Management of the Patient with Functioning Superior Mediastinal Metastasis from Follicular Variant of Papillary Thyroid Cancer: A Case Report and Review of Literature

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ABSTRACT

Superior mediastinal metastases are relatively uncommon findings in patients with well-differentiated thyroid cancer. We report a case of metastatic follicular variant of papillary thyroid cancer (FVPTC) in superior mediastinum which continued to produce thyroid hormone and was radioiodine avid without stimulation after thyroidectomy. A 62-year old woman presented for radio ablation therapy following thyroidectomy due to thyroid carcinoma. She underwent detailed examination including imaging and fine-needle aspiration cytology revealed a superior mediastinal mass of functioning metastasis from thyroid carcinoma. The post-therapeutic whole-body scan showed intense uptake of radioiodine (131I) in the metastatic lesion. A literature review reveals that FVPTC has a greater preponderance than papillary thyroid cancer (PTC) for distant metastases and that the majority of mediastinal metastases from either FVPTC or PTC are localized to the superior mediastinum. These lesions should be differentiated from the commonest mediastinal masses. They are very important to recognize as early recognition can lead to accurate and prompt diagnosis leading to timely treatment. The functioning metastases associated from differentiated thyroid cancer with euthyroidism or hyperthyroidism can be treated effectively with 131I without increasing TSH stimulation.

Key words: Follicular variant of papillary of thyroid cancer, superior mediastinal metastasis, 131I-therapy.

INTRODUCTION

Thyroid carcinoma is a malignancy of rapidly increasing importance in public health as well as research. The incidence of the disease has been steadily rising worldwide (1).

Differentiated thyroid cancer (DTC) which ordinarily behave in an indolent manner, can have unusual metastatic presentations and pattern (2).The most common histologic type of DTC is papillary thyroid cancer (PTC). Many subtypes of PTC have been described, of which classical PTC (cPTC) is the most common. The Follicular variant of papillary thyroid cancer (FVPTC) is the second most common morphologic subtype comprising 20-30% of all papillary carcinomas of thyroid (3,4). The FVPTC is characterized by nuclear features consistent with cPTC but having follicular rather than papillary architecture (5). Recent reports suggest that the incidence of FVPTC is on the rise, accounting for up to half of all PTC in some patient series (6). FVPTC presents several diagnostic and management challenges. They consist of different subgroups with varying pathology and clinical features (7).

The FVPTC is believed to behave in a clinical manner, similar to usual or cPTC and follow a similar indolent course. Although loco regional extension is lower in FVPTC than in cPTC, the distant metastasis rate is higher in FVPTC than in cPTC (8). Unlike the indolent clinical course that most FVPTC patients experience, patients with distant metastasis, either at

initial diagnosis or at recurrence, have a relatively poor outcome. It may, in rare cases, present as metastatic disease mainly to the lung, bone and mediastinum; however, it can also metastasize to other areas including the brain, liver and skin (9). The treatment usually involves surgical removal of the primary or metastatic tumor followed by radioactive iodine (RAI) therapy. Cancer itself is relatively hypo functional in relation to the normal tissue and rarely has the capacity to produce hormone. Metastatic FVPTC producing thyroid hormone remains extremely rare and has been reported in only a few cases (10). This is an extremely rare case of a patient who underwent thyroidectomy for thyroid cancer, yet she remained euthyroid as the metastatic tumor cells retained the ability to produce thyroid hormone and radioiodine avidity. A review of the literature on the possible explanation of hormone production by metastatic thyroid cancer and the factors involved in tumor metastasis follows the case presentation.

CASE REPORT

A 62-year-old woman was presented to our Institute of Nuclear Medicine & Allied Sciences (INMAS), Mymensingh after thyroidectomy for remnant radioiodine ablation (RRA) therapy. The following history and workup were extracted from the patient's medical records prior to visit our institute. The patient consulted with a head-neck surgeon for her neck swelling in September, 2016. An ultrasound scan revealed multinodular goiter, fine-needle aspiration cytology (FNAC) was suspicious for thyroid cancer. The concentration of triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) in blood serum of the patient were in normal range. Laboratory tests showed normal urine analysis, normal complete blood count, and basic metabolic panel. In radiological examination, the lungs were with normal appearance and translucency. The patient, however, underwent total thyroidectomy in early October of 2016. Histopathology of the surgical specimen revealed follicular variant of papillary thyroid carcinoma, totally encapsulated with no lymph vascular invasion (Fig.1). The TNM classification was pT1NXMX. Postoperatively, the patient was started on levothyroxine (LT4) replacement therapy and instructed to attend in a nuclear medicine institute for RRA therapy.

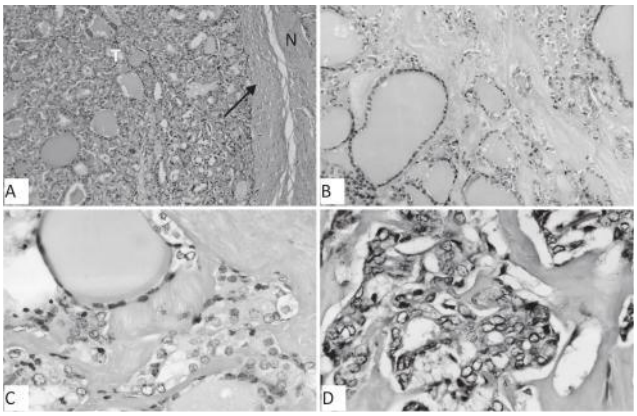

Figure1. Microscopic images of the follicular variant of papillary thyroid carcinoma (FVPTC). A, Low-power view showing the tumor (T), capsule (arrow), and adjacent nonneoplastic tissue (N).B, High-power view showing follicles of varying sizes and areas of sclerosis. C, D, high-power views showing follicles with and without nuclear features of papillary carcinoma.

The patient was seen in our institute for the first time in December, 2016. At that time her serum TSH was 4.76 μIU/ ml (normal, 0.3-5.0 μIU/ ml), T3 1.21 n mol/L (normal, 1.20- 3.55 n mol/L), T4 73.18 n mol/L (normal, 54- 173 n mol/L), Tg 7.12 ng/ml (normal, 13.36 ± 6.91 ng/ml) and Tg Ab 9.51% (normal, < 30%). An initial ultrasound examination of the neck showed no significant residual thyroid tissue in thyroid bed and no enlarged lymph node could be detected. Anticipating the rise of TSH (to at least 30 μIU/ml) for administering radioiodine therapy, she was advised to stop levothyroxine for 6 weeks. However, at the end of 6 weeks, TSH was found to be 5.13 μ IU/ml only. To evaluate the non elevation of serum TSH, high-resolution neck ultrasound was performed again, and failed to show loco regional recurrence or persistence of disease. With a high

probability of extrathyroidal sources of thyroid hormone, further evaluation was carried out.

In January 2017, a detail workup of pre ablation evaluation was conducted which included physical examination, repeat neck ultrasonography, thyroid scintigraphy, thyroid hormone profile and Tg reevaluation. Physical examination findings were noncontributory and the patient did not have shortness of breath, tremor, palpitation, heat or cold intolerance, constipation, diarrhea, weight changes, or fatigue. She did not have a family history of thyroid disorders. She had no prior history of head or neck irradiation. On neck examination there was a transverse incisional scar mark. The ultrasound examination of the neck revealed no significant residual thyroid tissue in the thyroid bed and no enlarged lymph node in the neck. The planar thyroid scintigraphy using ^{99m}Technetium pertechnetate (^{99m}TcO-4) showed no significant radiotracer concentration in the neck but an abnormal area of increased radiotracer concentration in the right superior mediastinum (Figure 2A). These findings were better defined by a CT scan of neck and chest performed without contrast media (Figure 2B). Thyroid function tests revealed TSH was- 5.49 µIU/ ml, FT3 6.23 f mol/ml (normal, 3.50-8.56 f mol/ml), FT4 16.35 f mol/ml (normal, 8.56 – 25.60 f mol/ml), Tg was 11 ng/ml. The RAI ablation therapy was delayed over the next few weeks as there was no expected rise of TSH.

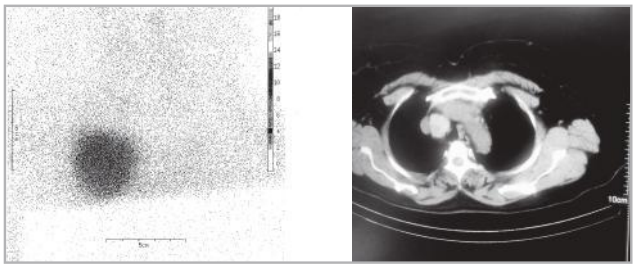

Figure 2. (A) 99mTcO-4 thyroid scintigraphy showing increased radiotracer concentration at the site of lesion in right superior mediastinum and no significant uptake in the neck. (B) CT scan of neck and chest confirmed the presence of a mass (3.1 X 2.9 cm) in the superior mediastinum.

In March 2017, she was further evaluated by means of extended scintigraphy and repeated thyroid function tests. To avoid excess iodine exposure interfering with radioiodine treatment and to obtain better definition of the metastatic mass, a ^{99m}TcO-4 whole body scan (WBS) with regional SPECT/CT of neck and upper chest was performed, showing an isodense soft tissue mass in the right superior mediastinum with intense radiotracer concentration. The mass measures ~3.1 X 2.9 cm and extended behind the medial end of right clavicle up to arch of aorta. No other abnormal area of radiotracer concentration is observed. The repeated analysis of thyroid function tests, has confirmed the normal concentrations of thyroid hormones and TSH in blood (TSH was- 3.46 µIU/ ml, FT3 6.48 f mol/ml, FT4 18.37 f mol/ml). The repeat Tg was 18 ng/ml. There was no significant residual thyroid tissue in the thyroid bed and even the patient was not taking levothyroixine for three months, TSH did not rise to levels adequate enough for radioiodine ablation therapy. A CT-guided FNAC from the mediastinal mass was consistent with papillary thyroid carcinoma (follicular variant).

The aforementioned data led to a diagnosis of metastatic thyroid cancer with euthyroid state sustained by functioning superior mediastinal metastasis. The thyroid hormone production in this patient was from the metastatic thyroid tissue that had spread to superior mediastinum. Following a multidisciplinary team discussion it was agreed the patient should undergo a mediastinal dissection for surgical removal of the metastatic mass followed by 131I therapy. For this the patient was sent to the department of Head-Neck Surgery of Mymensingh Medical College Hospital. But the patient had refused to undergo the second surgical intervention and returned to our institute. Her thyroid function tests repeated that showed TSH level was- 1.53 µIU/ ml, FT3 7.35 f mol/ml, FT4 20.47 f mol/ml, Tg 21.13 ng/ml and Tg Ab 10.97%. Further metastatic workup,

including abdominal ultrasonography, CT scan of brain and ^{99m}Tc-MDP whole body bone scan revealed no evidence of additional metastases. Since the diagnosis of functioning metastatic thyroid cancer had been reached from the thyroid scintigraphy, thyroid function tests and confirmed by FNAC, the patient was scheduled for radioiodine therapy.

She underwent radioactive iodine therapy with 75 mCi of ^{131}I on 23rd March, 2017 without a rise of TSH. Post-therapy whole-body scan (PTWBS), and SPECT-CT of neck and upper chest were acquired on March 28, 2017. Despite a persistently normal TSH level, the PTWBS showed intense focal uptake of ^{131}I in the mediastinal mass (Figure 3). Before ^{131}I therapy, the patient was treated for 2 weeks with carbimazole and methyl prednisolone to prevent possible thyrotoxic storm. She was discharged after 5 days from the hospital with recommendation to come for follow up.

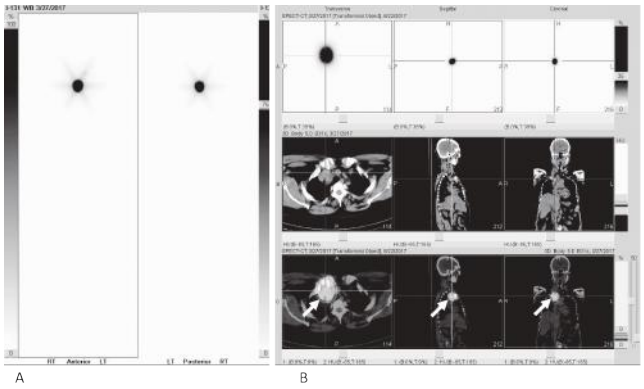

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Figure 3. Post-therapeutic 131I-WBS and SPECT/CT fusion images. (A) Anterior & posterior 131I-WBS images showed intense uptake of 131I in the metastatic mass with suppression elsewhere (arrow). (B) 131I-SPECT/CT fusion images provided metabolic and anatomic information that the focus of increased 131I uptake was localized in the right superior mediastinum (transaxial, sagittal & coronal images at lower row).

Two months later, symptoms of hypothyroidism occurred (TSH 30.96 µIU/ ml) and TSH suppression therapy with levothyroxine (100 µg/d) was started. Following thyroxine therapy, the patient's TSH level was lowering (14.6 µ IU/ml). The dose of thyroxine was then increased to 150 µg/d to keep her TSH concentration in the low normal range. Her hematologic values did not become abnormal after the therapeutic dose of ^{131}I was given. Follow-up, obtained 3 months after the first RAI therapy during TSH suppression by means of a chest radiograph, ^{99m}TcO-4 WBS and CT scan indicated a significant reduction of the size (1.4 X 1.2 cm) of the metastatic mass (Figure 4). There was poor concentration of ^{99m}TcO-4 in the residual tumor mass. Thyroglobulin decreased from 21.13 n g/mL to 16.5 n g/ml and TSH was 1.62 µIU/ ml. The patient was clinically well. Because there was a good response to the first therapy with ^{131}I, further therapy with a modestly higher dose of ^{131}I was planned.

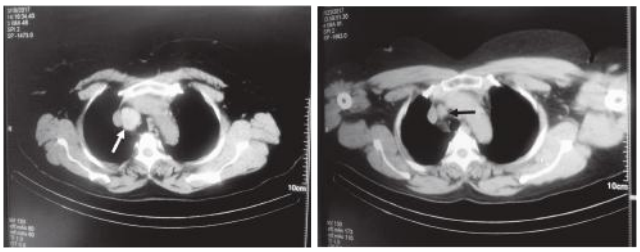

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Figure 4. CT images of neck and chest before and after radioiodine treatment. (A) Before 131I treatment, CT section shows a large soft tissue density mass (3.1 X 2.9 cm) in superior mediastinum (white arrow). (B) Three months after 131I treatment, the CT showed significant reduction of the size (1.4 X 1.2 cm) of the mass (black arrow).

In August 2017, the patient's thyroxine medication was discontinued for 6 weeks and 100 mCi of ^{131}I was administered when her TSH level rose to 32 µIU/ ml. At that time the thyroid hormones were also estimated where T3 was 1.57 nmol/L, T4 47.93 nmol/L, FT3 7.55 fmol/ml and FT4 6.62 fmol/ml. The Tg level was slightly rose to 17.6 ng/ml. The 7-day post-RAI WBS revealed good localization of radioiodine into the residual tumor, no new tumor was present. No side effects were experienced. The patient remains asymptomatic apart from mild xerostomia secondary to radiation induced damage to the salivary glands. She has restarted levothyroxine therapy, calcium supplements and is on regular follow up.

DISCUSSION

Thyroid carcinomas producing thyroid hormone to cause hyperthyroidism and thyrotoxicosis or maintaining euthyroid state remain quite rare. Since the first report of thyrotoxicosis due to autonomously functioning metastases by Leiter et al. (11) in 1946, fewer than 100 cases have been reported (12,13). The majority had follicular carcinoma with functioning metastases in the bone or lung at presentation but a few developed hyperthyroidism up to 15 years after the cancer diagnosis (12). The association of papillary thyroid carcinoma and functioning metastases has only been reported in few case reports in which three cases were mixed papillary and follicular carcinomas (12).

Pure PTC with functioning metastases has been reported in only a handful of cases (14, 15), one of which was a clear cell variant of PTC (16). Recently, Gardner et al. (10) reported a case of hyperthyroidism due to functioning bone metastasis from follicular variant of PTC. In our case report, the patient had a functioning thyroid cancer metastasis in the superior mediastinum. Superior mediastinal masses arise from a diverse group of conditions including thymoma, teratoma, retrosternal goiter, thoracic aortic aneurysms and lymphoma. Majority of anterosuperior mediastinal masses originating from thyroid are mediastinal goiter representing direct contiguous growth of goiter into the superior mediastinum. A large mediastinal mass producing thyroid hormone as a result of lymph node metastasis from FVPTC is a rare event. However, as reflected in this case report, thyroid cancer may present with hormone producing mediastinal metastases and should be considered amongst the potential differential diagnoses.

Although FVPTC is thought to behave in a similar clinical manner to classic PTC, in some cases it may present with pathologic features and clinical behavior similar to that of follicular carcinoma (17). As in our case report, the patient with FVPTC did not spread to regional nodes but metastasized to mediastinum. The ^{99m}TcO-4 scintigraphy demonstrated that mediastinal metastasis was capable of taking up radiotracer, whereas therewas no uptake in the thyroid bed and euthyroidism persisted after thyroidectomy and thyroxine withdrawal. Intense uptake of ^{131}I in the metastasis in post-therapeutic scan, in spite of the normal TSH levels in our case, indicates that the bulky mediastinal tumor mass functioned autonomously to maintain euthyroidism after total thyroidectomy. The hyper function of the metastatic thyroid cancer tissue usually is a result of the large autonomous metastatic tumor burden present in these patients or it may be explained by the stimulation of TSH receptors on metastatic cells by thyroid stimulating immunoglobulin (TSI) in certain cases of concomitant Graves' disease and thyroid cancer (18).

Similar to the patient presented in our case report, Boucher et al. (19) described a metastatic follicular cancer case wherein a patient remained euthyroid for three months after discontinuing oral T4 therapy in preparation for a whole body scan. The patient had undergone radical thyroidectomy years earlier and an ^{131}I scan confirmed the absence of thyroid tissue and demonstrated uptake in the skull, sacrum, pelvis, and lungs. The authors reasoned that tumor metastasis was at least partially TSH dependent and T3 administered indeed suppressed TSH production. However, despite several ^{131}I therapies, the tumor growth persisted and led to the patient's death (19). The authors acknowledge that it remains unclear how the same tumor can be both TSH dependent and autonomous. A possible explanation offered by the authors is that two distinct groups of cells with different degrees of differentiation exist in the same tumor: one which is TSH dependent and the other which is not hormonally controlled, the latter of which contributed to the growth of the tumor. An alternate explanation is that the same cell type became progressively less

differentiated as the tumor progressed, losing its ability to take up iodine, thus ceasing the potential to produce thyroid hormone and gaining the ability to resist ^{131}I therapy (19). In either case the tumor cells which were differentiated enough to retain a quasi normal thyroid hormone production may have perished with radioiodine ablation therapy and the undifferentiated cells persisted and multiplied. Well differentiated tumors have a better prognosis compared to poorly differentiated ones and the latter is seen more often in cases of late metastasis and is associated with absence of ^{131}I uptake (19).

The pathogenesis of hormone production with resulting hyperthyroidism or euthyroidism by metastatic thyroid cancer remains largely unknown but a few mechanisms have been proposed. Paul and Sisson suggested that TSI may play a role in the production of thyroid hormone by the direct stimulation and resulting growth of metastatic thyroid carcinoma (12). Ottevanger et al. (20) support the viewpoint that endogenous TSH stimulation may be responsible for enhancing the production of thyroid hormone by metastatic thyroid carcinoma. They described a patient who underwent total thyroidectomy and radioiodine ablation but posttreatment did not require levothyroxine therapy. The metastatic lesions were producing thyroid hormone and the TSH was suppressed during this replacement-free period. The TSH continued to fall while the patient was off therapy with a rise in T4 and T3 levels. It was not until after the thoracic wall lesion, thought to be responsible for the bulk of the hormone production, was removed and a second radioiodine was administered that TSH began to rise in concert with lowering T3 and T4 levels. However, during a later replacement-free period, the TSH began to rise but this time the T3 and T4 levels also increased demonstrating TSH dependency. After the sixth ^{131}I therapy, T3 and T4 levels finally began to decline. Initially the T3 and T4 levels were similar but during the course of the disease the ratio of T3 to T4 started to increase as the T4 levels began to dwindle; yet T3 levels remained steady. To explain this effect, Ottevanger and colleagues conducted in vitro studies which showed an impaired iodine uptake and iodination in thyroid cancer (20). The authors hypothesize that the increase in amount of T3 production is lent to in part to the amount of "dedifferentiation" and subsequent impaired iodine uptake leading to more mono iodotyrosinase production compared to di iodotyrosinase by the tumor. Lang et al. (21) proposed that environmental causes, particularly iodine deficiency, may play a role in thyroid hormone production by metastatic differentiated thyroid carcinoma. From the results of a cross-sectional study the authors concluded that long-standing goiter and iodine deficiency may have contributed to the slow growth of the metastatic lesions that retained hormone producing ability.

The management of DTC with functioning metastases is similar to patients with non-functioning metastases, but several issues require special attention. Radioactive iodine ablation therapy, in conjunction with antithyroid medication, has been successfully used in treating thyrotoxicosis and also in decreasing the size of the metastatic lesions with remission rates of approximately 33% (21). A 10-year survival of patients with DTC is 80-95% while it is reduced to 40% in presence of distant metastases (17). Early detection of metastasis improves the prognosis. This means presence of distant metastases worsens the prognosis which can be prevented by early diagnosis and treatment. In our case report, the patient has been diagnosed earlier during the pre-ablative evaluation and showed good therapeutic response after ^{131}I therapy. We believe that delayed diagnosis of the disease could lead to life threatening situations by provocating severe thyrotoxicosis and invasion of the disease into surrounding trachea, manubrium, and great vessels and pave way for extensive hematogeneous spread.

Current guidelines recommend patients receiving 131I therapy to have TSH levels above an arbitrary level of 30 μIU/ml to increase uptake. Hypothyroidism will increase the levels of circulating TSH, but carcinomas that are stimulated by TSI or that function autonomously may not gain much, if any, function from the actions of TSH (22). Moreover, if TSI is present, it is likely to persist as long as the neoplasm remains a source of antigen. Suspicion should be aroused when euthyroidism is reached with little or no thyroxine therapy after thyroidectomy. Then imaging should be performed when TSH levels are low, normal, or slightly elevated to determine the function of the neoplasm. If ^{131}I is reasonably sequestered by the tumors (as estimated from body retention of ^{131}I and scintigraphic patterns), then treatments with radioiodine may best be performed without increasing TSH stimulation by thyroxine withdrawal or by injections of recombinant human TSH. As in our patient, the first therapy showed significant reduction of the tumor mass depicted by CT and scintigraphy, as well as by the development of hypothyroidism following treatment.

Dosimetry permits administration of ^{131}I within safe limits. Benua et al. (23) recommended a body dose no greater than 2 Gy from any single treatment to avoid hematological morbidity. However, life-threatening acute toxicity is rare, and profound bone marrow depression is uncommon in patients treated with 131I for thyroid cancer. Moderate administered activities are unlikely to exceed the level of safety, but the presence of bulky functioning tumors, especially those that secrete thyroid hormone, warns that the margin for safety is reduced. Yet, patients with these manifestations also present an opportunity to impart radiation that will substantially reduce the morbidity of the carcinomas. Although ^{131}I can successfully eradicate functioning or hyper functioning metastases, release of thyroid hormone can follow tumor cell lysis which can precipitate a thyroid storm. Attempts to render the patient euthyroid prior to ^{131}I therapy with steroids, anti-thyroids and propanolol minimize this complication.

CONCLUSION

Functioning metastases from follicular variant of PTC is exceedingly rare but needs to be considered amongst the differential diagnoses, particularly when the cause of post total thyroidectomy euthyroidism or hyperthyroidism is unclear. Management comprises early diagnosis, anti thyroid medication, and occasionally steroids followed by radioactive iodine therapy. Metastatic lesions sequestering ^{131}I can be effectively treated without increasing stimulation by thyroxine withdrawal or by injection of recombinant human TSH.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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