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CASE REPORT

Unexpected symptoms after rhTSH administration due to occult thyroid carcinoma metastasis

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ABSTRACT

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scintigraphy is a useful imaging technique in the evaluation of metastasised thyroid carcinoma. Administration of recombinant human thyrotropin (rhTSH, Thyrogen®) increases the diagnostic yield of this procedure. Here we present a 64-year-old male who was followed for Hürthle cell carcinoma of the thyroid with several intrapulmonary metastases. He developed sudden complaints of neck pain following rhTSH administration as part of the routine preparation for a diagnostic ^{18}FDG-PET/CT procedure. This investigation subsequently revealed a previously undetected metastatic lesion in the first cervical vertebra, with no signs of spinal cord compression. Treatment with a nonsteroidal anti-inflammatory drug reduced the symptoms sufficiently, and a few weeks later the neurosurgeon performed a complete resection of the metastasis. It is likely that the symptoms were caused by oedema and/or increased blood flow to the lesion. Physicians should be aware that rhTSH administration to patients with disseminated thyroid carcinoma may lead to sudden onset of symptoms caused by previously occult metastases.

KEYWORDS

Carcinoma, rhTSH, metastasis, side effects, surgery

INTRODUCTION

Generally, patients with differentiated thyroid carcinoma have a good prognosis, although the number of recurrences – within the 20% range – remains relatively high. In patients in whom the clinical symptoms or elevated serum thyroglobulin (Tg) levels suggest such disease recurrence, fluorine-18-labelled 2-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography (PET) is often used to localise metastatic lesions. Already in 2002 our group and others showed that ^{18}FDG-PET during TSH stimulation was superior to ^{18}FDG-PET during thyroxin replacement and/or TSH suppression.[1,2] Several other reports and a recent meta-analysis have confirmed the added value of TSH stimulation, which leads to an increase in both the number of patients with ^{18}FDG-PET true-positive lesions and the number of detected lesions.[3] The application of ^{18}FDG-PET scans after recombinant human thyrotropin (rhTSH) administration can significantly alter clinical management,[3,4] and diagnostic sensitivity can also be improved by combining PET with a computed tomography (CT) scan.[5,6]

TSH stimulation in these patients can be achieved by means of either thyroid hormone withdrawal or administration of rhTSH (Thyrogen®). When there is a suspicion that metastases are localised in or near vital structures such as the spinal cord or cerebrum, thyroid hormone withdrawal may lead to prolonged TSH increase and subsequent stimulation of tumour growth, leading to neurological signs and symptoms. rhTSH is therefore often used to decrease the TSH exposure time. Although rhTSH administration is generally well tolerated, with minimal side effects, there have been reports of side effects in subjects with cerebral or spinal cord metastases.[7] Here we report a patient who, following rhTSH administration, developed complaints of neck pain due to a previously unknown metastatic lesion in the first cervical vertebra.

CASE

Our patient, born in 1947, was healthy until 2005 when he underwent a diagnostic hemithyroidectomy because of a 5 cm mass in the left thyroid lobe. Histological examination revealed Hürthle cell carcinoma. Subsequent treatment consisted of total thyroidectomy followed by ablation with 150 mCi radioactive iodine (^{131}I). A small thyroid remnant was seen on the post-ablation whole-body scan performed after ten days. Six months later, he received a second dose of 150 mCi ^{131}I. During thyroid hormone withdrawal, serum thyroglobulin (Tg) levels were 2.8 ng/ml (desired level <1.0 ng/ml) and serum was negative for anti-Tg antibodies. Post-therapeutic whole-body scintigraphy showed no abnormalities, and no signs of metastases were seen upon additional ^{124}I scintigraphy and magnetic resonance

Imaging (MRI) of chest and mediastinum

Subsequent treatment consisted of suppressive therapy with levothyroxine, and serum Tg levels decreased to 0.22 ng/ml. During the second half of 2007, serum Tg levels gradually increased to 6.2 ng/ml. rhTSH-stimulated ^{18}FDG-PET scintigraphy was therefore performed, revealing two small intrapulmonary metastases with tracer accumulation. A CT scan revealed multiple small (2-7 mm) intrapulmonary nodules suggestive of metastases. In the years that followed, his chest X-ray showed a gradual, albeit very slow, increase in the number and size of the intrapulmonary metastases, and serum Tg levels gradually increased. He experienced no health problems, and was able to exercise and continue all work activities without symptoms.

In the fall of 2011, we performed more extensive staging in order to assess the extent of tumour spread in addition to the pulmonary metastases, and to evaluate the possibility of repeated ^{131}I treatment. One day after administration of two intramuscular injections of 0.9 mg rhTSH, 24 hours apart, the patient developed severe localised neck pain, and was unable to rotate his neck. There were no signs of spinal cord compression. ^{18}FDG-PET with a CT scan revealed –in addition to the known intrapulmonary metastases – a large metastasis in the arch of the first cervical vertebra, with evident bone destruction, but with no compression of the spinal cord. He was treated with high doses of nonsteroidal anti-inflammatory drugs (NSAIDs), which reduced his symptoms, although he remained incapable of rotating his neck for at least 5-6 days. The pain gradually subsided, and he was able to stop NSAID treatment after 2-3 weeks. Four weeks later, the neurosurgeon performed a laminectomy and the metastasis was completely removed. This procedure went without significant blood loss and

Figure 1. *Total body ^{18}FDG-PET scintigraphy revealing multiple intrapulmonary metastases, as well as a metastasis on the left side in the neck, in the cervical vertebral column*

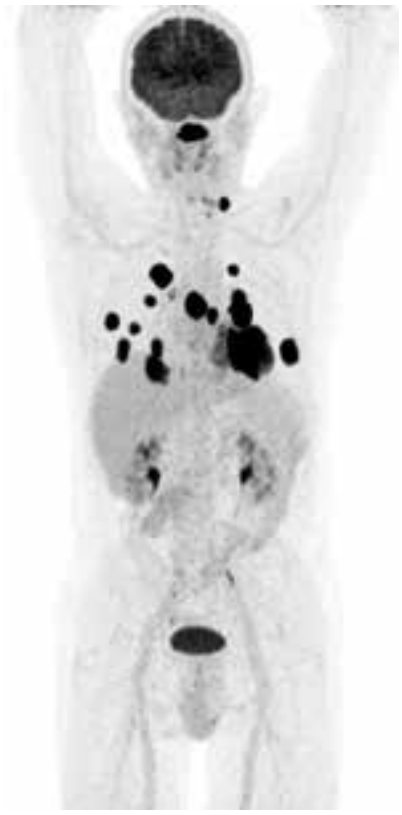
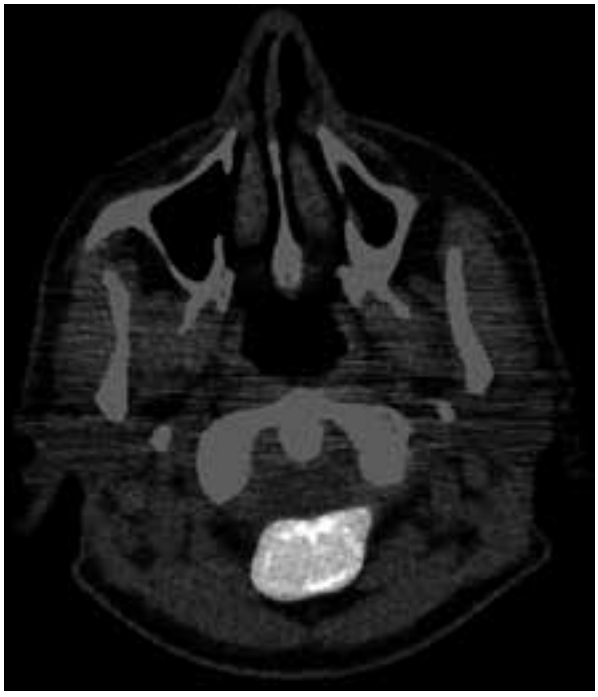


Figure 2. *Fusion of CT scan and ^{18}FDG-PET scan revealing a metastasis in the arch of the first cervical vertebra*



there was no need for instrumented fusion or postoperative immobilisation. Since selective arteriography performed before the operation demonstrated that blood supply to the tumour was limited, the metastasis was not embolised prior to surgery. The histological evaluation was consistent with a metastasis of Hürthle cell carcinoma of the thyroid. MRI of the neck five months later showed no residual tumour mass or recurrence in the neck. The patient did not opt for additional treatment with a targeted agent such as sorafenib.

DISCUSSION

In our patient, rhTSH administration led to symptoms caused by an undetected metastasis in the arch of the first vertebra, secondary to his thyroid carcinoma. His complaints were satisfactorily relieved with NSAID treatment alone. Because of his rapid recovery no glucocorticoids were prescribed and the metastasis was successfully removed by surgery.

In patients with differentiated thyroid carcinoma, rhTSH is frequently administered prior to ^{18}FDG-PET in order to raise circulating TSH levels, thereby improving assessment of the extent of metastases. Although such treatment is generally well tolerated, there are reports of side effects following rhTSH administration. The most common adverse events are nausea (12%) and headache (7%). Post-marketing experience has also shown that rhTSH administration may cause transient flu-like symptoms, including fever, chills, myalgia and headache. Adverse effects of relevance to this case have also been reported. For example, there have been a limited number of reports of patients with known metastases of the central nervous system (CNS) experiencing acute hemiplegia[7] one to three days after rhTSH administration. The package insert for rhTSH mentions that this happened in four out of 55 patients with CNS metastases who were followed in a special treatment protocol.[8] These symptoms have been attributed to local oedema, increased blood flow and/or focal haemorrhage at the site of the cerebral or spinal cord metastases. A case of acute visual loss was reported in a patient with metastasis to the optic nerve.[8] Others have reported sudden, rapid and painful enlargement of locally recurring papillary carcinoma, accompanied by dyspnoea, stridor or dysphonia, which was successfully treated with glucocorticoid therapy.[9,10] A further report concerned a patient who developed haemoptysis and hypoxia three days after rhTSH administration, explained by intratumoural oedema and haemorrhage.[11] Due to the possibility of such side effects, pretreatment with glucocorticoids has been recommended for patients in whom local tumour expansion may compromise vital anatomic structures.[8,9]

In patients with known distant metastases of thyroid carcinoma, doctors should anticipate the possible development of bone or brain metastases. The ^{18}FDG-PET technique is routinely used in our hospital to assess tumour dissemination after stimulation with rhTSH since numerous reports have shown that uptake of the ^{18}FDG-PET tracer is higher in both patients withdrawn from thyroxin to stimulate endogenous TSH and in those stimulated with rhTSH.[1,3,4,12] These findings have been supported by *in vitro* data showing increased uptake of ^{18}F-deoxyglucose in cultured thyroid cancer cells in the presence of TSH.[13] Despite these reports, the current guidelines of the American Thyroid Association (ATA) state that stimulation with endogenous TSH following thyroxin withdrawal or rhTSH may only minimally enhance the sensitivity and specificity of ^{18}FDG-PET scanning.[14]

In summary, we report a patient with sudden onset of neck pain following administration of rhTSH for diagnostic purposes. The symptoms were caused by vertebral metastasis. Patients and clinicians should be aware that rhTSH administration may lead to a sudden increase in blood supply to a tumour or an increase in oedema, thereby causing symptoms due to previously occult metastases of thyroid carcinoma.

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