Multi-focal metastatic papillary thyroid cancer to skeletal muscle with BRAFV600E mutation

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Abstract

Objective: Skeletal muscle metastasis in papillary thyroid cancer is extremely rare with a total of 32 cases reported in the literature. We are reporting a patient with multi-focal skeletal muscle metastases from papillary thyroid cancer (PTC) with a documented BRAFV600E mutation.

Methods: Report patient history and review of the literature.

Results: A 52-year-old man underwent total thyroidectomy with classic PTC with a BRAFV600E mutation and confirmed skeletal metastasis.

Conclusion: The case describes a unique and rare presentation of metastatic PTC to skeletal muscle that requires a unique approach to diagnosis and management.

Introduction

Skeletal muscle metastasis in papillary thyroid cancer is extremely rare with a total of 32 cases reported in the literature. We are reporting a patient with multi-focal skeletal muscle metastases from papillary thyroid cancer (PTC) with a documented BRAFV600E mutation.

Case report

A 52-year-old man underwent total thyroidectomy for an incidental thyroid nodule that was confirmed PTC via fine needle biopsy. Pathology confirmed a 5.5 cm papillary thyroid cancer (PTC) without aggressive histology or local extension. Five out of seven cervical lymph nodes were positive at level 6 of cervical lymph nodes. After surgery, he was treated with 177 mCi of I 131 . Post-treatment scan revealed right lower neck uptake and multi-focal thyroid bed uptake.

Two years later, he demonstrated detectable basal thyroglobulin (Tg) elevation with negative Tg antibody. Thyrogen stimulated Tg rose to 60 ng/mL (ref. 2.0-35). However, iodine (I 131 ) whole body scan revealed no evidence of uptake in thyroid bed or other sites. 18F-fluorodeoxy positon emission computerized tomography scan (18F DG PET-CT) demonstrated evidence of a 1.3 cm residual neck mass suggestive of residual thyroid cancer. Patient underwent repeat 156 mCi of I 131 ablation and post-treatment scan reported focus uptake in the right neck.

The following year, he was found to have persistent disease (1.5 cm nodule in thyroid bed) confirmed via magnetic resonance imaging (MRI) of the neck. Repeat Thyrogen stimulated serum Tg was 414 ng/mL. He subsequently received his third dose of 293 mCi I 131 treatment with a total of 626 mCi.

Due to the lack of response with RAI, the patient was offered a trial of BRAFV600E inhibitors. He declined treatment because of work obligations overseas and since he was overall asymptomatic despite his tumor burden. He opted for surveillance with consideration for future trials if his disease continued to demonstrate progression.

Discussion

There is a total of 32 reported cases of skeletal metastases from PTC in the literature over the past 110 years [1]. Generally, muscle metastases from solid tumors are rare. The majority of skeletal muscle metastases are from lung (25.1%), gastrointestinal (21%), and urologic tumors (13.2%) [2]. Muscle metastases from thyroid cancer is scarcer.

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There are several theories and studies that may explain the rarity of muscle metastases. Skeletal muscle produces several anti-tumor factors that are known to inhibit proliferation of malignant cells and these include low molecular weight factor, adenosine, leukemia inhibitor factor, and interleukin [3-6]. It is postulated that the microvasculature of skeletal muscle may biomechanically be damaged via tumor cells [5]. Variable blood flow within skeletal muscle may also limit tumor growth [6,7]. Lastly, the muscle’s ability to remove lactic acid inhibit may also inhibit tumor neovascularization [2,6].

The pathophysiology behind the spread of metastatic tumor into muscle is believed to occur through several mechanisms. One is through direct hematogenous spread of cancer cells, and studies have demonstrated tumor cells directly spreading via the arterial circulation [7]. Another process is through lymphatic spread to intramuscular lymph nodes [2,8]. There is also the possibility of skeletal muscle metastases occurring through perineural spread [9]. It may be hypothesized that given the propensity for PTC metastases to spread through regional lymph nodes, spread of PTC to muscle may occur through lymphatic proliferation.

The most common site for distal metastatic spread in PTC is the lungs. The second common is bone and then the brain [10]. There are other rare instances where PTC was reportedly found in the adrenals, kidney, ovary, orbit, and sphenoid sinus [10]. Only a third of the patients had pain from the muscle metastases from thyroid cancer, and the most frequent site of involvement was the gluteus muscle [1]. Median survival was found to be reduced by nearly half in patients with skeletal muscle metastases compared to other organ thyroid metastases [1].

Our patient was identified to have the BRAFV600E mutation. BRAF (kinase-activating mutation in the V-raf murine sarcoma viral oncogene homolog B1) is gene that encodes for a protein in the RAS/MAPK signaling cascade. The RAS/MAPK pathway regulates cellular proliferation, differentiation, migration, and apoptosis [11]. Alteration in BRAF affects the pathway and leads to tumor cell proliferation or loss of differentiation [12]. This proto-oncogene mutation was first discovered in 2002 as potentiator of various cancers [12]. The majority of BRAF mutations (90%) are due to a single amino substitution at codon 600 designated as BRAFV600E [13]. This BRAFV600E mutation is found in 43.8% papillary thyroid cancers and present in approximately 55-75% classical type PTC [14-16].

Papillary thyroid cancers that harbor BRAFV600E mutations are found to be resistant to radioactive iodine due to decreased expression of the sodium-iodide symporter [17,18]. Case reports on papillary thyroid cancer with muscle metastasis reported poor response to radioactive iodine [10]. The patient reported here demonstrated a poor
response to treatment with 131I. Radiodine scan with postoperative serum Tg levels are the standard for detecting metastatic disease [19]. However, the 131I WBS is negative in 20% of patients with disseminated thyroid cancer and several case reports have demonstrated negative radiodine scans in these patients [20]. 18F FDG-PET scan has been shown to be a valuable tool in identifying and localizing recurrences when serum Tg is elevated with a negative 131I WBS.

Multitargeted kinase inhibitors are now FDA approved for advanced or metastatic-radioactive iodine refractory thyroid cancer with extended progression free survival (PFS) ranging from 5 to 14.7 months [21,22]. However, the toxicity associated with tyrosine kinase inhibitors may limit its use in only advanced cases and may not be suitable for patients who are asymptomatic or with indolent slow growing metastases. Identification of BRAF mutation may serve as an important marker in the treatment of unresectable or metastatic-radioactive iodine resistant papillary thyroid cancer to skeletal muscle and these patients may be treated with of BRAF inhibitors. Though treatment with MEK (mitogen-activated protein kinase enzymes MEK1 and/or MEK2) inhibitors such as selumetinib have been tried in PTC, recent trials specifically targeting papillary thyroid cancer with the BRAFV600E mutation are ongoing [23]. The use of selective BRAF inhibitors may be a potential option in our patient although he is asymptomatic but demonstrates ongoing progression of his disease. Two selective BRAF inhibitors, dabrafenib and vemurafenib have demonstrated some success by restoring sensitivity to radioactive iodine by redifferentiation of iodine - refractory thyroid cancer [24,25]. The patient is planned for the possibility of treatment with BRAFV600E in the future.

Conclusion

In summary, we describe a rare case of metastatic PTC to skeletal muscle that was found to harbor the BRAFV600E mutation. Clinicians should consider genetic testing in patients with radioidine resistant thyroid cancer given the potential change in surveillance and treatment strategies in this unique patient population.

Acknowledgment

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Disclosure

The authors have no multiplicity of interest to disclose.

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