Papillary thyroid carcinoma with hyperthyroidism and multiple metastases
A case report
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Abstract
Rationale: Papillary thyroid carcinoma (PTC) is the most common type of primary thyroid cancer with a low incidence of distant metastases. PTC represents more than 70% to –90% of thyroid malignancies. Distant metastases have only been observed in only 1% to 15% of patients with PTC. In this article, we reported the case of a patient with PTC and hyperthyroidism as well as simultaneous multiple metastases.

Patient concerns: A 47-year-old man was admitted to our hospital on February 22, 2019, with several neck masses that had been present for 12 months, low back pain for 9 months, and lower limb paraplegia for 3 months.

Diagnoses: According to the patient physical examination, adjuvant examination (e.g., ultrasound, computed tomography, magnetic resonance imaging, blood test, and biopsy) and medical history, the clinical diagnosis was as follows: thyroid papillary carcinoma; cervical lymph node metastasis; multisite bone metastasis (6th and 7th cervical vertebrae, left clavicle proximal, right scapula bone, thoracic vertebrae, lumbar vertebrae, bilateral ilium, and left pubic bone); muscular metastasis (the right medial femoral muscle, the vastus lateralis muscle, left thigh muscle, and the flexor superficialis of the left forearm); possible mediastinal lymph node metastasis; and paraplegia due to the soft-tissue metastasis around the 9th thoracic vertebral spine; and hyperthyroidism (free thyroxine: 36.59 pmol/L, free triiodothyronine: 9.58 pmol/L, thyroid-stimulating hormone: 0.005 μIU/mL, thyroid autoantibody: 2.53 IU/L).

Interventions and outcomes: The patient refused to undergo further intervention or follow-up.

Lessons: In summary, this is the 1st case of in which a patient with PTC and hyperthyroidism, as well as simultaneous multiple skeletal muscles and bone metastases, lymph node metastasis, and paraplegia was observed. In practice, in cases where patients have PTC and hyperthyroidism, practitioners should perform further examinations to rule out the presence of distant metastases. We believe that the use of ultrasound has a unique advantage in the diagnosis of PTC and skeletal muscle metastasis.

Abbreviations: CT = computed tomography, 18F FDG PET-CT = 18-fluorodeoxyglucose PET-CT, FTC = follicular thyroid carcinoma, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, PTC = papillary thyroid carcinoma, T1WI = T1-weighted images, T2WI = T2-weighted images, TRAb = thyroid autoantibody, TSH = thyroid-stimulating hormone.

Keywords: hyperthyroidism, metastases, papillary thyroid carcinoma, skeletal muscles, thyroid cancer
1. Introduction

Papillary thyroid carcinoma (PTC) is the most common type of primary thyroid cancer. This form of carcinoma represents more than 70% to 90% of thyroid malignancies.[1] PTC is a slowly progressive cancer with high survival rate.[2,3] Distant metastases have only been observed in only 1% to 15% of patients with PTC. Metastases are most observed in the lungs, followed by the bones.[4,5] Muscular and soft-tissue metastases of PTC are very rare.

In this article, we reported the case of a patient with PTC and hyperthyroidism as well as simultaneous multiple skeletal muscles and bone metastases, lymph node metastasis, and paraplegia. We also present a literature review, aiming to provide further evidence regarding the diagnosis, intervention, and prognosis of PTC with distant metastasis.

2. Case report

2.1. Patient information

A 47-year-old man was admitted to the First Hospital of Jilin University on February 22, 2019, with several neck masses that had been present for 12 months. The patient had also experienced low back pain for 9 months and lower limb paraplegia for 3 months. The patient had no family history of thyroid disease or any history of exposure to external or accidental radiation.

2.2. Clinical findings

Physical examination of the patient revealed the presence of multiple masses in the area of the right supraclavicular fossa and the right neck. The largest lump, of approximately 2 × 2 cm, was hard, mobile, and painless. Three additional lumps were identified in the left forearm, the anterior side of the right thigh, and the lateral side of the right thigh. These lumps were 3 × 2 cm, 3 × 2 cm, and 2 × 2 cm, respectively. All 3 lumps were hard, solid, and tender. No sensation or pain was observed below the line of the anterior superior iliac spine, and the lower extremities were paraplegic.

Blood tests for thyroid function revealed that the free thyroxine level was 36.59 pmol/L (reference value 11.50–22.70 pmol/L), the free triiodothyronine level was 9.58 pmol/L (reference value 3.50–6.50 pmol/L), the thyroid-stimulating hormone (TSH) level was 0.005 IU/mL (reference value 0.550–4.780 IU/mL), and the thyroid autoantibody (TRAB) level was 2.531 IU/L (reference value 0.30–1.22 IU/L). No abnormalities were observed in the expression of tumor markers.

Ultrasound examination of the thyroid and neck revealed a 4.2 × 2.6 cm hypoechoic nodule with blurred borders, an irregular shape, and uneven and visible internal scattered punctate hyperechoic signs on the right lobe of the thyroid gland (Fig. 1A). A rich blood flow signal was detected by Doppler ultrasound. Another similar nodule, 1.5 × 0.9 cm in size, was observed in the thyroid isthmus. Multiple malformed lymph nodes (levels III and IV) were observed in the right neck, in which the structure of the hilum was unclear. There were solid hyperechoic and cystic areas in the lymph nodes and multiple punctate hyperechoic signs in the solid components of the nodules. The size of the larger lymph node was 2.9 × 2.3 cm (Fig. 1B). Ultrasound examination of the right thigh revealed a 2.4 × 2.1 cm substantial hypoechoic mass in the middle of the medial femoral muscle with a blurred boundary, irregular shape, uneven internal echo, and multiple punctate hyperechoic signs (Fig. 1C). A rich blood flow signal was detected by Doppler ultrasound. Two additional lumps of the same nature were observed in the middle of the vastus lateralis muscle and the flexor superficialis of the left forearm, with sizes of 3.1 × 1.6 cm and 4.0 × 1.5 cm, respectively (Fig. 1D). The ultrasound findings were as follows: hypoechoic thyroid nodules with calcification, considered to indicate thyroid cancer; cervical lymphadenopathy with calcification, considered to indicate lymph node metastasis; right thigh and left forearm muscle tissue lump with calcification without excluding to thyroid cancer metastasis.

Computed tomography (CT) scan results revealed multiple points of bone destruction in the 6th and 7th cervical vertebrae, right clavicle proximal, right scapula bone, thoracic vertebrae, lumbar vertebrae, sacral vertebrae, bilateral ilium, and left pubic bone (Fig. 2). The 9th thoracic vertebrae had obvious bone destruction, the spinal canal was destroyed, and the imaging of the spinal cord revealed a blurred structure. Pulmonary CT revealed a slight inflammation of the left lower lobe and enlarged mediastinal lymph nodes. The CT findings were as follows: multiple site bone destruction, not excluding metastatic cancer, and mediastinal lymphadenopathy, not excluding metastatic cancer.

Magnetic resonance imaging (MRI) revealed a 3.6 × 1.5 cm elliptical abnormal signal in the soft tissue of the left forearm ulnar with equal signal intensity on T1-weighted images (T1WI) and slightly high and low mixed signals on T2-weighted images (T2WI; Fig. 3A). Two other nodular abnormal signals were observed in the right thigh muscle group in the lower middle horizontal part and outer part separately with equal and slightly lower signals on T1WI and equal signals on fat-suppression images. A number of small mass signals were observed in the left thigh muscle group, with equal signal on the T1 image (Fig. 3B). Thoracic MRI with enhanced scanning revealed multiple thoracic vertebral bodies with multiple patchy abnormal signals, and an enhanced scan revealed mild uneven enhancement. The body of 9th Thoracic Vertebra was wedge shaped with a high patchy fat-suppression signal in the spinal cord. In some of the soft tissues around the thoracic vertebral body, strip-like abnormal signals were observed with low signal on T1WI, and high and low mixed signals on T2WI; enhanced scanning revealed mild uneven enhancement (Fig. 3C and D). The MRI findings were as follows: a muscle mass occupying lesion was observed in the left forear
and bilateral thigh; there was horizontal spinal cord compression at the 9th thoracic vertebral body and edema due to the soft-tissue metastasis around the spine, and the 9th thoracic vertebral compression fracture.

The patient underwent an ultrasound-guided biopsy of the thyroid nodules, right cervical lymph nodes, and right thigh mass under local anesthesia on February 26, 2019. The postoperative pathologic report revealed: pleomorphism of the follicular epithelium, partial papillary hyperplasia, and glassy nuclei presence in the thyroid nodule sample with a diagnosis of thyroid papillary carcinoma (Fig. 4A and B); the biopsy tissue in the right cervical lymph node was consistent with thyroid papillary carcinoma metastasis with immunohistochemical results of cytokeratin 19 (CK19) (+), cytokeratin 7 (CK7) (+), thyroglobulin (TG) (weak +), TTF-1(+) (Fig. 4C), thyroglobulin (TG) (weak +), TTF-1(+) (Fig. 4C).
(−), napsin A (−), and villin (−) (Fig. 4C and D); the biopsy tissue in the right thigh mass was consistent with thyroid papillary carcinoma metastasis with immunohistochemical results of CK19(+), CK7(+), TG(+), TTF-1(+), CK20(−), napsin A(−), and villin(−) (Fig. 4E and F). The patient refused to undergo further examination, such as positron emission tomography-CT (PET-CT), to determine whether additional lymph node or distant metastases were present.

2.3. Diagnostic assessment

According to the physical examination, adjuvant examination, and medical history of the patient, the clinical diagnosis was as follows: thyroid papillary carcinoma; cervical lymph node metastasis; multisite bone metastasis (6th and 7th cervical vertebrae, left clavicle proximal, right scapula bone, thoracic vertebrae, lumbar vertebrae, sacral vertebrae, bilateral ilium, and left pubic bone); muscular metastasis (the right medial femoral muscle, the vastus lateralis muscle and the flexor superficialis of the left forearm); possible mediastinal lymph node metastasis; and paraplegia due to soft-tissue metastasis around the 9th thoracic vertebral spine; hyperthyroidism.

2.4. Treatment and follow-up

The patient refused to undergo further intervention and asked to be discharged from the hospital on March 20, 2019. He did not consent to take part in any follow-up observations.

### Table 1

| Author | Publication date | Patient’s age | Patient’s gender | Subtype | Nodular size, cm | Muscle metastases |
|--------|-----------------|---------------|-----------------|---------|-----------------|------------------|
| Baloch et al(30) | 2000 | 43 | F | Follicular variant | 1.1 | The left psoas muscle |
| Karvoski et al(31) | 2002 | 59 | F | NA | 2.1 × 1.9 × 1.8 | The sternocleidomastoid muscle |
| Cokela et al(32) | 2003 | 50 | F | NA | NA | NA |
| Pucci et al(33) | 2006 | 77 | M | Follicular variant | 3.5 | NA |
| Tamolakis et al(34) | 2006 | 45 | F | NA | 2.5 × 1.5 × 2 | Stenoncleidomastoid muscle |
| Panoussopoulos et al(35) | 2007 | 69 | F | Tall cell type | 4.5 | The trapezius muscle |
| Kim et al(36) | 2007 | 25 | F | NA | 3.1 | The sternocleidomastoid muscle, the strap muscle |
| Luo et al(37) | 2008 | 29 | M | NA | NA | The erector spinae muscle |
| Qiu et al(38) | 2009 | 82 | F | NA | NA | The erector spinae muscle |
| Qiu et al(39) | 2009 | 63 | M | Follicular variant | NA | The left lower erector muscle |
| Bruglia et al(40) | 2009 | 44 | M | NA | 1.1 | The right erector muscle |
| Zhao et al(41) | 2010 | 53 | M | NA | NA | The left rectus abdominis muscle |
| Krajewska et al(42) | 2010 | 55 | M | NA | NA | The pterygoid muscle |
| Carrel et al(43) | 2011 | 68 | F | NA | NA | The adductor longus, iliopectos muscles |
| Bae et al(44) | 2011 | 31 | F | NA | 1.5 × 0.9 | The vastus medialis muscle |
| Li et al(45) | 2012 | 39 | F | Columnar cell type | 2.9 × 2.0 | The sternocleidomastoid muscle |
| Mohapatra et al(46) | 2012 | 42 | M | NA | NA | The luteus and paraspinal muscle |
| Morita et al(47) | 2012 | 74 | M | NA | NA | The muscles around the infratemporal fossa |
| Ceriati et al(48) | 2013 | 50 | F | NA | NA | The trapezius and subscapularis muscles |
| Catalano et al(49) | 2013 | 26 | M | NA | NA | The cervical muscles |
| Catalano et al(50) | 2013 | 64 | F | Follicular variant | NA | The gluteus muscle |
| Yun et al(51) | 2014 | 43 | M | NA | NA | The gastrocnemius muscle |
| Yang et al(52) | 2015 | 31 | M | NA | 3.0 | NA |
| Portela et al(53) | 2015 | 44 | F | NA | NA | The stenoncleidomastoid muscle, the strap muscle |
| Cassidy et al(54) | 2015 | 89 | F | NA | NA | The latissimus dorsi |
| Sinha et al(55) | 2015 | 66 | M | Micro PTC | 0.1 × 0.1 | The deltoid muscle |
| Li et al(56) | 2016 | 84 | M | NA | 2 × 3.3 × 4 | The not specified |
| Kusic et al(57) | 2016 | 68 | M | Follicular variant | NA | The thigh |
| Vardar and Dabholkar(58) | 2017 | 45 | F | NA | NA | The sternocleidomastoid muscle |

NA = not available, PTC = papillary thyroid carcinoma.
disorders, and nerve root pain at the corresponding metastatic site due to compression of the spinal cord.[43] In this case, the mass transfer in the para-thoracic soft tissue of the 9th thoracic vertebra invaded the spinal canal and compressed the spinal cord, which likely resulted in the symptoms of lower back pain, paraplegia of both lower limbs, sensory disorder, and defecation disorders.

Skeletal muscle metastasis of PTC is very rare. Herbowski reviewed the literature and calculated the incidence of skeletal muscle metastases in PTC and follicular thyroid carcinoma (FTC) to be around 4/10.[36,49] There is a hypothesis that skeletal muscle can tolerate lactic acid produced by tumor cells, thereby inhibiting the neovascularization of tumors; in addition, the pH environment in skeletal muscle and the movement of skeletal muscle can inhibit the proliferation of tumor cells.[100] We reviewed the literature from 1999 to 2018 and found that only 29 cases of PTC skeletal muscle metastases were diagnosed, affecting 18 parts of the skeletal muscle (Table 1). Among these 29 cases, we found the most common site of metastases was the sternocleidomastoid muscle (6 cases in total), which included 4 cases of needle biopsy or implant transfer after laparoscopic treatment, and the 2nd common metastatic site was the thigh and buttock muscle (3 cases in total). For the pathologic category, only 5 cases were reported as being of follicular subtypes, and 2 cases were reported as columnar epithelial subtypes. The maximum diameter of PTC nodules with skeletal muscle metastases ranged from 1.1 to 4.5 cm. In the present case, the patient had multisite muscle metastases, including the forearm and thigh muscles. This is the first report of such a case. Another interesting case of skeletal muscle metastasis of PTC was reported by Sarma et al.[29] in which the patient had both FTC (3.3 × 2.3 × 2 cm) and micro PTC (0.1 × 0.1 cm). The left deltoid muscle metastasis from micro PTC was found 6 months after total thyroidectomy. It was believed that the FTC was more likely to be the cause of the distant metastasis.[9,29] However, in the case reported by Sarma and colleagues, the metastatic carcinoma of the skeletal muscle came from a small positive micro PTC.[29]

In the present case, the blood test results (free thyroxine: 36.59 pmol/L, free triiodothyronine: 9.58 pmol/L, TSH: 0.005 μIU/mL, and TRAb: 2.53 IU/L) indicated that the patient had hyperthyroidism with no systemic treatment. This may have been a factor in the development of multiple bones and skeletal muscle metastases in this patient, as the high blood flow state that occurs during hyperthyroidism may have promoted the spread of tumor cells, making thyroid cancer more prone to distant metastasis. This hypothesis is consistent with the idea of Ito et al.[43]

Doppler ultrasound is the 1st choice for the examination of the thyroid and soft-tissue masses due to its economic and convenient advantages. Although the transfer of PTC to skeletal muscle is very rare, it is necessary to consider the possibility of PTC metastasis when encountering a substantial mass of microcalcification in the skeletal muscle. For the overall assessment of PTC distant metastasis, 18-fluorodeoxiglucose PET-CT[19] imaging can accurately assess the disease by detecting the local lymph node involvement and distant metastasis.[24] Unfortunately, in this case, the patient refused to undergo PET-CT examination.

In summary, this is the 1st case in which a patient with PTC and hyperthyroidism was shown to have simultaneous multiple skeletal muscle and bone metastases, lymph node metastasis, and paraplegia. The point of interest in the present case is that the high blood flow state of hyperthyroidism may be one of the factors that contributed to the occurrence of multiple distant metastases.

Therefore, in practice, for patients with PTC and hyperthyroidism, practitioners should perform further examinations to rule out the presence of distant metastases. We believe that the use of ultrasound has a unique advantage in the diagnosis of PTC with skeletal muscle metastasis.

Author contributions
Lili Zhang, Bin Liu, and Lirong Zhao designed the study, conducted all searches, appraised all potential studies and wrote and revised the draft manuscript and subsequent manuscripts. Fangfang Sun and Hongyu Li revised the draft manuscript and subsequent manuscripts. Shuang Li assisted with the presentation of findings and assisted with drafting and revising the manuscript. All authors read and approved the final manuscript.

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