CASE REPORT

Long-term survival in a patient with brain metastases of papillary thyroid carcinoma

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SUMMARY

We present the case of a 43-year-old woman who underwent total thyroidectomy with bilateral lymphadenectomy for a papillary thyroid carcinoma (PTC), solid variant (T4bN1bMx), with V600E *BRAF* mutation. After ablative therapy, she presented undetectable thyroglobulin (Tg) but progressively increasing anti-Tg antibodies (TgAbs). During follow-up, nodal, lung and brain metastases were identified. She was submitted to surgical excision of lung lesions, radiosurgery of brain metastases and five radioiodine treatments. The latest brain MRI showed no lesions, pulmonary CT showed stable micronodules and there was progressive reduction in TgAbs. This is a peculiar case of a PTC with lung and brain metastatic lesions detected through TgAbs. Initial histological and molecular study suggested a more aggressive clinical behaviour, which was eventually confirmed. Although PTC brain metastases are extremely rare and present poor prognosis, our patient presented a good response to treatment and longer survival than usually reported for similar cases.

BACKGROUND

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma, representing almost 85% of newly diagnosed cases.[1] PTC has a relatively benign course, with a 10-year survival rate of 90–95%.[2] In adults, the frequency of nodal metastasis may approach 90%, and is minuscule in half the cases, without repercussion on patient prognosis.[3 4] Only 10–15% of patients with differentiated thyroid carcinoma develop distant metastasis, with lungs and bones as the most frequently involved organs.[5 6] Brain metastasis occurs only in 0.1–5% of cases.[7] These lesions can be either totally silent or very symptomatic and life-threatening. When present, they can cause a significant reduction in survival. The median overall survival reported in a previous series after brain metastasis diagnosis is 9.4 months.[8–18]

We report a peculiar case of a young woman with PTC. This patient not only had positive thyroglobulin autoantibodies (TgAbs), used as a marker of clinical evolution, but also developed brain metastasis. After being submitted to an aggressive multimodal treatment approach, she presented a significantly longer survival than that usually described for similar situations.

CASE PRESENTATION

We report a case of a 43-year-old woman with a history of PTC (pT4N1bMx) submitted to total thyroidectomy with bilateral lymphadenectomy followed by radioactive iodine (RAI) remnant ablating after levothyroxine withdrawal (April 2000). The histological study confirmed a PTC, solid variant, devoid of capsule and with extra-thyroid tissue invasion; massive metastases were found in 9 left and 13 right cervical lymph nodes. The molecular study of the tumour revealed the presence of the V600E BRAF mutation with neither telomerase reverse transcriptase (TERT) nor NRAS alterations.

The patient received 170mCi of RAI (^{131}I) for ablation; a post-therapy whole body scan (WBS) showed strong cervical uptake compatible with thyroid remnants, together with a lesion on the suprasternal notch area and diffuse bilateral pulmonary uptake. Subsequently, the patient was maintained under suppressive therapy with levothyroxine.

After initial treatment, her thyroglobulin (Tg) levels progressively reduced to values <1 ng/mL after 14 months, but her TgAbs never decreased below the positive cut-off level, and after an initial fluctuation period, gradually increased over time, reaching values of 4349 UI/mL (figure 1). At this time, neck ultrasound revealed no significant alterations, but RAI WBS showed suprasternal, laterocervical and pulmonary uptake. Chest and abdomen CT scans revealed bilateral multiple small pulmonary lesions <8 mm in size. The patient received two other RAI treatments (December 2000 and July 2001, respectively), following levothyroxine withdrawal, with a total dose of 147mCi and 162mCi of ^{131}I, respectively. Over the next 8 years, she presented good general performance and continual echographic surveillance revealed no new lesions. Analytical follow-up showed stable TgAbs (between 2000 and 3000 UI/mL), with undetectable Tg levels (figure 1).

Later, there was an exponential increase of TgAbs, which reached values of 17 781 UI/mL in February 2009 (figure 1), and she was submitted to a fourth course of RAI therapy with 135mCi of

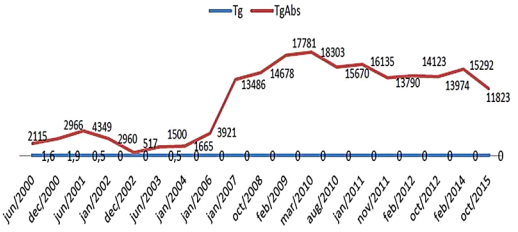

Figure 1 Thyroglobulin (Tg) and Tg antibody (TgAb) evolution during follow-up.

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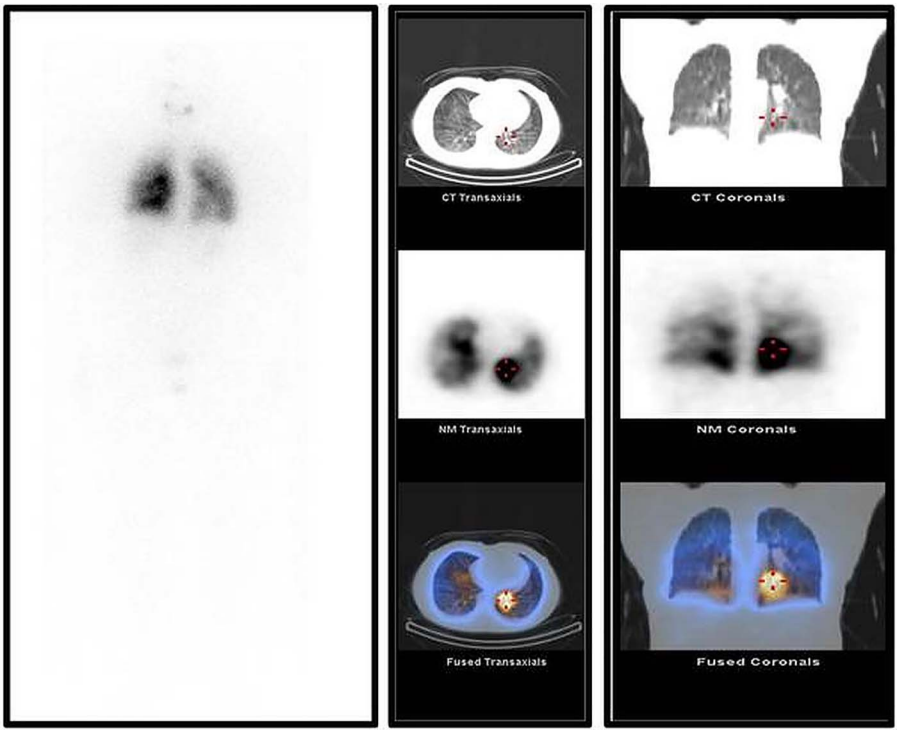

Figure 2 Post-treatment scintigraphy (with single photon emission CT) after administration of 135mCi of ^{131}I (February 2009) showing a strong bilateral pulmonary uptake more pronounced in inferior lobes.

^{131}I, following levothyroxine withdrawal, which showed strong bilateral pulmonary uptake that was more pronounced in inferior lobes at post-treatment scintigraphy combined with single photon emission CT (SPECT/CT) (figure 2). The patient performed a brain, neck and chest CT (December 2009), which not only confirmed the multiple known pulmonary nodules but also showed a brain lesion, characterised by brain MRI as a lesion of the right frontoparietal lobe, 10 mm in diameter. She was submitted to a surgical excision of pulmonary lesions (January 2010), with histological study confirming them as PTC metastases, and to a fifth RAI treatment with 190mCi of ^{131}I (April 2010); the post-treatment WBS showed strong pulmonary uptake and also uptake in frontoparietal and cerebellar areas of the brain (figure 3). These lesions were confirmed through brain MRI (figure 4). At that time, the TgAbs reached 18 483 UI/mL. The patient was submitted to gamma knife radiosurgery (GKR) in June 2010, 18 Gy, in frontoparietal and cerebellar lesions. She received oral dexamethasone 2 mg four times a day, beginning the day prior to GKR and lasting for 3 months after treatment. In June 2011, after an initial slight increase of the cerebral lesion documented by MRI, a sixth course of RAI therapy was performed with 238mCi of ^{131}I; the WBS showed

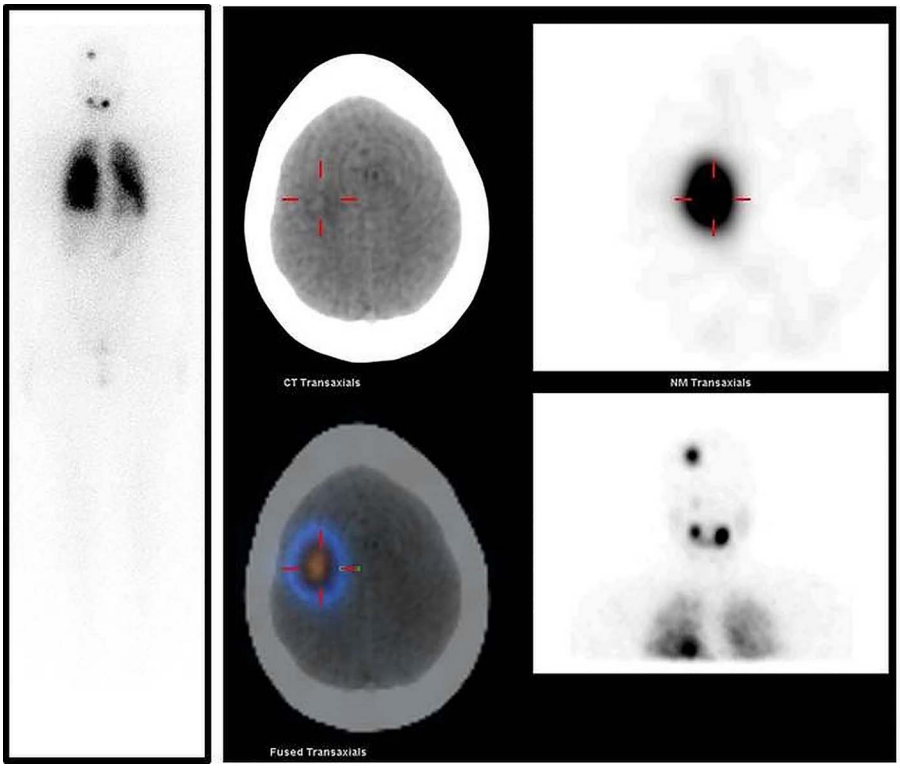

Figure 3 Post-treatment scintigraphy (with single photon emission CT) after administration of 190mCi of ^{131}I (April 2010) showing strong pulmonary uptake and an uptake in frontoparietal and cerebellar areas of the brain.

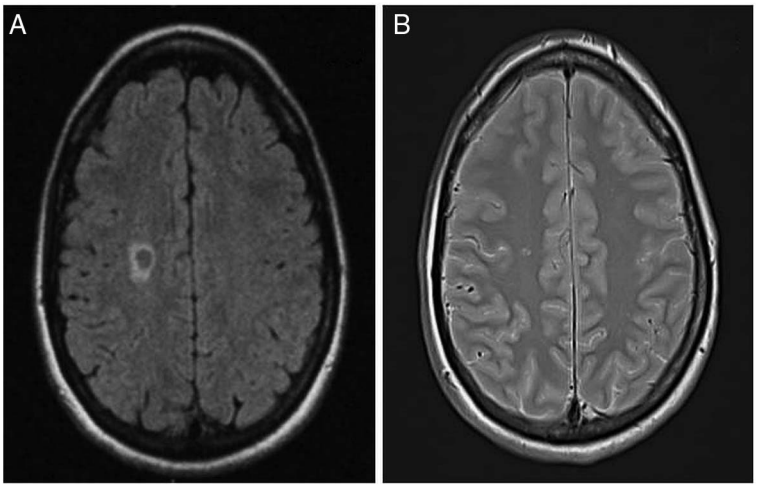

Figure 4 Brain MRI showing frontoparietal brain lesion before (A) and after (B) gamma knife radiosurgery treatment.

no uptake in cerebral lesion and a less intense uptake in bilateral pulmonary small nodules. In December 2011, the patient was submitted to the last cycle of RAI therapy with 213mCi of ^{131}I; the WBS showed remnant pulmonary bilateral small lesions. The last two courses of RAI therapy were performed under recombinant human thyroid-stimulating hormone (TSH) stimulation. At this point, the patient had been submitted to a total cumulative dose of 1255mCi of ^{131}I. Just before the last round of RAI therapy (December/2011), we performed positron emission tomography (PET/CT) with ^{124}I, which showed a slight uptake in pulmonary lesions, and an ^{18}F-fludeoxyglucose PET/CT, which showed no pathological uptake (figure 5). Serial brain MRI performed over time showed reduction of brain metastases (figure 4), punctiform in the latest evaluations, and there was a progressive reduction of TgAbs (figure 1).

OUTCOME AND FOLLOW-UP

The patient has now been followed for 15 years, presenting stable cerebral and pulmonary lesions, absence of new structural lesions, progressively decreasing TgAbs levels and no significant alterations in biochemical tests of liver and kidney function or blood count. In addition, she has been clinically free of intracranial hypertension and demonstrates good performance in her daily activities, more than 60 months after the diagnosis of brain metastases.

DISCUSSION

We report a situation of a young woman with an aggressive histological subtype of PTC diagnosed in an advanced stage, with the presence of one mutation conferring a worse prognosis, and the other mutations analysed being negative. BRAF V600E mutation has been associated with lower sodium-iodide symporter (NIS) expression and radioiodine-resistant metastatic lesions; this is in agreement with the evolution of the patient being presented, who was submitted to seven courses of radioiodine therapy with a large cumulative dose to control the disease.[19 20] After initial treatment, her follow-up was particularly interesting as the marker of persistent or recurrent disease was the titre of TgAbs. These antibodies are identified in about 20–25% of patients with differentiated thyroid carcinoma.[21] When present, they interfere with the measurement of Tg, the primary biochemical marker used for thyroid carcinoma surveillance, which precludes Tg use for patient monitoring. There has been growing evidence that TgAbs levels themselves may serve

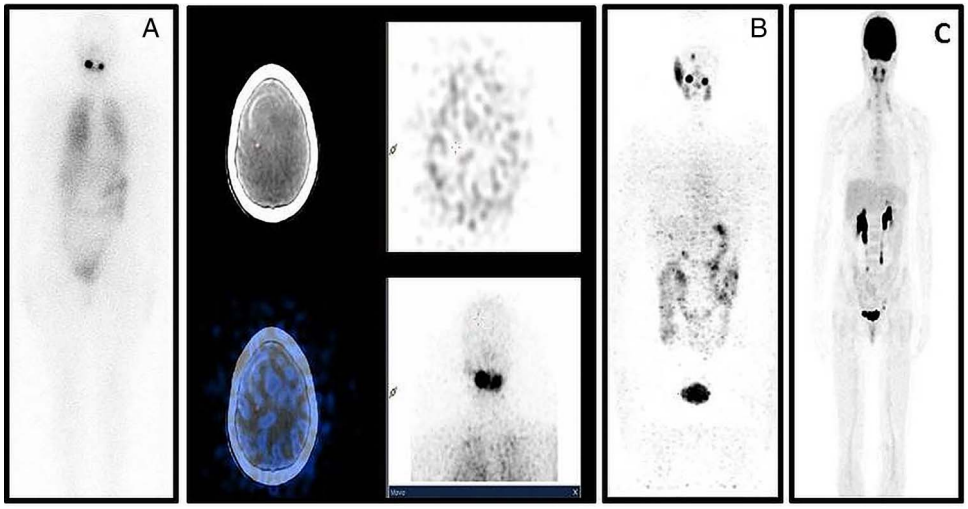

Figure 5 (A) Post-treatment scintigraphy (with single photon emission CT) after administration of 213mCi of ^{131}I (December 2011) showing only remaining pulmonary bilateral small lesions; (B) positron emission tomography CT (PET/CT) with ^{124}I showing a slight uptake in pulmonary lesions (December 2011); (C) ^{18}F-fludeoxyglucose PET/CT showing no abnormal uptake.

as a surrogate biochemical marker of disease persistence and response to therapy. However, the timing of testing and the duration to the maximal response seems to differ from Tg. For instance, there may be an initial transient rise in TgAbs after RAI therapy.[22] Also, it has been shown that the eventual disappearance of TgAbs takes approximately 2–3 years on average, with some patients having a very slow decrease of TgAbs levels that can take much longer than 3 years to resolve.[22–24] We and others advocate that the best approach for patients with persistently detectable (or even rising) TgAbs is to perform a prompt evaluation;[25] this was carried out in the case we report and led to the diagnosis of distant metastases. The approach should be different for patients with rising TG, in whom the performance of a WBS is indicated. However, we must take into account that neither the probability of finding thyroid cancer in this setting nor the best method for disease localisation has been firmly established. In our patient, the ultrasound evaluations were persistently normal but the exponential rise of TgAbs led to the performance of WBS and CT, which confirmed the presence of secondary lesions.

Compared to other locations, brain metastases from PTC are extremely rare and are often associated with poor prognosis.[7] The majority of brain metastases involve brain parenchyma, as in our case, probably due to the blood–meningeal barrier, and blood distribution within the brain and central nervous system.[26] As shown in previous case reports,[27 28] patients with brain metastases usually showed other secondary localisations such as in the lungs, bones or liver, which may be primary metastatic sites potentially through haematogenic dissemination. Brain metastases can be unique or numerous, clinically silent or very symptomatic, leading to intracranial high pressure and strong headaches, vomiting or focal neurological complications.[29] Fortunately, in our patient, these lesions were always completely silent. According to different authors, the reported median survival of PTC brain metastases varies from 4 to 33 months.[8–18] Predictive factors of survival seem to be advanced age, male gender, extra-thyroidal invasion and metastases at presentation, histological grade and incomplete resection of primary thyroid cancer.[30] In our patient, the early detection of recurrent disease inferred by indirect markers (TgAbs) led to a more aggressive approach, which probably contributed to the unusually good outcome.

Several treatment modalities have been used in a limited number of patients with intracranial metastatic PTC, including surgical resection, external beam radiation, radiosurgery (including GKR) and radioiodine therapy.[16] To date, chemotherapy has not been recommended in patients with brain metastases from PTC.[16] Surgical resection is only possible for accessible lesions, and external beam radiation for cerebral metastases can also cause complications such as cerebral oedema and trans-stentorial herniations.[31] Thus, in our patient, we chose to perform GKR. The use of this technique has not been well defined and only scattered data have been reported.[17 32] This approach has the advantage of being minimally invasive and, in our case, it improved tumour control. Some authors have also suggested that the combination of GKR with RAI therapy, in comparison to each modality alone, would improve tumour management.[33] Once cerebral lesions in our patient showed radioiodine uptake, she was also submitted to two additional RAI treatments. Given the possibility that even small metastatic brain tissue growth can cause significant symptoms, we decided to avoid the prolonged stimulation by TSH that occurs during thyroid hormone withdrawal. Even without a formal indication, we decided to use recombinant human TSH stimulation because we think it is the most reasonable approach. Although guidelines for clinical practice cannot be derived from isolated reports, the authors think that this case illustrates how different modes of follow-up and treatment can be used to promote asymptomatic and prolonged survival.

In conclusion, we present an atypical case of brain metastasis of PTC in a young woman, whose follow-up was performed using TgAbs levels. Pulmonary and brain metastases were surgically, radiosurgically and radiometabolically treated, resulting in a longer survival rate than those reported in similar cases. Early detection and specific treatment may have been key factors to maintain the patient's quality of life, avoiding the development of complications such as brain hypertension, and to prolong her survival.

Learning points

- Thyroglobulin antibody (TgAb) levels can be a surrogate biochemical marker of papillary thyroid carcinoma (PTC) persistence and response to therapy.
- Persistent or rising levels of TgAbs should lead to a prompt evaluation similar to that in a patient with persistent or rising Tg.
- The early detection and treatment of selected PTC brain metastases with GKR and RAI can result in a long survival.

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