Papillary Thyroid Cancer Presenting as a Uterine Metastasis

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Abstract

The objective of this case is to report the highly unusual occurrence of uterine metastasis from a papillary thyroid cancer (PTC). PTC is rarely associated with distant metastases and typically spreads to bone or pulmonary tissue. In this case a 69-year-old female presented with post menopausal bleeding (PMB). She was otherwise well with no significant medical history or regular medications and reported no family history of thyroid disease. A subsequent endometrial polyp was identified as the cause of her PMB and removed. In addition as part of her clinical examination a goitre was noted and radiological imaging (including an ultrasound, magnetic resonance imaging of the neck and computer tomography of thorax, abdomen and pelvis) was performed and demonstrated a large thyroid mass which extended retrosternally and caused tracheal narrowing. The remainder of the imaging was unremarkable. The endometrial biopsy demonstrated morphological features of PTC. BRAF V600 mutation was not detected. A subsequent core biopsy of the mediastinal mass displayed morphological and immunohistochemical characteristic similar to that of the endometrial polyp. In combination this confirmed a diagnosis of primary papillary thyroid carcinoma. Surgical treatment included a total thyroidectomy, sternotomy and left neck dissection. Lymph node involvement was demonstrated at levels II-VI. Despite radioactive iodine and the use of tyrosine kinase inhibitors this lady died from complications of her disease.

Keywords: Papillary thyroid cancer; Metastases; Treatment

Introduction

Papillary thyroid cancer (PTC) is the most common form of thyroid cancer and the incidence is increasing globally. Despite this, PTC rarely metastasises outside of the neck and normally carries an excellent prognosis with 5-year survival approaching 100%. We describe a highly unusual case of PTC presenting as a uterine metastasis. Ultimately this proved to be an aggressive form of PTC and displayed progression and radioactive iodine (RAI) resistance. Only three additional cases of PTC and uterine metastasis had been described in the literature.

Case Report

A 69-year-old female presented to the gynecology service with a short history of post menopausal bleeding. She was otherwise well with no significant past medical or family history. During the course of routine physical examination goitre was noted.

Investigation

An endometrial biopsy was performed to investigate the cause of post menopausal bleeding (PMB). Histology revealed strong thyroid transcription factor-1 (TTF-1) expression. Pax 8 was positive and thyroglobulin was negative. Surprisingly the morphology demonstrated features of PTC with nuclear clearing and overlap and with a rare intranuclear inclusion (Fig. 1a, b). The BRAF V600 mutation (a marker with high negative predictive value for PTC) was not detected. This case presented a diagnostic challenge as TTF1 expression is seen in uterine tumors, particularly those of mesonephric type; however the morphology was extremely suggestive of PTC.

Given this unusual morphology the patient went on to have an ultrasound of her thyroid, computed tomography (CT) thorax and magnetic resonance imaging (MRI) of neck. These investigations demonstrated a large $10 \times 6 \times 5$ cm heterogeneous, complex, partially solid-cystic mass in the left anterior triangle replacing the left hemithyroid. The right side of thyroid appeared normal. The mass extended retrosternally to the level of the arch of the aorta and displaced the trachea towards the right, causing approximately 50% stenosis. There were multiple subcentimeter bilateral cervical lymph nodes present. The mediastinum was otherwise normal with no suspicious pulmonary nodules. The liver, kidneys, spleen, pancreas and adrenal glands were normal. There was no evidence of retroperitoneal,
mesenteric or pelvic lymphadenopathy. There were no destructive bone lesions and a bone scan was normal.

A mediastinal core biopsy was performed and the results showed tubulo-papillary and tubular growth pattern. The nuclei show cytoplasmic clearing and overlap. Intranuclear cytoplasmic inclusions are present. The specimen stained positive for cytokeratin 7 (CK7) and TTF-1, however monoclonal anti-carcinoembryonic antigen (mCEA) was negative (Fig. 1c, d). The histology was identical to the endometrial samples taken; confirming a diagnosis of PTC with uterine metastasis.

**Treatment**

Surgical treatment consisted of a total thyroidectomy, sternotomy and left neck dissection. Surgical specimens demonstrated PTC, with focal “tall cell” features and lymphovascular invasion. Lymph node involvement was demonstrated at level (II, III, IV) (2/14 nodes) and level (V, VI) (1/22 nodes). Thymic tissue was unremarkable. The final grade was pT3N1b.

A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed 8 weeks later and histology confirmed that the two lesions were cytologically identical (Fig. 1).

Following RAI ablation of 7,400 Mbq, a post treatment scan showed some residual uptake in the left side of the thyroid bed and in the midline superior to the expected position of the thyroid. There were no visible iodine-avid metastases and patient was clinically well. The patient continued on regular surveillance and received a suppressive dose of levothyroxine to aim for a thyroid stimulating hormone (TSH) level of < 0.1
PTC (outside of thyroid surgery, RAI and suppressive doses of thyroid hormone replacement) are limited by both burden of disease and toxicity of the available treatments. As seen in this case, RAI is the first-line treatment for metastatic disease. For patients exhibiting satisfactory responses following RAI therapy the overall survival at 10 years is 92%, versus 19% in those who display persistent disease [9]. Despite the greatly reduced overall survival in the group with persistent disease, outcomes are still preferable to those who display no RAI uptake at all-survival rates of 15% vs. 8% respectively [9].

Indications for moving on from RAI to other forms of treatment include disease which becomes refractory to RAI (25-50% of metastatic PTC) or receiving a cumulative dose of RAI > 22,000 MBq [10].

Currently two tyrosine kinase inhibitors (TKIs) (lenvatinib and sorafenib) have Food and Drug Administration (FDA) approval for the treatment of metastatic PTC. Though showing improvements in progression-free survival and objective response rate, changes in overall survival have been disappointing. A number of other TKIs are at earlier stages of trial and show promising results in terms of progression-free survival. There is also evidence to suggest some additional benefit from the use of alternative TKI therapy when one has been unsuccessful [10].

Despite promising benefits the side effects of TKI therapies are significant and include cardiac, hepatic, cutaneous and renal complications. These medications are also teratogenic, myelosuppressive and cause elevations in TSH. As such a comprehensive evaluation of pre-existing symptoms and thorough counselling of patients are advised before initiation of therapy. As our ability to obtain molecular profiles of thyroid cancer causing mutations becomes more sophisticated, other therapies also become available. Such examples include vemurafenib and dabrafenib, selective inhibitors of the BRAF mutation which is present in 51% of PTC. In small studies, use of these agents produced a partial response rate of over 30%, and despite being associated with significant side effects, they are potentially future therapeutic options [11]. Additional small molecules which have been studied in clinical trials with limited numbers include MEK inhibitors which serve to cause re-sensitisation of thyroid tumor to RAI, phosphoinositide 3-kinase (PIK3) and tropomyosin-related kinase (TRK) inhibition.

Systemic chemotherapy can be considered in RAI refractory patients in whom other therapies (including TKIs) are unsuccessful or unsuitable. At present there are too few data to recommend any specific regimen.

Finally the most recent development for treatment of metastatic PTC to show promise is peptide receptor radionuclide therapy (PRRT); a method of targeting somatostatin receptors which has been used successfully in the treatment of neuroendocrine tumors. Though very few studies using PRRT have shown overall survival benefit in PTC, this area shows significant therapeutic promise and warrants further study [12].

Conclusions

We present the case of a highly unusual pattern of metastatic
spread in the setting of PTC. This displayed an aggressive phenotype, and ultimately displayed RAI and TKI resistance. More recent developments in the treatment of PTC were unavailable to the patient at the time of disease presentation and progression.

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None to declare.

Conflict of Interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Informed Consent
Informed consent was obtained from the family of this patient.

Author Contributions
CN and DTO’K contributed equally to the writing of the case report. SP, DQ, AL, MO’L all contributed to patient’s case and MB was the physician in charge of the patient’s care and edited the case report.

References