Clinical note

Disseminated bone metastases from occult thyroid cancer effectively treated with debulking surgery and a single dosimetry-guided administration of radioiodine

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A R T I C L E   I N F O

Article history:
Received 6 August 2014
Accepted 30 September 2014
Available online 6 November 2014

Keywords:
Thyroid
Bone metastases
Dosimetry
Surgery
rTSH

A B S T R A C T

In this paper we report on a successful management of multiple bone metastases from differentiated thyroid cancer. In 2007, a 75-year-old female patient, previously referred for thyroidectomy for multinodular goiter, underwent surgical removal of a lumbar mass with histological findings of metastasis from well differentiated thyroid cancer. After surgery, serum thyroglobulin (sTg) was 204.4 ng/mL. A diagnostic/dosimetric 123I WBS was performed, following stimulation by rTSH. Serial WBSs were acquired, along with SPECT/CT and bone scan for localization of lesions. sTg raised to 3.810 ng/mL, and 123I WBS showed thyroid remnants and numerous areas with high iodine-uptake corresponding to skeletal sites, the two largest loading on the skull, with osteolytic pattern. Calculated radiation absorbed dose for skull lesions, determined by mean of MIRD methodology, was 63.5 mGy/Mbq.

The patient underwent surgical removal of the two major skull lesions. Successively, 100 mCi 131I was administered after stimulation by rTSH, with stimulated sTg 297 ng/mL. After 8 months, diagnostic WBS was negative both for remnants and metastases and rTSH-stimulated Tg was 0.6 ng/mL. To date, the patient has maintained sTg values <1 ng/mL during L-T4 suppressive therapy and after rTSH stimulations.

In this unusual case of extensive bone cancerous involvement with high iodine avidity, a multidisciplinary approach based on surgery and dosimetry-guided radiometabolic therapy allowed to accurately assess the patient, execute a small number of treatments and achieve a complete remission of the disease in a very short time, with no additive morbidity.

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Metástasis óseas diseminadas de un carcinoma de tiroides oculto tratado efectivamente con cirugía citorreductora y administración simple de radioyodo rastreado con dosimetría

R E S U M E N

En este trabajo presentamos el abordaje adecuado de múltiples metástasis óseas de un cáncer diferenciado de tiroides.

En 2007, una mujer de 75 años previamente remitida para tiroidectomía por bocio multinodular, se sometió a la extirpación quirúrgica de una masa lumbar con resultado histológico de metástasis de cáncer bien diferenciado de tiroides. Tras la cirugía, los niveles séricos de tiroglobulina (Tgs) fueron 204.4 ng/mL. Se realizó un rastreo de cuerpo completo diagnóstico/dosimétrico con 123I después de la estimulación con rTSH. Se adquirieron rastreos seriados junto con SPECT/TC y gammagrafía ósea para la localización de las lesiones. Los niveles de Tgs se elevaron a 3810 ng/mL y el rastreo de cuerpo completo con 123I demostró captación en restos tiroides y en numerosas localizaciones esqueléticas, las dos de mayor tamaño en la calota con un patrón osteolítico. La dosis absorbida calculada para las lesiones de calota, determinada mediante metodología MIRD, fue 63,5 mGy/Mbq.

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Introduction

Although differentiated thyroid cancer (DTC) accounts for only 1–2% of all new malignancies, it is the most common endocrine tumor and its incidence has been constantly rising over the last 20–30 years. Well-established patient-related and tumor-related factors which influence prognosis are age at diagnosis, tumor size and follicular histology. Other unfavorable prognostic factors include the presence of distant metastasis, age at the time of their discovery, their localization (osseous vs. nonosseous) and extension. The lack of (radio)iodine avidity predicts poor prognosis.

Bone metastases account for about 2–13% of all DTC distant metastases and are more prevalent in follicular histotype. They are predominantly osteolytic, and localized in regions where blood flow is high, such as the axial skeleton red marrow (vertebrae, ribs and hips). Radiometabolic therapy with $^{131}$I radioiodine (RAI) remains the prime treatment modality in patients whose bone metastases maintain iodine avidity, possibly associated with local treatments such as external beam radiation therapy or debulking surgery when indicated. The main criteria for therapeutic decisions include: risk of pathologic fracture and neurologic damage from spinal cord compression in the case of vertebral lesions, presence of pain, RAI avidity, and potential bone marrow damage from radiation. The guidelines of the American Thyroid Association recommend complete surgical resection of isolated symptomatic metastases, especially in patients <45 years old with slowly progressive disease. Even though it is defined as “rarely curative”, RAI therapy is nonetheless recommended in patients with multiple iodine-avid bone metastases. RAI activity to be administered can be chosen empirically (100–200 mCi) or determined by dosimetry. In order to optimize the complex management decisions in such patients, multidisciplinary care has been advocated.

We describe here a peculiar case of a patient with extensive, disseminated bone metastases from DTC in whom combined surgery and low RAI treatment following radiosimetry estimates led to effective, ongoing recovery of the disease.

Case report

In January 2007, a 75-year-old woman was admitted to the Neurosurgery Department due to a swelling in the median thoracolumbar region. The patient had previously undergone thyroïdectomy (in 2004) for multinodular goiter and had been subsequently treated with substitutive L-thyroxine (L-T4). The back lesion was not painful, and neurological examination was negative. TC showed a neof ormation with modest contrast enhancement, originating from the spinous process of L1. The initial diagnostic suspicion included possible neoplastic nature or an aneurys mal bone cyst.

A D12-L1 spinolaminectomy was performed, with “en-block” removal of the 6.4 cm × 5 cm × 3.7 cm neoplasm which bled very easily. There was no impairment of the dural sac evident macroscopically. Conventional Hematoxylin & Eosin (H&E) stain ing showed diffuse infiltration of the bone by thyroid-like tissue, consisting of follicles of variable size, lined by epithelial cells with occasionally enlarged and clear nuclei (Fig. 1). At immunohistochemistry the neoplastic cells were positive for both thyroglobulin and thyroid transcription factor (TTF-1). The final diagnosis was bone metastasis from well differentiated thyroid carcinoma.

In February 2007, the patient was referred to the Nuclear Medicine Department for comprehensive re-assessment of her thyroid cancer disease. She was asymptomatic and ultrasonography of the neck revealed only minimal post-thyroidecotomy fibrous tissue without loco-regional recurrences. Her serum thyroglobulin (sTg) level during substitution T-T4 therapy was 204.4 ng/mL. A stimulation test with recombinant thyrotropin (rTSH) was then performed, based on sequential sTg measurements and a radioiodine whole-body scan (WBS) for diagnostic and radiodismetric purposes. A standard dose of 0.9 mg rhTSH (Thyrogen®, Genzyme Transgenics Corp., Cambridge, MA) was injected i.m. on two consecutive days. On the third day, the sTg level reached 3810 ng/mL and the patient experienced clinically obvious painful swelling at the vertex of her skull.

For WBS, $^{123}$I sodium iodide (444 MBq, 12 mCi) was administered i.v. on the day after the second rhTSH injection, and serial WBS acquisitions were recorded with a dual-head gamma camera at 6, 24, 30 and 48 h (Fig. 2). A calibrated reference source of $^{123}$I (74 MBq, 2 mCi) was included in the field of view. After acquiring the 48-h WBS, $^{99m}$Tc HDP (370 MBq, 10 mCi i.v.) was injected and a simultaneous double-peak whole-body bone scan was acquired 3 h later (Fig. 2). SPECT/CT imaging of the head and neck region was also acquired at 24 h, using a hybrid dual-head SPECT/CT gamma camera (Infinia Hawkeye, GE Healthcare).

$^{123}$I WBS showed obvious thyroid remnants and more than 30 areas with high radioiodine uptake. The $^{99m}$Tc-HDP bone scan confirmed that all foci of $^{123}$I uptake corresponded to skeletal sites, although only few of the metastatic sites exhibited an enhanced uptake of the bone-seeking radiopharmaceutical. SPECT/CT showed that the two largest lesions located in the posterior parietal skull had a prevalent osteolytic pattern.

A diagnostic CT of the skull without contrast described the lesions in the parieto-occipital median region and in the parietal right-paramedian region of the vertex. No intracerebral metastases were detected, whilst impairment of the superior sagittal sinus (SSS) was not assessable without administration of iodinated contrast medium. Additional imaging (chest X-ray and ultrasonography of the abdomen) excluded visceral metastases.

Dosimetric estimates

The absorbed doses in the metastatic lesions were estimated according to MIRD methodology as follows. Selected areas of abnormal radioiodine uptake in the $^{123}$I WBS images were evaluated quantitatively, using computerized analysis of regions of interest obtained from conjugate planar views. The masses of the relevant
Figure 1. Diffusely infiltrated bone with clearly identifiable thyroid tissue, consisting of follicles of variable size (A, H&E staining, original magnification 10×), sometimes dilated in cystic structures filled with colloid and lined by epithelial cells (parietal cells) with occasionally enlarged and clear nuclei (B, arrow, original magnification 40×). Immunohistochemistry (streptavidin-biotin peroxidase complex, original magnification 40×) confirmed thyroid differentiation with positive staining for TTF-1 (nuclear staining, C) and thyroglobulin (cytoplasm staining, D).

Table 1
Dosimetric calculated absorbed doses. Dosimetric estimates.

<table>
<thead>
<tr>
<th>Lesion site</th>
<th>Mass (g)</th>
<th>Maximum uptake (%)</th>
<th>$^{131}$I effective half-life (h)</th>
<th>Absorbed dose (mGy/MBq)</th>
<th>Absorbed dose for 100 mCi (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parieto-occipital</td>
<td>17.7</td>
<td>21</td>
<td>28.5</td>
<td>63.5</td>
<td>235</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.88</td>
<td>0.3</td>
<td>23.6</td>
<td>15.5</td>
<td>57</td>
</tr>
<tr>
<td>Left parietal</td>
<td>0.01</td>
<td>0.08</td>
<td>72.4</td>
<td>818.4</td>
<td>3026</td>
</tr>
</tbody>
</table>

Figure 2. (A) Anterior and posterior views of WBS acquired 6 h after $^{123}$I injection, showing multiple abnormal uptake areas beyond the expected thyroid remnants. Underfoot a tube containing $^{123}$I 90 MBq was positioned as an external reference source for dosimetric purposes. (B) Anterior and posterior views of simultaneous double-peak WBS acquired 48 h after $^{123}$I injection and 3 h after $^{99m}$Tc-HDP injection (energy peaks: 159 KEV for $^{123}$I and 140 KEV for $^{99m}$Tc, energy window 15% for both). Bone scan confirmed the correspondence of all foci of iodine-uptake to skeletal sites: spine, ribs, left scapula, right humerus, pelvis, right femur and right tibia. Bone images showed a large uptake in the skull and some areas with weak uptake in the spine.
metastases in the skull were calculated from CT images of the head. Fractional uptake in the lesions was calculated by extrapolating the sequential 6-h, 24-h, 30-h, and 48-h measurements back to time zero, corrected for physical decay and background activity to obtain the effective half-time of $^{123}$I in lesions; these values were then converted into the effective half-time of $^{131}$I. The lesions were assumed to have a spherical shape. The dose conversion values reported in OLINDA/EXM were used. The estimated absorbed dose in the major skull lesions was 63.5 mGy/MBq, hence administering 3700 MBq (100 mCi) of $^{131}$I was expected to deliver around 250 Gy to the lesions (Table 1).

For the absorbed doses estimation in the red bone marrow, blood activity was measured. The calculated bone marrow absorbed dose deriving from 3700 MBq $^{131}$I was expected to be extremely low, <0.02 Gy.

Further treatments

In June 2007, the patient underwent a second neurosurgical procedure, i.e., resection of the two skull metastases with a large bone flap, spanning across the SSS, which was not involved; cranioplasty with polymethylmethacrylate (PMMA) were performed. Histology confirmed metastases from well differentiated thyroid cancer (Fig. 3).

In July 2007, RAI therapy was performed by administering 3700 MBq $^{131}$I following stimulation with rhTSH. TSH-stimulated sTg was 297 ng/mL. Post-therapy WBS confirmed high RAI uptake in disseminated bone lesions and in the thyroid remnants. Some residual RAI uptake was also detected in the skull, corresponding to the surgical bed (Fig. 2).

Long-term follow-up

Three and five months after RAI therapy, sTg was 0.7 ng/mL and 0.0 ng/mL, respectively, under suppressive L-T4 therapy. In March 2008 (8 months after RAI therapy), tumor response to treatment was assessed through a diagnostic $^{123}$I WBS and sTg assays after stimulation with rhTSH. TSH-stimulated Tg was 0.6 ng/mL and WBS was negative for both remnants and metastases (Fig. 3B). To date, the patient has maintained sTg values ranging from 0.0 to 0.7 ng/mL during L-T4 suppressive therapy. rhTSH stimulation tests performed in 2010 and 2012 were negative, with sTg peaks of 0.3 ng/mL and 0.0 ng/mL, respectively.

Histopathological re-assessment

Tissue samples from the patient’s thyroid and bone metastases were retrieved and re-examined. No tumoral foci were present in the thyroid samples. Immunohistochemistry of metastatic tissues revealed marked thyroid cellular differentiation with positive staining for TTF-1 and thyroglobulin (Fig. 2). Molecular analysis did not reveal BRAF and RAS gene mutation.

Discussion

Bone metastases as the first manifestation of DTC are rare, and generally associated to poor response to radiation treatments.
Our case is additionally unusual for two reasons: (1) missed histological diagnosis of the primary tumor, and (2) disseminated skeletal metastases characterized by a very high radioiodine uptake. Because of the extensive metastatic involvement of the skeleton, the advanced age at diagnosis, and the high sTg values, the patient was initially stratified in a poor prognostic category. Therefore, our intention to treat was more likely to be palliative than curative.

The first therapeutic approach took into special consideration the two major metastases in the skull. On the one hand, the use of RAI therapy could prevent surgery-related risks, especially SSS damage, with possible thrombosis and hemorrhage. On the other hand, local accumulation of $^{131}$I (delivering more than 200 Gy to lesions) could cause brain/meningeal damage, considering the dose limits to normal tissues for brain irradiation. In this regard, Sisson et al. reported an analogous case of skull metastasis from DTC, in which the RAI therapy was calculated to have delivered 100 cGy to the brain at 1–2 cm distance from the tumor. Therefore, RAI uptake in the tumor was only 4–6%, 5-folds lower than in this case.

Surgery combined with RAI therapy represents a convincing therapeutic option for bone metastasis from DTC, as it contributes to a statistically significant benefit in overall survival. In this patient, the CT scan did not show any brain involvement, thus ruling out the bleeding risk associated with surgical intervention possibly involving cerebral parenchyma. The surgical resection of a wide bone flap ensured maximal removal of the metastatic lesions, and cranioplasty with PMMA minimized the esthetic damage. This synthetic resin is used to repair cranial damage/defects. It does not stick to the underlying dural patch, and its pliability ensures satisfactory cosmetic results.

For the second step of therapy, high iodine avidity of the metastatic lesions played a key role in the favorable clinical outcome of the patient. In fact, the minimum recommended RAI activity to treat metastatic disease resulted to be fully curative. A quite low success rate has been reported for RAI therapy in DTC patients with bone metastasis, negative WBS being usually attained only after multiple RAI courses and in patients with small lesions. Furthermore, dosimetric estimates regarding RAI therapy for DTC bone metastases have rarely been reported. A dosimetric study conducted in 19 RAI treatments estimated tumor radiation doses varying widely between 1.3 and 368 Gy, with effective half-lives ranging from 0.5 to 6.5 days for different lesions. In our patient, the estimated absorbed doses ranged between 57 and 3026 Gy across different metastatic lesions in the body, with effective half-lives ranging between 0.9 and 3.0 days. These values are of the same order of magnitude as those usually reported for thyroid remnants. In a more recent study based on quantification of radioiodine uptake using PET with T1-124 iodide, the lesion absorbed dose calculated for $^{131}$I was classified with high potential for cure if greater than 10 Gy/GBq. In our patient, the absorbed dose ranged between 15.5 and 818.4 Gy/MBq for different metastatic lesions.

Such a high iodine avidity correlates with certain biological and genetic features, i.e., the marked cellular differentiation as assessed both by conventional H&E staining and by immunohistochemical staining for TTF-1 and Tg. Furthermore, such a highly differentiated histologic pattern was consistent with the absence of oncogenic BRAF activation and RAS mutations. In this regard, some unfavorable features associated with reduced expression of thyroid-specific genes have been reported in DTC. In particular, reduced expression of the sodium-iodide symporter (NIS), which is the main factor controlling iodide uptake by thyroid-derived cells, has frequently been associated with worse response to RAI, and reduced expression of TTF-1 and Tg have also been described in some DTCs. BRAF V600E and RAS mutations, although present with different prevalence among thyroid cancer histologic subtypes, have also been identified as a negative prognostic factors. Finally, it is essential to emphasize the crucial role that a multidisciplinary clinical approach involving specialists in nuclear medicine, neurosurgery and medical physics played in this case. This approach made it possible to accurately assess the patient, to plan and perform the therapeutic interventions and to achieve complete remission of the disease in a very short time, with no additional treatment-related morbidity.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**

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