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ORIGINAL

Hepatocellular carcinoma eats medullary thyroid carcinoma, a case of tumor-in-tumor metastasis

Tae-Yon Sung[1)], Sang-Ryung Lee[2)], Jae Hoon Lee[3)], Yu-mi Lee[1)], A-Lan Lee[1)], Dae-Wook Hwang[3)], Jong Ho Yoon[1)], Gyungyub Gong[2)], Suck Joon Hong[1)] and Kwang-Min Park[3)]

[1)] *Division of Endocrine Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[2)] *Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[3)] *Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

Abstract. Carcinoma metastasis to the thyroid is uncommon, but may be increasing. We describe here a patient with a metastasis of hepatocellular carcinoma (HCC) presenting within a medullary thyroid carcinoma (MTC). The thyroid tumor was detected synchronously with the hepatic lesion by FDG-PET imaging, and HCC metastasis within MTC was confirmed by histological analysis of the thyroid gland.

Key words: Tumor-in-tumor, Hepatectomy, Thyroidectomy, Fine-needle aspiration biopsy, Immunohistochemical staining

METASTASIS to the thyroid gland is uncommon, with previous autopsy series showing incidence rates ranging from 0.5% to 10.1% [1-7]. Clinical reports have suggested, however, that the incidence of these metastases is increasing. The most common primary carcinoma sites in clinical reports are the kidneys, breasts, and lungs [8-14], although other primary carcinomas can also metastasize to the thyroid gland [15-27].

Hepatocellular carcinoma (HCC) rarely metastasizes to the thyroid [6, 23, 25-27]. Here, we describe a patient with an HCC metastasis to within a medullary thyroid carcinoma (MTC), that is, a tumor-in-tumor metastasis. To our knowledge, this is the first such clinically diagnosed case.

Due to the relatively short survival times of patients with distant metastases, solitary thyroid tumors in patients with advanced carcinoma are not routinely evaluated. However, imaging modalities, including fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and ultrasonography (US) guided fine-needle aspiration biopsy (FNAB) of newly detected lesions may help in making a definite diagnosis [13, 14, 17-22, 24, 28] and suggest further treatment.

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Correspondence to: Kwang-Min Park, M.D., Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwan-gil, Songpa-Gu, 138-736, Seoul, Korea. E-mail: kmpark@amc.seoul.kr

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Case Report

A 62-year-old male with a history of hepatitis B virus infection presented with dyspepsia, vomiting and right upper quadrant abdominal pain. Abdominopelvic CT and MRI revealed multiple HCC lesions with portal vein invasion in the right lobe of the liver (Fig. 1). FDG-PET also showed a synchronous tumor in the right thyroid gland (Fig. 2), but no other distant metastases. Preoperatively, this patient had an alpha fetoprotein (AFP) concentration of 1,940.0 ng/mL and a PIVKA II concentration of 2,880.0 mAU/mL. US guided FNAB of the thyroid suggested a 1.9 cm indeterminate tumor (Fig. 3A) consistent with a poorly differentiated carcinoma, including anaplastic carcinoma and metastasis (Fig. 3B), but not expressing thyroglobulin on immunohistochemical (IHC) staining (Fig. 3C). Thyroid function tests showed no abnormalities. Serum calcitonin concentration one day before surgery was 265.0 pg/mL.

After consultation with medical oncologists and radiation oncologists, we decided that systemic disease would have a better prognosis after surgical treatment of the liver. Thyroid gland surgery was also rec-

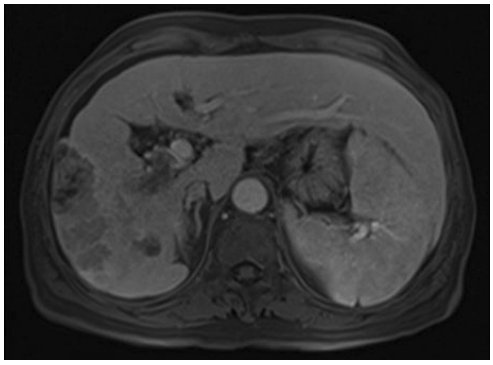

Fig. 1 Preoperative MRI image of the abdomen showing a large irregular conglomerated mass with partial necrotic cystic changes in the inferior segment of the right lobe of the liver. A right posterior portal vein thrombus was detected through the first order branch.

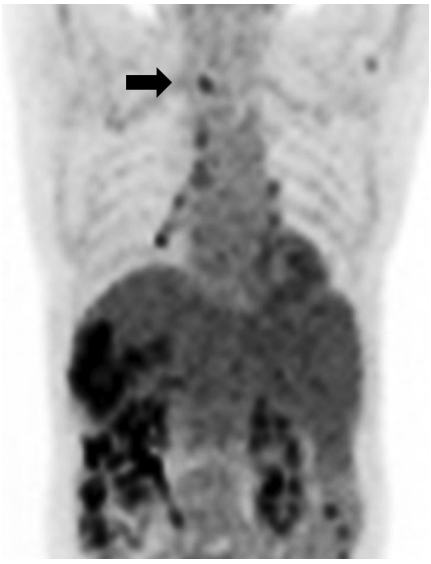

Fig. 2 Preoperative FDG-PET image revealing a hypermetabolic nodule in the right thyroid gland (black arrow) and calcified reactive lymph nodes around the bilateral paratracheal and hilar areas with a hypermetabolic right hepatic lesion.

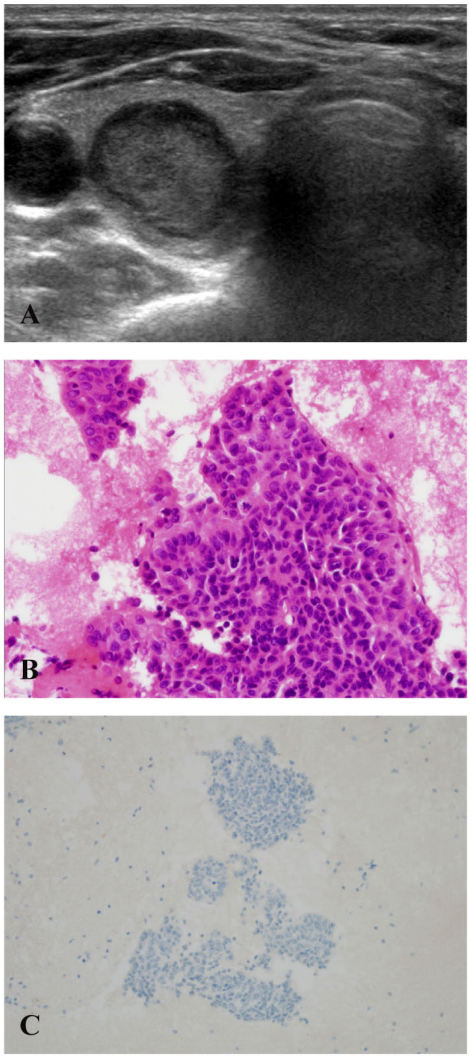

Fig. 3 A: Preoperative ultrasound of the neck showing homogeneous parenchymal echo texture with an indeterminate looking solid 1.9 cm nodule at the mid pole of right thyroid gland. B: Histologic examination of the cells in a cell block preparation showing a poorly differentiated carcinoma (H&E stain, x400). C: The tumor cells were immunonegative for thyroglobulin (x200).

ommended to obtain a definitive diagnosis and to rule out the possibility of a poorly differentiated thyroid carcinoma. The patient was otherwise quite healthy and wanted to undergo surgery. He underwent a right hemihepatectomy and total thyroidectomy with ipsilateral central node dissection.

The hepatic lesion was an HCC, 11.0x8.0x6.0 cm in size, with a right posterior portal vein tumor thrombus. Interestingly, the thyroid tumor in the right mid portion presented as a metastatic HCC within an MTC (Fig. 4A). This lesion was confined to the thyroid parenchyma without nodal metastasis. Histologically, the tumor composed of two different components (Fig. 4B). Outer portion of the tumor showed organoid pattern of polygonal cells having abundant granular cytoplasm and round nuclei with “salt-and-pepper” chromatin pattern (Fig. 4C). These tumor cells showed immunopositivity for synaptophysin (Fig. 4D) and calcitonin (Fig. 4E), suggesting MTC. Inner portion of the thyroid tumor consisted of anastomosing trabeculae

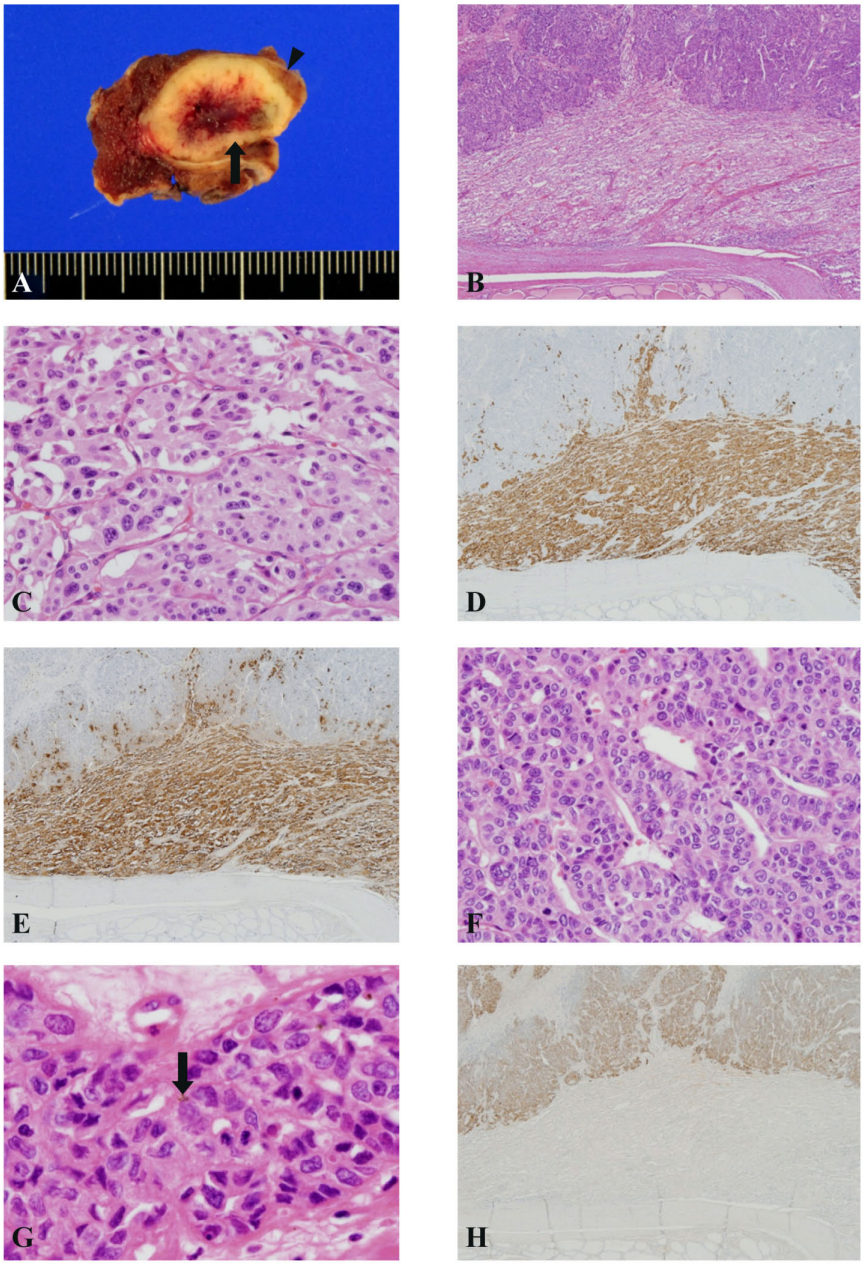

Fig. 4 A: Cut surface of the right thyroid specimen showing a metastasis from hepatocellular carcinoma (HCC) measuring 1.8x1.1 cm (black arrow), within a medullary thyroid carcinoma (MTC) of 2.0x1.7 cm (arrow head), confined to the thyroid parenchyma. B: The tumor composed of two different areas (H&E stain, x40). C: Outer portion of the thyroid tumor cells showing abundant granular cytoplasm and "salt-and pepper" pattern of nuclear chromatin. (H&E stain, x400) D&E: Ancillary studies with immunohistochemical staining revealing immunopositivity for synaptophysin (D) and calcitonin (E) (x40). F: Inner portion of the thyroid tumor showing anastomosing trabeculae of epithelial cells with eosinophilic cytoplasm and mild nuclear atypia (H&E stain, x400). G: Tumor cells containing bile pigments (black arrow) (H&E stain, x1000). H: Inner portion of the thyroid tumor showing immunopositivity for alphafetoprotein (x40).

or solid nests of epithelial cells having eosinophilic cytoplasm (Fig. 4F) and intracytoplasmic bile pigments (Fig. 4G), suggesting metastatic HCC. Lastly, in inner portion of the thyroid tumor (Fig. 4H) and HCC of the liver demonstrated immunoreactivity for AFP.

One month after the surgery, the patient had a serum AFP concentration of 168.3 ng/mL, a PIVKA II concentration of 22.0 mAU/mL, and a calcitonin concentration of 1.5 pg/mL.

Discussion

The incidence of thyroid metastasis in autopsy series has been found to vary from 0.5% to 10.1%, with the breast being the most common primary carcinoma site [1-7]. The incidence of thyroid metastases in clinical reports seems to have increased recently [8-22], with the most common primary carcinoma site being the kidney, followed by breast and lung [8-14].

Liver tumors rarely metastasize to the thyroid, with the incidence at autopsy of thyroid metastases in patients with HCC reported to be 0.8% [6]. The first to report clinical thyroid metastasis from HCC were Masuda *et al*. diagnosed by the core needle biopsy [23] followed by others [25, 26]. The thyroid gland has a rich arterial blood supply, suggesting metastasis by hematogenous spread of the primary carcinoma [2]. The low rate of metastasis to the thyroid is likely due to screening of tumor cells by the lungs and the high-velocity blood flow in the thyroid [29, 30]. Also, epidemiological prevalence and clinical behavior of the primary carcinoma may be responsible for the relative frequencies of thyroid metastases.

FDG-PET is frequently used to evaluate the status of the primary carcinoma. The hepatic lesion in our patient was first detected by abdominopelvic CT and MRI, with the thyroid tumor synchronously detected by FDG-PET. Although most patients reported to have thyroid metastases had advanced primary carcinomas, in some patients [27], including ours, the thyroid gland was the only site of metastasis. US guided FNAB is optimal in the diagnosis of thyroid tumors [28], with many reports of thyroid metastases also based on FNAB results [13, 14, 17-22]. FNAB of the thyroid in our patient suggested a poorly differentiated carcinoma favoring metastasis but not expressing thyroglobulin, leading us to perform thyroid surgery. This surgery enabled a definitive diagnosis of HCC metastasis within an MTC, making this an extremely rare case of clinically diagnosed metastasis of tumor-in-tumor. The recently coined term entosis, defining a cell-in-cell or cell-eat-cell mechanism [31], suggests the need for *in vivo* evidence of this HCC within MTC as being caused by a tumor-eat-tumor mechanism.

We were able to diagnose the MTC in our patient by histopathologic findings after the thyroid surgery. To support this diagnosis, his serum calcitonin concentration had decreased from 265.0 pg/mL to 1.5 pg/mL one month later, suggesting that the patient was relieved from the possibility of prompt MTC spreading which might have been left unknown. In selecting further treatment in such patients, life expectancy is significant. Isolated thyroid tumors in patients with advanced primary carcinoma are not routinely evaluated, due to the relatively short survival of patients with distant metastasis. However, it has been recommended that newly diagnosed thyroid lesions be evaluated in patients with a history of carcinoma [14, 21], with the thyroid gland treated as a metastatic lesion until proven otherwise [32]. In addition, the results of a study of a series of thyroid metastases in our institution suggested that newly developed thyroid lesions be diagnosed at any time [22].

Although thyroid metastases are associated with poor patient prognosis [7], life expectancy depends on the prognosis of the primary carcinoma [12, 33]. Since treatment should be individualized to each patient, aggressive surgical treatment of isolated thyroid metastases has been recommended [30, 34, 35].

Thyroid metastasis from HCC is extremely rare, with total thyroidectomy preferred as palliative therapy. In our patient, an HCC metastasis within an MTC was detected in the thyroid at the same time that HCC was detected in the liver. Although the prognosis of these patients is generally poor, thyroidectomy may benefit patients with isolated thyroid metastases, both for a definitive diagnosis and to guide appropriate treatment. Unfortunately, such tumor-in-tumor cases are too rare to determine the prognosis of these patients.

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