CASE REPORT

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Papillary Thyroid Carcinoma with Thigh Muscle Metastases and Dramatic Response to Radiation and Targeted Therapy: a case report and review of The literature

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ABSTRACT

Soft tissue metastases are extremely rare in differentiated thyroid cancers. We hereby present a man with a history of papillary thyroid cancer (PTC) at the age of 46, who was referred to cancer Institute due to raised serum thyroglobulin (Tg) and a new mass in the thigh. Imaging studies were suggestive of recurrence of the disease in the tumor bed, neck nodes and lungs, and also a mass in his left thigh, based on positron emission tomography (PET) scan, without radioactive iodine uptake. The excision of the mass revealed metastatic PTC. After management of symptomatic local recurrence with external beam radiotherapy (EBRT), he received sorafenib. After three years he is doing well and serum Tg is stable.

Keywords: Papillary thyroid cancer, muscle metastases, FDG-PET

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INTRODUCTION:

Differentiated thyroid carcinomas (DTC), including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), are considered as indolent slow-growing malignancies that are associated with long-term survival rates[1,2]. The main treatment is total thyroidectomy followed by adjuvant radioactive iodine (RAI) in high-risk cases. Even involvement of usual sites of metastasis, i.e., cervical lymph nodes and lungs, does not confer a poor prognosis[3,4]. Sometimes DTC tends to transform to poorly differentiated forms of thyroid cancer (PDTC), in which the tumor behaves more like anaplastic thyroid cancer (ATC) with absent iodine uptake but keeps the ability to release thyroglobulin (Tg) in serum[5]. In these cases, metastases may occur in bone and brain as well as usual sites for DTCs.

Although the PDTCs are aggressive malignancies and tend to recur in multiple sites, the involvement of soft tissues, especially skeletal muscles, is extremely rare[6]. This type of metastatic disease usually is accompanied by multiple metastases in lungs, bones and cervical nodes and is indicative of a very advanced disease[7]. In these cases, patients eventually die of their metastatic disease and treatments are not much of benefit.

We hereby present a rare case of recurrent PDTC with unusual metastases to thigh skeletal muscles and concomitant involvement of tumor bed, cervical lymph nodes and lungs.

CASE PRESENTATION:

A 46-year-old man, without any remarkable past medical history, including radiation exposure or familial history of thyroid cancer, was evaluated for an incident of neck mass with rapid progression in 2008. After appropriate diagnostic workup that led to the diagnosis of papillary thyroid cancer, he underwent total thyroidectomy and central and bilateral neck dissection. The specimen acquired by total thyroidectomy revealed a 4 cm mass with histological appearance of moderately differentiated papillary carcinoma associated with infiltration into peri-thyroidal fibro-fatty tissue, vascular invasion, and microcalcification. The surgical margins were positive. Out of 25 dissected lymph nodes, levels II to IV and level VI, 15 showed metastatic disease. After surgery, he received ^{131}Iodine as the adjuvant treatment due to the high risk of recurrence.

His regular follow up visits were uneventful until April 2014 (six years after initial presentation), when he presented with a non-painful mass on his left thigh. On physical examination, a palpable, firm, non-tender, fixed mass was found in the left thigh. The rest of the examination was non-specific. The level of serum thyroglobulin (Tg) was elevated. The mass was not avid in radioactive iodine whole-body scan. To evaluate the presence of distant recurrence, we performed 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) scan with suspicion of transformation to PDTC. The FDG-PET scan showed several lesions with high FDG uptake in lungs, abdomen, and muscles of the left thigh (**figure 1 &2**). In order for us to obtain a tissue diagnosis for this unusual presentation, the patient underwent excision of the palpable thigh mass in April 2014. The light microscopic examination was in favor of metastatic poorly differentiated papillary carcinoma with positive reactivity to pan-cytokeratin (PAN-CK), cytokeratin (CK7) and thyroid transcription factor -1 (TTF1) antibodies in immunohistochemical (IHC) study.

During the diagnostic evaluations, the patient complained of respiratory distress. Neck and thoracic computed tomography (CT) scans showed thyroid tissue

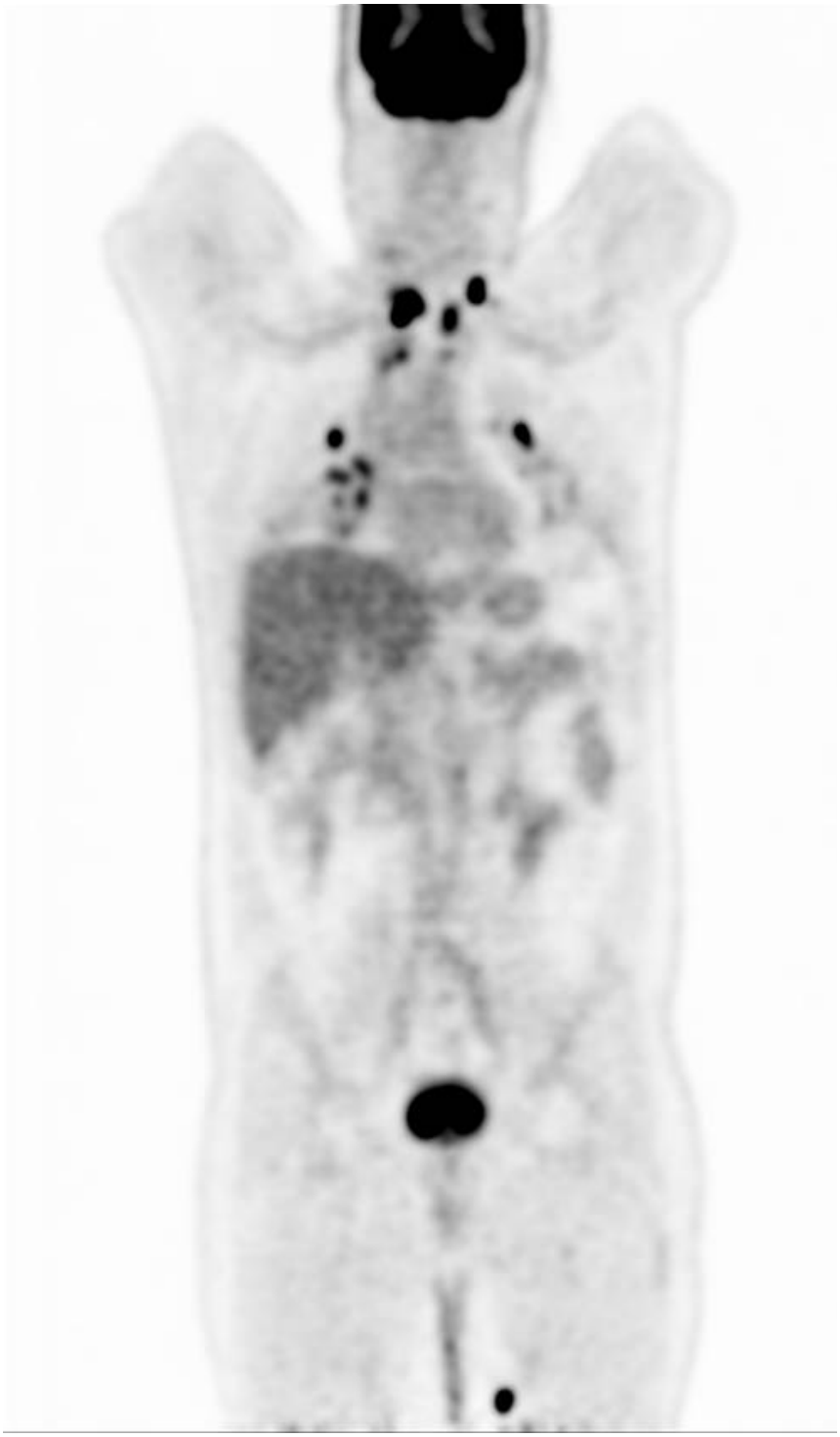

Figure 1. Initial FDG-PET scan showing hypermetabolic foci in left thigh and bilateral lungs, upper mediastinum and neck

residue with extension to the thoracic inlet, bilateral necrotic neck nodes in internal jugular chains and diffuse bilateral metastatic pulmonary nodules. He underwent tracheostomy tube placement and then became the candidate to receive external beam radiation therapy (EBRT) to control the mass effect on airways. He received 56 Gray in 28 daily fractions to his neck and superior mediastinum in 6 weeks in August and Sep-

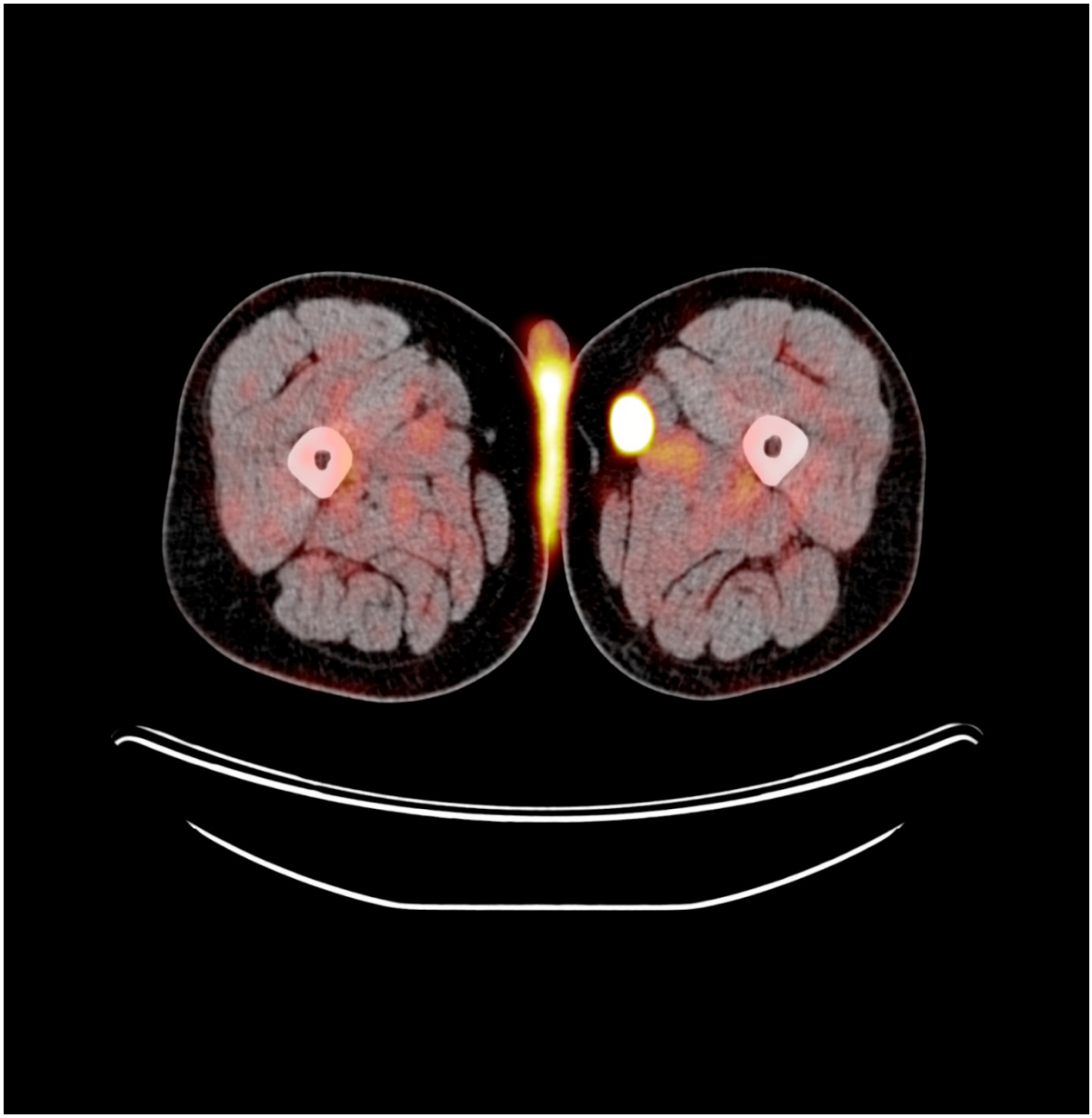

Figure 2. Initial FDG-PET/CT fusion scan showing a hypermetabolic focus in medial part of thigh

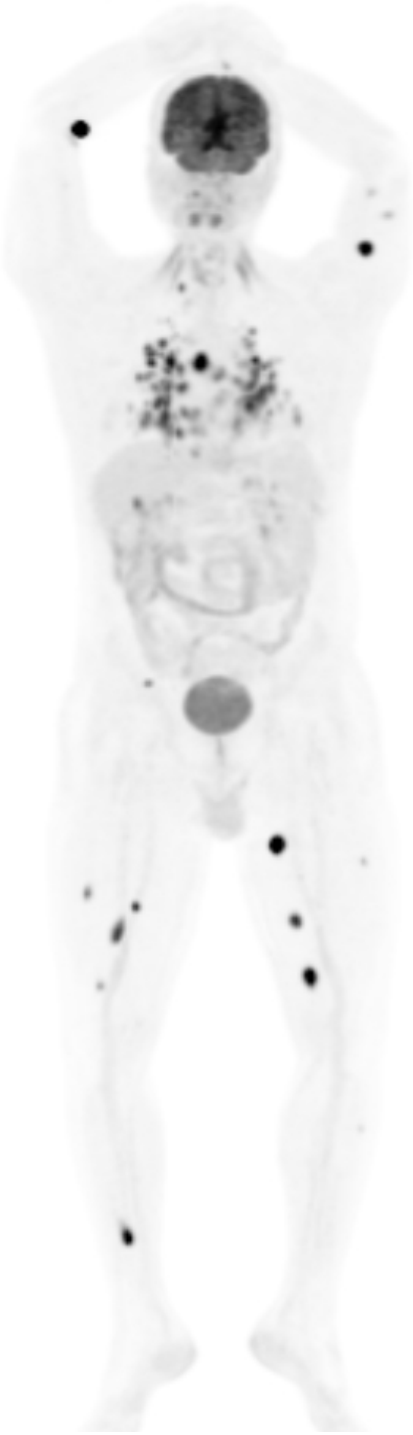

Figure 3. Second FDG-PET scan showing multiple hypermetabolic areas in lungs, mediastinum, arms, and thighs and right leg

tember 2014. The severe respiratory symptoms were relieved by EBRT leaving non-productive cough due to metastatic lung nodules. One month after EBRT he was placed under oral sorafenib, a multi-kinase inhibitor, with a dose of 800 mg daily. The serum Tg gradually decreased, and the patient became asymptomatic. To evaluate the progression of the disease, we performed another FDG-PET scan in July 2016 (**Figure 3**). In this scan, the metastatic sites progressed, but the patient did not have any new complaint. At present (October 2017), he is 55 years old and has been consuming sorafenib for three years. His latest Tg levels have been stable around 100 ng/ml with negative Tg-antibodies. He is doing well and able to perform his daily routine activities without any complaint.

DISCUSSION:

PTCs are usually non-aggressive tumors that respond well to total thyroidectomy followed by RAI and levothyroxine suppression therapy. The rate of distant recurrences is less than 20%[8,9]. When some of the tumor clones become poorly differentiated, the disease recurs with an aggressive behavior and in unusual sites other than cervical lymph nodes, lungs, and bone[10]. These rare sites of PTC metastasis include brain, liver, orbit, ovary, breast, and skin, described in the previous case-reports[11]. These involvements often develop years after remission of first presentation[10]. Metastases from primary thyroid tumors to skeletal muscles have rarely been reported (as far as we know only 11 cases up to 2011)[12]. The primary tumors were FTC in the majority of previous cases[13,14]. It is believed that the rarity of skeletal metastases is due to the fact that muscular environment is hostile to circulating cancer cell exploring a spot for nesting. This hostility is believed to have roots in low muscle pH (due to lactic acid accumulations) and movements[15].

In the patient in this study, the lung and muscle metastases occurred at the same time. This co-existence has been previously reported three times. The first was about a 44-year-old man with PDTC in whom the tumor metastasized to the thigh muscle, skin, lung, mediastinum, and brain. That patient died of his aggressive disease after failure of radiation and systemic therapies[10]. The second case, reported by Luo et al, muscle (erector spinae) and lung metastases occurred concurrently with metastatic kidney involvement from PTC in a 29-year-old man[16]. The third one was a 31-year old man with lung and muscle (gastrocnemius) metastasis from PTC[17]. These three cases and the patients in this study share numerous similarities and just a few differences; all are men with primary tumors having a high risk of recurrence (locally advanced), and are of poorly differentiated histology, but the case in the study was relatively older than the three and his muscular involvement was not evident on ^{131}I- the whole body scan.

The skeletal muscle metastases are usually asymptomatic so they may remain undetected. This type of metastasis can be found during the autopsy in one out of five patients with cancer[18]. Among primary sites reportedly associated with skeletal metastases, we can lung, colon and kidney[19,20]. According to the results of our study, the FDG-PET scan is a beneficial method to detect skeletal metastasis in patients with differentiated thyroid cancers and elevated serum Tg, whose metastatic foci have not RAI uptake[21]. These tumors constitute around 20% of DTCs. It is therefore not strange to say that, by gaining popularity, PET scan will be used more in the near future to deect skeletal metastases from thyroid cancer[22,23].

It is interesting that despite extensive multi-organ metastases, our patient had a durable response to EBRT and systemic therapy, using a multi-kinase inhibitor (sorafenib). He survived nine years after his thyroidectomy and three years after the distant metastases in

multiple organs. Among previous reports with documented survival time, similar findings have also been reported by Bruglia et al and Yang et al[10,7]. These cases were also poorly differentiated PTC with multiple organ metastases that survived a long time after primary diagnosis. Nevertheless, their patients died about 6 to 18 months after the emergence of metastases in the thigh and other sites. The first one died of the brain metastasis and the second refused to receive treatment with radioactive iodine. All previous cases with recurrence in the neck and superior mediastinum were treated with EBRTas in ours. Thus, we believe the long-term disease control in the patient is due to continued targeted therapy with a potent multi-kinase inhibitor, sorafenib. However, there are no previous reports about using sorafenib in muscular metastases of thyroid cancers to compare the outcomes.

In this study, we presented a rare case of PTC with concurrent lung, muscle and lymphatic metastasis nine years after total thyroidectomy that responded clinically well to local and systemic treatments. This study showed that FDG-PET is a useful tool to locate the uncommon sites of the disease in patients with abnormal serum Tg and negative uptake in RAI whole body scan.

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