Skin and thigh muscle metastasis from papillary thyroid cancer

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ABSTRACT

A 44-year-old man with total thyroidectomy for papillary thyroid carcinoma (PTC) performed at the age of 38 years was referred for mediastinal metastases demonstrated on chest radiograph and high serum thyroglobulin (Tg 328 ng/ml). Computed tomography revealed mediastinal lymph node enlargement with left bronchial compression and reduction of bronchial diameter, as well as two metastases in the left lung. Bronchoscopic biopsy findings showed a poorly-differentiated PTC, while a whole body scan after 131-Iodine therapy demonstrated uptake in the right subclavicular region. External beam radiotherapy and chemotherapy yielded no benefit; the neoplasm was aggressive, diffuse and experienced fast growth, leading to the formation of metastases also at unusual sites, such as the skin and thigh muscle. The patient died from a brain metastasis. We report a rare case of PTC metastasis with a poorly-differentiated component in a young patient. Rapid and diffuse metastases also to unusual sites led to death eight years after the initial diagnosis and treatment.

Keywords: papillary thyroid carcinoma, skin metastasis, thigh metastasis, thyroglobulin, thyroid cancer

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INTRODUCTION

Papillary (PTC) and follicular (FTC) thyroid carcinomas are follicular cell-derived carcinomas. They are differentiated forms of thyroid carcinoma (DTC) and are characterised by slow growth and an indolent biological behaviour. 80% of patients with DTC respond to total thyroidectomy, radioiodine ablation and levothyroxine suppression therapy.[1,2] This treatment is associated with ten-year survival rates of 80%–90% in PTC patients, including young subjects with lymph node or lung metastasis at diagnosis.[3,4] Metastases are mainly to regional lymph nodes and, less frequently, to the lung and bone. In contrast, poorly-differentiated thyroid carcinoma (PDTC) is an invasive cancer characterised by a rapid and fatal outcome despite appropriate treatment.[1] Based on its clinical features, PDTC is an intermediate form between well-differentiated and anaplastic thyroid cancer.[2] Poorly-differentiated tumour foci have been identified on histopathology in predominantly well-differentiated areas of thyroid cancers.[5] PDTC loses some characteristic features of DTC, and it still produces thyroglobulin (Tg) but may not show radioiodine uptake. Serial Tg monitoring can therefore be helpful in detecting recurrences.[6] Radioiodine imaging, ultrasonography (US), computed tomography (CT), magnetic resonance (MR) imaging and, recently, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) have proved useful in detecting the disease and assessing its extent.[7] PDTC frequently recurs in the thyroid bed or the cervical lymph nodes, or invades the trachea. The most common sites of distant metastasis are the lung, bone and brain.[6] We report a rare case of PTC with a PDTC component in a young patient with thigh, skin, lung and brain metastases six years after total thyroidectomy. The tumour was aggressive and led to death eight years after initial diagnosis and treatment.

CASE REPORT

In 1997, a 38-year-old man underwent neck US, total body CT and MR imaging for supraclavicular lymph node enlargement on the left side of the neck. He had no family history of thyroid disease and reported no exposure to external or accidental radiation; he had previously been a smoker for ten years (about ten cigarettes/day). The radiological work-up demonstrated bilateral cervical lymph node enlargement, a 1.1 cm hypoechoic thyroid nodule and homogeneous Tc-99 uptake in the thyroid. Fine-needle biopsy of lymph nodes and the thyroid nodule was not performed. The supraclavicular lymph nodes were removed two months later. PTC metastases found on histology led to total thyroidectomy and dissection of the left cervical, peri- and paratracheal and superior mediastinal lymph nodes. Histological demonstration of classic PTC in all surgical specimens demonstrated infiltration of the perithyroid soft tissue.

The patient received two consecutive ^{131}Iodine treatments (262 mCi in total). The serum Tg levels during these procedures were not available. Whole body scan (WBS) after the second treatment revealed ^{131}Iodine uptake in the thyroid bed and the left neck region, demonstrating

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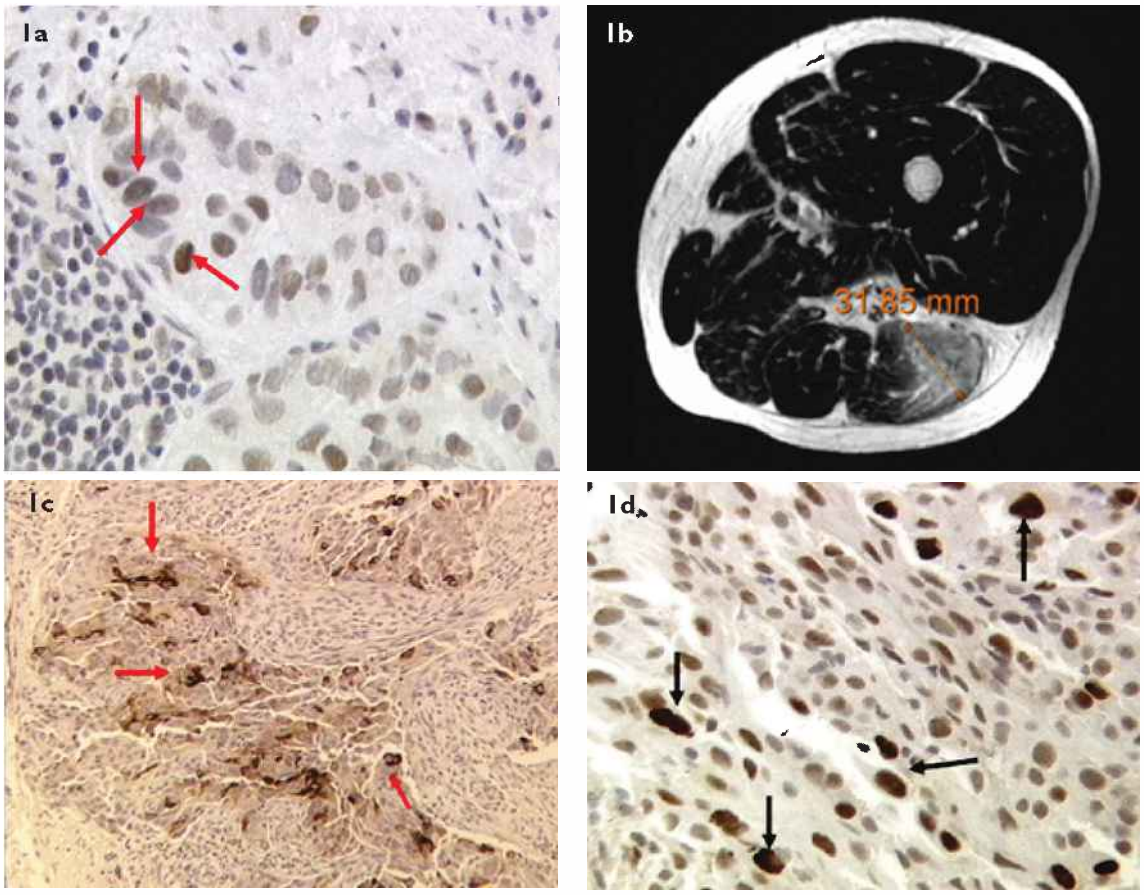

Fig. 1 (a) Thyroid photomicrograph shows p53-positive cells. (b) Axial contrast-enhanced MR image shows thigh muscle metastasis in the biceps femoris (c,d) Photomicrographs from the microbiopsy of the thigh lesion show cells positive for (c) Tg (arrows) and (d) p53 (arrows).

complete thyroid removal and lymphadenectomy. In 1999, a cutaneous metastasis on the neck scar was removed. In July 2000, no uptake was demonstrated on WBS; serum Tg during levothyroxine withdrawal was 3 ng/ml with negative anti-thyroglobulin antibodies (TgAb). Although negative WBS but measurable Tg levels do not rule out a recurrence or residual thyroid tumour, the patient was considered disease-free and no further follow-up was recommended.

The patient was referred to us in December 2003 for suspected mediastinal metastases found on chest radiographs. Physical examination was negative for cervical lymph node enlargement or signs and symptoms of mediastinal syndrome. Laboratory findings were thyroid-stimulating hormone (TSH) values in the normal range (1.65 mcU/ml), Tg 328 ng/ml and negative TgAb. Chest CT showed enlargement (about 5 cm) of mediastinal and tracheal carina lymph nodes, left bronchial compression and diameter reduction, and two metastases in the same lung. A PTC metastasis with a PDTC component was confirmed on a bronchoscopic biopsy, the PDTC being diagnosed on some focal Tg-positive cells (rabbit anti-human Tg polyclonal antibody) and diffuse cell positivity for p53 (mouse anti-human p53 monoclonal antibody). The unusual behaviour of the PTC in a young patient and identification of metastases containing PDTC cells prompted us to analyse the original slides to verify the initial diagnosis. p53 immunostaining of the original thyroid specimen, not performed at the time of diagnosis, showed some positive cells in the classic PTC, consistent with PDTC foci in the primary tumour (Fig. 1a).

Diagnostic WBS after the administration of recombinant human TSH (Thyrogen, Genzyme) demonstrated no ^{131}Iodine uptake, but serum Tg rose to 580 ng/ml.[4] The patient was considered inoperable and in March 2004, underwent ^{131}Iodine treatment (100 mCi) after levothyroxine withdrawal. ^{131}Iodine uptake was shown only in the right subclavicular region; Tg rose to 1.335 ng/ml. A month later, external beam radiotherapy (6,120 Cgy over 34 sessions) and chemotherapy (0.3 mg/kg/week IV cisplatin for four consecutive weeks) were initiated for the mediastinal lesions. During the last week of radiotherapy, the patient reported posterior pain in the left thigh. An indolent mass was found in the biceps femoris on physical examination. A 3.5 cm × 12 cm solid, inhomogeneous mass was confirmed on US

and MR imaging (Fig. 1b). Histological examination of a microbiopsy revealed a lesion with the same Tg and p53 immunostaining patterns as the lung metastasis (Figs. 1c & d). In July 2004, a CT of the brain performed for a drug-resistant headache demonstrated a secondary lesion in the occipital-parietal region. Surgical removal of the mass led to improvement of the headache. The patient was administered a course of polychemotherapy. Two months later, another brain lesion infiltrating the corpus callosum was identified on CT. The patient died in January 2005 after 15 days in a coma.

DISCUSSION

PTC and FTC are slow-growing tumours; metastases are more frequent in lymph nodes and less in the lung and bone. DTC have a good overall prognosis after total thyroidectomy, radioiodine ablation and levothyroxine suppression therapy. Metastases at unusual sites are typical of dedifferentiation and often arise several years from onset. PDTC is a subset of thyroid tumours characterised by intermediate aggressiveness between DTC and anaplastic thyroid cancer. It may arise through a recurrence of previously-treated DTC or may be found at the time of diagnosis of a classic PTC.[8]

We reported an unusual case of PTC associated with diffuse metastases to the skin and thigh muscle six years after diagnosis in a patient considered disease-free after total thyroidectomy and radioiodine treatment. The neoplasm's aggressive course can probably be ascribed to the PDTC component, which was already present in the primary tumour, but was not investigated at the time of diagnosis. p53 immunostaining of the primary thyroid cancer demonstrated two neoplastic cell populations at onset, of which the PDTC one was the likely cause of the fast metastasis process, the subtype probably being responsible for their unusual sites. In fact, DTC usually metastasises to the lymph nodes, lung and bone, and less commonly to the brain. Besides the lung, mediastinal lymph node, bone and brain metastases, our patient also had secondary lesions to the skin and muscle. The skin recurrence in the thyroidectomy scar and the thigh muscle metastasis both arose some years after the initial diagnosis and treatment. The rare cases of muscle metastasis described in the literature are all connected with FTC.[9] To the best of our knowledge, this is the first report of a PTC metastasising to the thigh muscle.

In our patient and in cases associated with kidney rupture, the unusual sites of metastasis probably depend on the PDTC component in the primary tumour, documented by p53 positivity. Overexpression of the p53 gene is considered a prognostic factor for thyroid carcinoma.[10,11]

Moreover, p53 protein overexpression has been detected in PDTC in the absence of p53 mutation. According to some studies, p53 inactivation plays a key role in chemoresistance. It may be surmised that the metastatic lesions with p53-positive cells caused chemoresistance in our patient.[12,13] The patient was considered disease-free on negative WBS but measurable serum Tg. PTC or PDTC recurrences may show no radioiodine uptake, but are still capable of producing and secreting Tg, as in the case of our patient. The best marker of disease recurrence with negative TgAb is therefore serum Tg during levothyroxine suppression and/or during levothyroxine withdrawal, or after rhTSH stimulation.[14] Patients with a measurable Tg and negative WBS should also undergo further investigation with a neck US, chest CT, bone scintiscan and CT-PET.[7] In our experience patients with a measurable Tg frequently have lesions in the neck, mediastinum or lung—which are easily revealed by conventional imaging methods—and rarely in the bone and liver. Levothyroxine suppression should be performed during follow-up because low TSH values appear to decrease the risk of cancer progression.[15]

In conclusion, we have reported a case of PTC with a PDTC component and metastases to the thigh muscle, skin, lung, mediastinum and brain. The tumour's aggressiveness led to death eight years after total thyroidectomy. Histological re-evaluation, including p53 immunostaining, is therefore recommended when a classic PTC arises with diffuse or necrotic lymph node metastases. Patients with measurable Tg and negative WBS should be closely followed-up for possible dedifferentiation of the thyroid neoplasm.

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