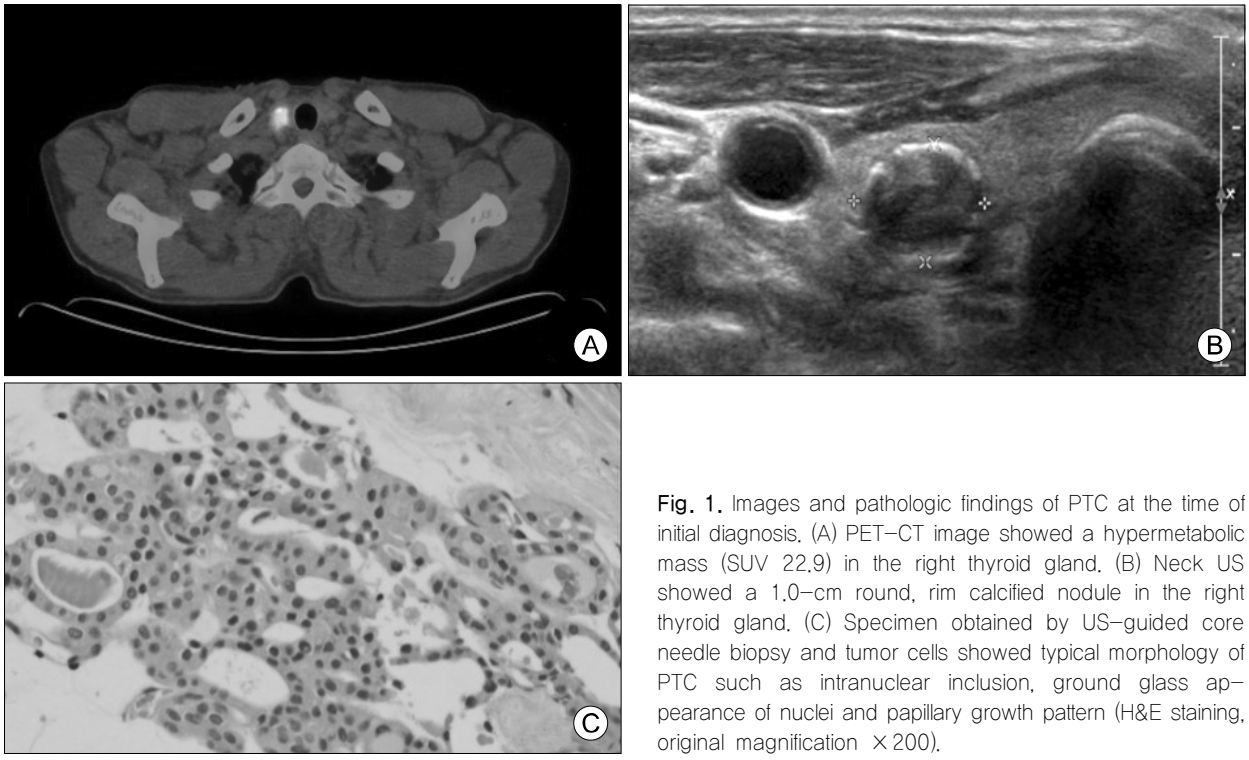

Fig. 1. Images and pathologic findings of PTC at the time of initial diagnosis. (A) PET-CT image showed a hypermetabolic mass (SUV 22.9) in the right thyroid gland. (B) Neck US showed a 1.0-cm round, rim calcified nodule in the right thyroid gland. (C) Specimen obtained by US-guided core needle biopsy and tumor cells showed typical morphology of PTC such as intranuclear inclusion, ground glass appearance of nuclei and papillary growth pattern (H&E staining, original magnification ×200).

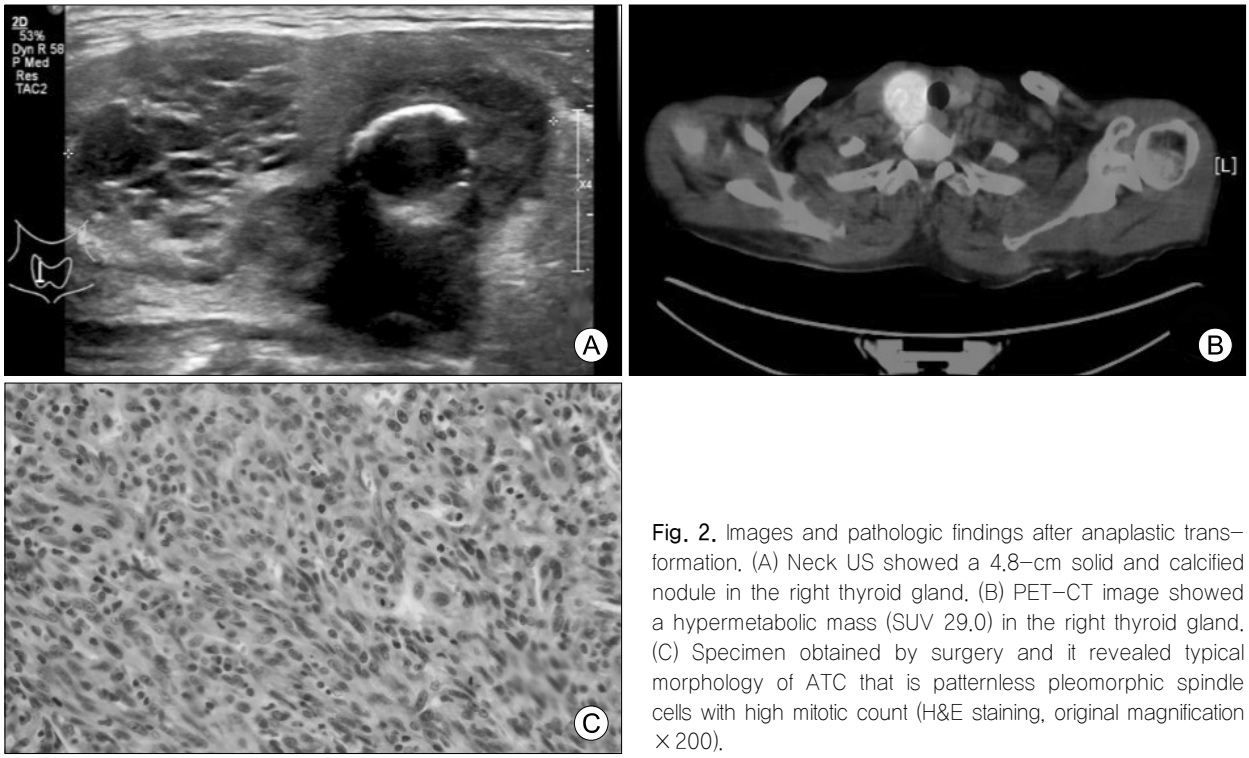

Fig. 2. Images and pathologic findings after anaplastic transformation. (A) Neck US showed a 4.8-cm solid and calcified nodule in the right thyroid gland. (B) PET-CT image showed a hypermetabolic mass (SUV 29.0) in the right thyroid gland. (C) Specimen obtained by surgery and it revealed typical morphology of ATC that is patternless pleomorphic spindle cells with high mitotic count (H&E staining, original magnification ×200).

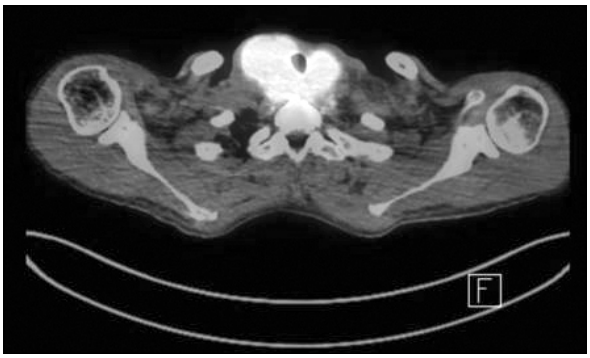

Fig. 3. PET-CT scan 4 months after total thyroidectomy. PET-CT image showed a markedly increased hypermetabolic mass (SUV 43.9) in the neck.

showed the presence of a 5.1×3.0 cm ATC with extrathyroidal extension in the right thyroid gland (Fig. 2C) and a 1.1×1.0 cm PTC in the left thyroid gland; no LN metastasis was observed. After surgery, there was no voice defect. Radiation therapy was recommended, but the patient refused.

Four months after surgery, his voice changed and right vocal cord palsy was observed on laryngoscopy. Locally advanced recurrence and lung metastasis were found on PET-CT (Fig. 3). To avoid airway obstruction, the patient underwent tracheostomy, followed by radiation therapy (30 Gy). Thereafter, chemotherapy (dabrafenib and trametinib) was administrated, but it had to be stopped because of hyponatremia. Despite these treatments, the patient died because of airway obstruction 7 months after the diagnosis of ATC.

Discussion

The incidence of PTC has increased, probably owing to the increased early detection of PTMC on neck US and US-guided fine-needle aspiration.[17,18] Because PTMC is indolent and has an excellent prognosis, active surveillance without immediate surgery can be one of management approaches. However, patients should be carefully selected for active surveillance and followed-up regularly, because some PTMCs can increase in size and metastasize to LNs.[2-4] In previous observational studies, subjects with unfavorable features were excluded, such as those in whom the tumor was adjacent to the trachea or recurrent laryngeal nerve and those with the presence of clinically apparent LN metastasis.[3,4] Therefore, the results from these observational studies cannot be applied to all patients with PTMC. In addition, 7-16% of subjects

underwent surgery after observation in such studies, due to tumor enlargement, LN metastasis, or a change of mind in the patient.[2,4] This may be the reason for the absence of distant metastasis or cancer-specific death in the observational studies, although 2.8% of patients died of thyroid cancer and small PTCs of 2.0 cm or less accounted for 12% of cancer-specific deaths.[1] Therefore, regular examination and surgery, if the PTMC progresses significantly, is important during active surveillance.

Anaplastic transformation usually arises in long-standing DTCs, and the time interval between the diagnosis of DTC and anaplastic transformation has been reported to range from 5 to 20 years.[11,19] However, in this case, anaplastic transformation was noticed at only 37 months after the initial diagnosis of PTMC. This is markedly faster than that reported in previous studies. It is possible that anaplastic foci existed at the time of the initial PTC diagnosis. The proportion of DTC with anaplastic foci, as compared to that of conventional ATC, has been increasing.[13,15] Anaplastic foci can also be detected in PTMC. The early detection and surgery of DTC owing to the frequent use of neck US may have increased DTC with anaplastic foci.

PTMC in the elderly, which was found to be less progressive in the observational study, is considered the best candidate for observation.[4] However, ATC manifests in the 6th to 7th decade of life,[20,21] which is the age during which anaplastic transformation usually occurs. Our patient was also 73 years old. This case highlights that it can be dangerous to neglect DTC in the elderly. After anaplastic transformation, thyroid cancer follows the same disease pattern as classical ATC, as it also did in this case.[10,11,21]

The mean survival time for ATC is approximately 5-6 months; this patient died 7 months after initial diagnosis. A young age and small tumor size have been associated with lower mortality for ATC.[22] DTC with anaplastic foci has a better outcome than does conventional ATC.[13,14,23] ATC does not respond well to various treatment modalities. For resectable disease, surgery (total thyroidectomy and therapeutic LN dissection) and adjuvant radiation therapy should be considered.[24] Survival is significantly higher in patients with resectable tumors than in those with unresectable tumors. In patients with unresectable ATC, radiation therapy can be considered, and it can improve survival.

In conclusion, although PTC is indolent and generally has a good prognosis, it can progress and transform to ATC. Anaplastic transformation is rare, but fatal. Therefore, when active surveillance is opted for in elderly people, follow-up examinations should be performed regularly.

Acknowledgments

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