Clinical case

Thyrotoxicosis revealing metastases of unrecognized thyroid cancer: a report on two cases

Thyrotoxicose révélant un cancer thyroidien métastatique méconnu : à propos de deux cas

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Résumé

Nous rapportons le cas de deux patientes ayant présenté une thyrotoxicose révélant des métastases fonctionnelles d’un cancer thyroïdien folliculaire. Ces métastases étaient localisées au niveau hépatique, rénal et osseux dans un cas ; pulmonaire dans l’autre cas. Ces deux patientes avaient bénéficié d’une thyroïdectomie pour un nodule bénin plus de 15 ans avant le diagnostic des métastases fonctionnelles. Dans les deux cas, le cancer n’avait pas été identifié lors de la première intervention, mais a été révélé plusieurs années plus tard par la thyrotoxicose. Un traitement par iode radioactif a eu, dans les deux cas, une efficacité rapide sur la thyrotoxicose, mais l’efficacité sur l’extension métastatique a été différente pour chaque patiente. Dans le premier cas, la patiente est décédée après quelques années sans aucun contrôle du tissu métastatique, alors que celui-ci a disparu en quelques mois pour la seconde patiente qui reste en rémission plus de dix ans plus tard. La physiopathologie et l’évolution de ces deux cas sont discutées avec les données de la littérature.

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Abstract

We report two cases of thyrotoxicosis-revealing functional metastases of a follicular carcinoma that extended to the bones, liver and kidneys in one case and to the lungs in the other. Both patients had undergone surgical intervention for a thyroid nodule more than 15 years before the diagnosis of thyrotoxicosis and metastatic dissemination. In both the cases, the carcinoma was not recognized by the pathologist after the first surgical intervention, but was finally diagnosed several years later due to the occurrence of thyrotoxicosis. Iodine-131 therapy was effective at suppressing the thyrotoxicosis in both the patients. The effectiveness on the metastatic extension was very different for each patient: in the first case, the patient died a few years later without any control of the metastatic tissue. For the second patient, the metastases disappeared a few months after radioiodine treatment, with the patient still in remission more than 10 years later. The physiopathology and the evolution of these two cases are discussed with the data available in the literature.

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Mots clés : Nodule thyroidien ; Cancer folliculaire ; Métastases ; Thyrotoxicose ; Traitement radio-isotopique

Keywords: Thyroid nodule; Follicular carcinoma; Metastases; Thyrotoxicosis; Radioiodine therapy

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1. Introduction

Thyrotoxicosis associated with a carcinoma of the thyroid is not a frequent occurrence [15,21]. Most cases are common associations of a cancer and a multinodular goiter or Grave’s disease. Rarely, hyperthyroidism can be related to functional metastases of a well-differentiated cancer. This situation was recently observed in two of our patients, and was singular since the cancer was revealed by functional metastases a long time after surgery for an apparently benign goiter or nodule. Moreover, the prognosis was very different in both cases.

2. Case 1

The first patient was 46 years old; in 1968, when she underwent a partial right thyroidectomy because of a bulky multinodular goiter that was responsible for a tracheal dyspnoea. Thyroid function tests were normal at this time.

During the surgical procedure, examination of the left thyroid showed no abnormalities and it was therefore not removed.

Histological analysis concluded that the lesion was a benign goiter that included a hematocoele. Thus, no suppressive treatment was prescribed.

One year later, she developed a goiter on the remaining part of the gland, which led to further surgery where a subtotal thyroidectomy on the left lobe was performed. The pathological examination concluded again that it was a benign multinodular goiter, with local inflammatory and necrotic regions.

Because of the severe and compressive recurrence and the inability to realize a complete surgical thyroid removal, LT3 (25 μg per day) was prescribed to avoid the growth of the remaining gland (LT3 was chosen because this history takes places during the sixties, when LT3 therapy was considered as a more suppressive therapy than LT4). This treatment was stopped by the patient after a few years.

Twenty-four years after the first surgical intervention, the patient consulted her physician for symptoms of thyrotoxicosis that were evolving since several months. The hyperthyroidism was confirmed by laboratory tests. Serum TSH level was low (0.15 μUI/mL), and FT3 and FT4 were elevated at 11 and 27 ng/L, respectively (normal values 2.6–5.2 ng/L and 7–17 ng/L, respectively). Serum thyroglobulin level was high at 8500 ng/mL (normal range, 0–43 ng/mL). There were no TSH-receptor antibodies.

Surprisingly, she had presented with three separated right humeral fractures during the past 3 years. On the third presentation (a few days after the biological confirmation of the thyrotoxicosis), a humeral head prosthesis was installed, and a histological examination of the pathological bone found a metastatic localization of a well-differentiated follicular thyroid carcinoma.

X-ray and technetium scintigraphy of the extension showed that there were multiple uptake points in the entire skeleton. The abdominal CT-scan revealed multiple metastases of the liver and kidneys. There was a heterogeneous laterotracheal nodule in the neck. All these lesions were visualized using iodine-131 whole-body scintigraphy (Fig. 1). For this reason, hyperthyroidism was referred to the residual thyroid and the functional metastases of the thyroid carcinoma.

A second evaluation of the histological slides of the first intervention (slides of the second intervention were no longer available) identified the presence of a well differentiated follicular (trabeculo-vesicular) cancer of the thyroid, that had not been diagnosed 24 years earlier (data concerning vascular invasion and thyroid capsule were not available, due to the retrospective histological confirmation of the carcinoma, 24 years after the surgery). Residual thyroid tissue was not removed. The treatment consisted of seven doses of iodine-131 (total dose 1050 mCi). The effectiveness of the treatment was rapidly apparent on the hyperthyroidism. FT3 and FT4 were normalized after two doses of radioiodine. Then, the oral hormonal suppressive therapy was started with LT4 25 μg per day and gradually increased to 75 μg per day. There was no decrease in bone pain. No complete effect on the total corporeal radioiodine was observed, nor in the thyroid bed nor in the other uptake sites: uptake initially slightly decreased in abdominal sites, but then rapidly reincreased. A slight transient decrease of thyroglobulin level was also observed, suggesting partial control of the metastatic extension, but it later increased (Fig. 2).

The disease kept advancing and surgical intervention was needed for a threatening vertebral metastase.

Despite the radioisotopic, surgical and hormonal therapies and general nursing, the condition of the patient continued to deteriorate. She died 2 years after the diagnosis of metastatic carcinoma, 28 years after the first surgical intervention.

3. Case 2

The second patient was 29 years old in 1970 when she first discovered a solitary thyroid nodule of 5 cm.
Because of the progressive growth of the nodule, surgical treatment consisting of an enucleation of the nodule was carried out 3 years later. The scintigraphy showed that it was hot and extinctive on the rest of the gland, but there were no clinical signs of thyrotoxicosis, FT4 was normal at 11 ng/L (normal range 9–22 ng/L). The chest X-ray was normal.

Histological examination of the nodule showed no sign of malignancy and it was interpreted as a microfollicular adenoma.

The patient was then treated by LT3 (25 μg per day) for 1 year.

Twenty-one years later, she exhibited symptoms of a mild thyrotoxicosis, confirmed by biological tests that showed low levels of TSH (0.12 μU/mL; normal range, 0.46–4.9 μU/mL), elevated level of FT3 (6.5 ng/L; normal range, 2.6–5.2 ng/L) but normal level of FT4 (11.4 ng/L; normal range, 7–17 ng/L). The serum thyroglobulin level was 80 ng/mL (normal range 10–40 ng/mL). No stimulating TSH-receptor antibodies were detected.

Three months later, a chest X-ray revealed bilateral multiple nodular shadows indicating metastatic lesions (Fig. 3). While TSH level was < 0.02 μU/mL, radioactive iodine (5 μCi) administration showed no uptake at the thyroid level, but an intense uptake in the pulmonary nodules without any other uptake zone (Fig. 4). Histological examination of one of the pulmonary nodules confirmed the diagnosis of metastatic dissemination from a follicular thyroid carcinoma.

With the aim of obtaining histological data and improving the efficacy of radioactive iodine and the survey, residual cervical thyroid tissue was surgically removed. There was no evidence of carcinoma on histological examination. However, a review of the first pathological specimens of the nodule removed 21 years earlier favored a well-differentiated follicular carcinoma.

Just before surgery, 4 months after the initial biological evaluation, TSH was inferior to 0.02 μU/mL, FT3 and FT4 levels were both elevated, respectively, at 10 ng/L and 26 ng/L, and the thyroglobulin level was high (450 ng/mL, normal range 10–40 ng/mL).

The treatment consisted of radio-iodine therapy. After one dose of Iodine-131, the thyrotoxicosis dissipated and the TSH level increased. A suppressive treatment (levothyroxin, 125 μg per day) was started. After only two doses of iodine-131 (total dose 200 mCi), thyroglobulin (with thyroxin withdrawal) was undetectable (Fig. 5), and whole-body scintigraphy did not show any uptake.
Fig. 5. Évolution des taux de thyroglobuline (Tg) et de TSH de la patiente 2 avant et après traitement par iode radioactif. Les étoiles indiquent les dates des traitements par iode 131. Valeurs normales : TSH : 0,35–5,5 μ UI/ml, thyroglobuline : 10–43 ng/ml.

Thirteen years after the second surgical intervention, the patient remains asymptomatic, her thyroglobulin level is still undetectable, and follow-up chest X-rays and chest CT show no abnormal features.

4. Discussion

The association of hyperthyroidism and thyroid carcinoma is considered as being rare or even antinomic [15,21]. More than one mechanism can explain this coincidence. Firstly, juxtaneoplastic hyperthyroidism concerns incidental cancers in patients who are operated on for a thyroid nodule, a goiter or Grave’s disease. Secondly, paraneoplastic hyperthyroidism is related to tumors that produce HCG, TSH or improbably TRH. Finally, neoplastic hyperthyroidism results from gonadal teratomas or functional metastases of a thyroid cancer that directly produces thyroid hormones (Table 1). This third situation is the one concerning the two patients we have described here. This situation has already been reported about fifty times, mostly in case reports, during the last 30 years [1,3,6–9,11–17, 19,20,22].

In our two cases, metastatic disease was revealed by thyrotoxicosis, as in 50% of the published cases of functional metastases of thyroid cancer [15,21].

The thyrotoxicosis and the cancer are synchronous in half the cases, and separated by a few months to 20 years in the other half [15,21].

The event-free times elapsed between the first manifestation of the thyroid cancer (missed at the first histological examination in our two present cases) and the expression of the metastases, observed through the thyrotoxicosis in these observations, are among the longest described in the literature: 24 and 21 years (Table 2).

These two observations confirm the difficulties of histopathological diagnosis of follicular carcinomas, for which it is sometimes difficult to distinguish from a follicular benign adenoma, principally when they are well differentiated. Indeed, it is said that “thyroid cancers give to the pathologists the greatest lessons of humility” (P MASSON).

Thyrotoxicosis caused by thyroid follicular metastases is principally the consequence of multiple metastatic localizations, with a large tumoral volume [15], because there is in fact a small functionality of these metastases when compared to the normal thyroid [19]. This functionality is also a consequence of the good differentiation of the tumors, giving them the capacity to uptake iodine and to produce thyroglobulin (this is also the cause of the misinterpretation at the first pathological examination in our two observations). In some cases, this situation could be explained by mutations of the TSH-receptor gene that have been found in one case of hyperfunctionning insular thyroid carcinoma [18]. Such mutations stimulate both the growth and function of the tumoral tissue by the bias of a constitutive activation of the cAMP cascade. This functionality of the metastatic tissue is more frequently observed in patients living in an iodine-deficient environment [6], and the thyrotoxicosis can be induced by iodinated contrast media [12]. Stimulating anti-TSH-receptor antibodies have also been observed in a few cases and can also take part to the functionality of the metastatic tissue [2,5,10].

In the two observations described here, as in most of the cases of functional metastases of thyroid cancer described in the literature, FT3 levels were higher than FT4 levels [6–9, 11,17]. The mechanism responsible for this phenomenon is unclear, but the role of the iodine-deficient environment should be considered [6], as well as the inability of thyroid cancer cells to take up iodine [19] and the levels of type 1 and type 2 deiodinases expression in the tumoral tissue [17,20].

The treatment is based on intensive postsurgical radioiodine therapy. The efficiency of this treatment is evident concerning the thyrotoxicosis, but less evident with respect to the meta-

Table 1

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<th>Classification of the associations of hyperthyroidism and cancer [1]</th>
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**Juxtaneoplastic hyperthyroidism:**
- Coincidence of cancer and hyperthyroidism in:
  - Multinodular goiter
  - Grave's disease
  - Solitary toxic nodule

**Paraneoplastic hyperthyroidism:**
- Cancers thyro-stimulating:
  - Secretion of HCG: testicular, ovarian, placental and extra gonadic choriocarcinoma
  - Secretion of TSH: thyreotropic pituitary carcinoma
  - Secretion of TRH (?)

**Neoplastic hyperthyroidism:**
- Hyperthyroidism caused by excessive thyroid hormone production by:
  - Functional metastases of thyroid cancer
  - Carcinomatous toxic nodule
  - Carcinomatous Grave’s goiter (?)
  - Toxic ovarian goiter
static tumors particularly when they are large, and it is this second element that determines the prognosis [15].

Finally, the prognosis of these thyroid carcinomas associated with thyrotoxicosis is not different from the prognosis of the other well-differentiated cancers. It principally depends on the age of the patient and the stage of the disease (tumoral volume) as well as differentiation degree and ability to uptake iodine. Indeed, the cancers that cause thyrotoxicosis are frequently discovered at more advanced stages [1]. Differences of evolution observed between our two patients can then be explained by the younger age and the less important volume of metastases in patient 2, which both are important prognosis factors determining the response to radioactive iodine and the survival in follicular cancers [4], independently of the presence of thyrotoxicosis. Unfortunately, it was not possible to determine exactly the histological characteristics of the tumors in reason of the retrospective diagnosis of the cancer in both cases, a long time after the initial surgery. Moreover, we did not have the opportunity to study metastases histologically in order to see if their pathologic characteristics were concordant with the primary tumor.

In conclusion, neoplastic hyperthyroidism occurs only rarely. It must be evoked when there is no increase of the TSH after a thyroidectomy, or during the period of interruption of the suppressive treatment. The level of thyroglobulin is elevated (permitting the differential diagnosis with factice thyrotoxicosis), and whole-body scintigraphy reveals the metastatic extension. Treatment consists of iodine-131 therapy, and is effective for thyrotoxicosis. However, the prognosis is not good and is principally dependent on the degree of metastatic extension.

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