Occult Papillary Thyroid Carcinoma in Hashimoto’s Thyroiditis Presenting as a Metastatic Bone Tumor

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Abstract. Some occult thyroid carcinomas are hypothesized to regress and be eventually obliterated. We report here a patient whose condition supports this hypothesis. A 51-year-old male with primary hypothyroidism due to Hashimoto’s thyroiditis suffered from a rib bone tumor. He had a diffuse goiter with no nodular lesion. Serum FT4 and TSH concentrations were 0.8 ng/dl and 36.4 tU/ml on taking 100 µg/day of T4. Anti-Tg- and -TPO-Ab were strongly positive (99 and 1380 U/ml). The iodine 123 scintigraphy demonstrated clear accumulation in the rib tumor, whereas the thyroid was scarcely visible. Biopsy of the rib tumor showed papillary proliferation of large atypical cells, which were immunohistochemically positive for thyroglobulin. Metastatic bone tumor of papillary thyroid carcinoma was therefore strongly suspected. He underwent a total thyroidectomy and the thyroid was stepwise sectioned completely at 3 mm intervals. The thyroid condition was diagnosed as Hashimoto’s thyroiditis demonstrating diffuse and dense fibrosis, lymphocyte infiltration with lymphoid follicles and flattened atrophied follicles, but no carcinomatous foci were found. He was treated with I-131 and scintigraphy after the ingestion showed distinct accumulation in the rib tumors similar to that before thyroidectomy. No other abnormal uptake was observed. It is suggested that the primary occult thyroid papillary carcinoma regressed and was obliterated possibly by some immunologic or other host-resistance factors after it metastasized to the distant bone.

Key words: Thyroid cancer, Hashimoto’s disease, Metastasis, Scintigraphy, Regression


OCCULT thyroid carcinomas with a diameter of 1 to 1.5 cm or less, usually papillary and often sclerotic, have been found in 5.6-6% of thyroids of adults coming to autopsy in the United States and Canada, and the prevalence is significantly higher in Japan (28.4%) and in Hawaiian Japanese (24.2%) [1, 2]. As occult thyroid carcinomas can metastasize to cervical lymph nodes and to other distant sites [3–5], it is reported that they do not differ from other papillary cancers with respect to morphological, clinical and prognostic factors and that they differ only in size [6]. On the other hand, it is hypothesized that such lesions may spontaneously regress [7] or that some immunologic or other host-resistance factor prevents further growth of these occult cancers and may cause eventual obliteration in some instances [2, 8, 9], but this hypothesis has been proven in few patients. We report here a patient with primary hypothyroidism due to Hashimoto’s thyroiditis whose condition supports this hypothesis.
Case Report

The 51-year-old male had been healthy until 1994, when he noticed a cervical mass. He was diagnosed as having primary hypothyroidism due to Hashimoto’s thyroiditis and treated with thyroxine (T4) by a local physician, but his goiter became bigger and he was referred to our hospital in July, 1996. Family and past histories were non-contributory. He was 165 cm tall and weighed 45 kg. No anemia or jaundice was found. He had a big diffuse goiter approximately 9.6 cm in diameter with no nodular lesion. No lymph node was palpable.

Routine laboratory findings were normal, including complete blood count, serum electrolytes, urea nitrogen, creatinine, aspartate aminotransferase and alanine aminotransferase concentrations. C-reactive protein and anti-nuclear antibodies were positive (3.6 mg/dl and × 640, respectively). The carcinoembryonic antigen concentration was normal. The serum free T4 (FT4) concentration was 0.80 ng/dl (normal: 0.99–1.71 ng/dl), triiodothyronine (T3), 91 ng/dl (84–174 ng/dl) and thyrotropin (TSH), 36.4 µU/ml (0.42–5.80 µU/ml) when he was taking T4 of 100 µg/day, showing that he was still in a mild hypothyroid state. Anti-thyroglobulin and anti-thyroperoxidase antibodies were strongly positive (99 and 1380 U/ml; normal, less than 0.3), but anti-TSH receptor antibodies were negative (−0.3%; normal, ± 15%).

Magnetic resonance imaging (MRI) of the thyroid revealed a diffusely enlarged thyroid with no localized mass. 67Garium citrate scintigram showed a high uptake region in the lower part of the left thyroid lobe, and the distribution in the remaining thyroid was uneven. The thyroid echogram revealed an enlarged thyroid with some high echo spots, low echo lesions and an extremely low echoic region in the right lower lobe. These findings were compatible with Hashimoto’s thyroiditis. But since malignant lymphoma could not be ruled out because of the garium scintigram and echogram findings, thyroid open biopsy was performed. The thyroid biopsy specimen revealed diffuse dense fibrosis with moderate folliculoid lymphocyte infiltration. A small number of atrophied follicles were seen, but no malignant cells were observed.

Thus the diagnosis of Hashimoto’s thyroiditis was confirmed and the replacement dose of T4 was increased to 150 µg/day. A few months later, however, he began to complain of a tumor (approximate diameter: 4 cm) at the right 9th rib.

Fig. 1. Left: I-123 scintigram before total thyroidectomy, demonstrating clear accumulation in the rib tumor (arrow) with scarcely visible thyroid image. Right: I-131 scintigram after total thyroidectomy, showing hot spots (arrows) in the rib tumors which increased in number to two.
Iodine 123 scintigraphy clearly demonstrated an accumulation in the rib tumor, but the thyroid was scarcely visible (Fig. 1, Left).

Biopsy of the rib tumor showed massive papillotubular proliferation of large atypical cells with columnar glassy or vacuolated cytoplasms and relatively small and basal-situated oval nuclei with hyperchromasias and a few mitoses (Fig. 2a). Histochemically, tumor cells were glycogen rich and, in some places, homogeneously PAS-positive materials, like those of thyroid colloid, were demonstrated intra- and intercellularly (Fig. 2b). Immunohistochemically, using streptavidin biotin peroxidase method (Histofine, Nichirei, Tokyo), tumor cells were positive for epithelial membrane antigen, AE-1 (low molecular cytokeratin) and thyroglobulin (anti-thyroglobulin antibodies; from Dako Japan, Kyoto) (Fig. 2c), and negative for vimentin, so that metastatic bone tumor from the papillary thyroid carcinoma was highly suspected.

He underwent a total thyroidectomy. The thyroid weighed approximately 90 g and was diffusely enlarged, but there were no visible tumors. No enlarged adjacent lymphnode was found. The thyroid was stepwise sectioned completely at 3 mm intervals, but close histological examination showed

Fig. 2. Biopsy specimen of the rib bone tumor. a: Papillotubular proliferation of large atypical cells with hyperchromatic nuclei (original magnification, ×250). b: Homogeneously PAS-positive materials, like those of thyroid colloid in tumor cells (original magnification, ×250). c: Tumor cells were immunohistochemically positive for thyroglobulin (original magnification, ×380).

Fig. 3. The totally resected thyroid specimen, showing diffuse dense fibrosis with moderate lymphocytic infiltration and marked atrophic follicles. No cancerous foci were detected (original magnification, ×125).
similar changes (Fig. 3) as in the biopsy specimen: diffuse dense collagenous fibrosis, moderate lymphocytic infiltration with lymph follicles accompanied by germinal centers, and scattered atrophic follicles with foci of squamous cell metaplasia. No cancerous foci were detected in the thyroid and the adjacent tissues.

He was treated with I-131 of 120 mCi (4440 MBq). The scintigram after the ingestion (Fig. 1, Right) showed distinct accumulation in the rib tumors, which had increased in number to two, similar to that before the thyroidectomy (Fig. 1, Left). No abnormal uptake was observed other than in the salivary glands and gastrointestinal tract which normally trap iodine. No abnormal mass suggesting the primary lesion of the carcinoma was found by repeated chest roentgenography, computed tomography of the chest and abdomen, intravenous pyelography, abdominal echography, gastric endoscopy, barium examination for the upper and lower gastrointestinal tract and repeated cytological examination of the sputum and the urine.

Discussion

The patient’s rib tumor was diagnosed as a metastatic bone tumor from the papillary thyroid carcinoma based on the facts that: (1) the tumor was epithelial in origin since tumor cells had an epithelial arrangement and papillotubular pattern, and they were positive for epithelial membrane antigen and AE-1, but negative for vimentin by immunohistochemistry, (2) the tumor cells produced PAS-positive materials, compatible with colloid and consistent with thyroglobulin, (3) they produced thyroglobulin detected by immunohistochemistry and (4) it accumulated iodine demonstrated both by I-123 scintigraphy preoperatively and I-131 postoperatively.

The false positive I-131 image for thyroid carcinoma [10, 11] includes lung cancer, gastric adenocarcinoma, meningioma, thymus and so on as well as normal and pathologic and inflammatory body secretion from saliva, the gastrointestinal tract, skin and breast, etc. These possible primary sites were denied in the present patient by scrutinizing the examination described in the text.

In the present case, it is likely that the primary site of the occult thyroid papillary carcinoma regressed and was obliterated after it had metastasized to the distant bone, although the possibility cannot be excluded that the primary thyroid carcinoma was, or became, so small that it could not be detected in spite of the complete examination of the sections. Fibrosis is common in and around papillary carcinomas, and occasionally, when fibrosis is very extensive, almost no neoplastic cells can be found [12]. The grounds of the hypothesis that occult thyroid carcinomas can be obliterated are: (1) the prevalence of occult carcinomas in men and women is about equal in the necropsy series in contrast to the higher prevalence in women (2.9:1.0) in the surgical material, (2) the number of occult carcinomas do not appear to increase in frequency with age and the occult carcinomas are all small regardless of the patient’s age, and (3) collections of psammoma bodies also exist in tiny scarred areas in some glands [2, 8, 9]. The probability of progressing to clinical cancers from occult cancers is 1/20,000 in males and 1/6,000 in females [13].

The mechanism for the possible regression of the cancer cell in the present patient is unclear, but it is of interest that he had Hashimoto’s thyroiditis with diffuse and dense fibrosis and lymphocyte infiltration. The immune system plays a major role in the clinical evolution of papillary thyroid cancer [14–16]. The diffuse sclerosing variant of papillary thyroid carcinoma is characterized by diffuse involvement of the thyroid without a palpable nodule, accompanied by severe lymphocytic thyroiditis and interstitial fibrosis [12, 17]. Hashimoto’s thyroiditis was suspected before the definite diagnosis in nine of 14 patients with this variant [17]. In addition, lymphocytic infiltration surrounding the papillary thyroid cancer is reported to be a favorable prognostic sign [15]. Furthermore, the presence of neoplastic cell phagocytosis by macrophages in papillary thyroid cancer is demonstrated and it is associated with a less advanced tumor stage and a favorable outcome [16]. Therefore, it is possible that, in the present patient, diffusely infiltrated lymphocytes and macrophages associated with Hashimoto’s thyroiditis might have played an important role in the regression of the papillary thyroid cancer. It is also unclear why the metastatic bone tumor progressed rapidly without no other metastatic foci,
including the lymphnodes adjacent to the thyroid, whereas the primary lesion within the thyroid regressed or remained minimal, but the circumstances for the tumor proliferation, including blood or nutritional supply and fibrosis or lymphocyte infiltration as well as numerous other factors, might have differed in these two sites. The metastatic tumor did not seem to be TSH-dependent for its growth, because it became manifest after the dose of T4 was increased and serum TSH normalized.

Since ectopic thyroid tissue can be located from the foramen cecum to the anterior mediastinum along with the embryological migration of the thyroid [18], it is not reasonable that the ectopic thyroid was located at the rib bone and that the carcinoma arose there. But papillary carcinoma can arise in ectopic thyroid tissue which has dissociated from the thyroid and is located from the foramen cecum to the anterior mediastinum, in the presence of the normal main thyroid [19], so that an alternative possibility is that the carcinoma developed in the ectopic thyroid and then metastasized to the bone. Nevertheless, it is not likely in the present case because no primary site was visible in the radioiodine scintigram obtained in both the pre- and postoperative states where the metastatic bone tumor clearly accumulated the radioiodine and because no mass or cancerous lesion was detected on thorough examination.

Paksoy et al. [20] reported a case similar to the present one: the patient had a large intratracheal tumor which was histologically a papillary carcinoma with immunohistochemically positive thyroglobulin. No primary tumor was found in the thyroid gland. A review of the literature indicates that the present case is the first one that presented with bone metastasis from an occult papillary thyroid carcinoma with Hashimoto’s thyroiditis without the primary thyroid lesion. It is suggested that some occult thyroid carcinomas can regress and be obliterated by some immunologic or other host-resistance factors after they metastasize to a distant site.

References