

Papillary Thyroid Carcinoma with Brain Metastases: An Unusual 10-Year-Survival Case

Elizabete R. Miranda,¹ Eduardo L. Padrão,² Barbara C. Silva,^{1,3} Luiz De Marco,³ and Marta S. Sarquis¹

Background: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy with indolent clinical course and good prognosis. Brain metastases are extremely rare and the average survival time after diagnosis has been reported to be around 12 months.

Summary: We here report a 69-year-old patient who was admitted to the emergency room in January 2000 with progressive dizziness, headache, and vomiting. Five years before admission the patient underwent partial thyroidectomy for goiter. On admission, a diagnostic evaluation that included brain magnetic resonance imaging showed multiple brain lesions, and a stereotactic biopsy demonstrated a metastatic carcinoma from primary PTC, with the neoplastic cells staining for thyroglobulin. Total thyroidectomy was then performed, which showed colloid goiter and a PTC metastasis on a cervical lymph node. The patient received 200 mCi of radioactive iodine (¹³¹I) with suppressive therapy with L-thyroxine thereafter. Subsequently, serial whole-body scanning and magnetic resonance imaging showed multiple brain metastases and the patient received further ¹³¹I treatment, with a total dose of 1.2 Ci in a 10-year span. She also underwent partial surgical resection of brain metastases because complete resection was not feasible. Thereafter, the patient was subjected to whole-brain body radiotherapy with a dose of 44 Gy, followed by two brain gamma knife radiosurgeries (15 Gy each). To date, biochemical tests are within the normal range and the patient remains asymptomatic.

Conclusions: To our knowledge, this is the first report of a 10-year-survival case of brain metastases from PTC, despite this being a bad prognostic factor. A combined approach of surgical excision, ¹³¹I, whole-brain radiotherapy, and gamma knife radiosurgery was successful to treat metastases derived from primary tumor.

Introduction

PAPILLARY THYROID CARCINOMA (PTC) is the most common endocrine malignancy with indolent clinical course and good prognosis. In younger patients the tumor is nearly always confined to the neck with or without spread to cervical lymph nodes (1,2). In general, the prognosis is good, better than any other type of thyroid tumor, but in older patients, PTC behaves in a more aggressive manner and may give rise to distant metastases (3). Brain metastases are extremely rare, occurring in 0.15–1.3% of all cases of thyroid carcinoma (4). Distant metastases are rare, more commonly to lungs and bones, and suggest an aggressive disease. The mean survival time after the diagnosis of brain metastases is reported to be about 1 year (5). We report here a patient with brain metastases as the first sign of PTC, who has been followed up for 10 years. An aggressive multimodal approach to treatment was under-

taken with good results. To our knowledge, this is the first time that such a long survival has been reported.

Patient

A 60-year-old woman presented at the emergency room in June 2000 with progressive dizziness, headache, and vomiting. She had a history of partial thyroidectomy for treatment of a goiter at 5 years before admission. However, histopathological report was unavailable. A diagnostic evaluation that included magnetic resonance imaging (MRI) showed two lesions, one in each cerebral hemisphere (Fig. 1). Histopathological analysis of stereotactic biopsy of the brain lesions was diagnostic for metastatic carcinoma from a primary PTC. The neoplastic cells showed positive immunohistochemistry staining for thyroglobulin. She was referred to a neurosurgeon to have the brain lesions resected, but she refused this procedure at that time. Thereafter, she underwent total

¹Department of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

²Nuclear Medicine Unit, Hospital Biocor, Belo Horizonte, Brazil.

³Department of Surgery, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

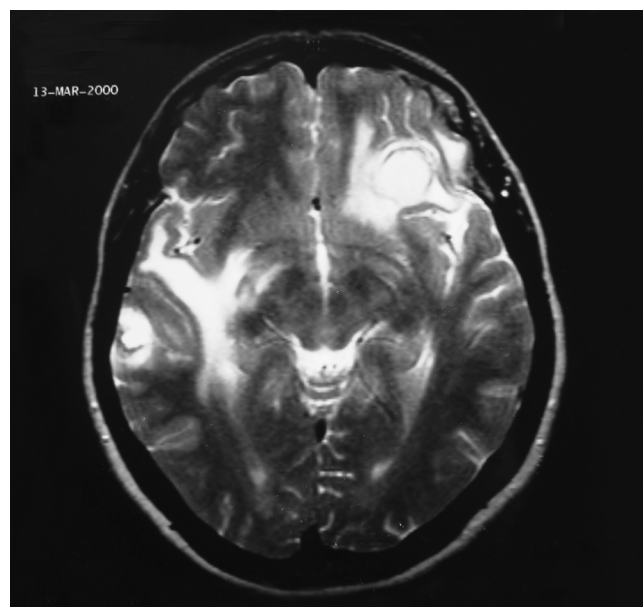


FIG. 1. Axial magnetic resonance imaging after gadolinium administration showing irregular enhancing mass in both cerebral hemispheres (2000).

thyroidectomy. Pathology results showed a colloid goiter and a cervical lymph node with atypical cells, with fine chromatin pattern, papillary structures, and nuclear features of PTC. The patient received 200 mCi of radioactive iodine (^{131}I), which showed strong cervical uptake, compatible with thyroid remnants, together with the two already identified brain metastatic lesions (Fig. 2). Subsequently, she was treated with suppressive therapy with L-thyroxine. Serial measurements of serum thyroglobulin never became normal (1 ng/mL), varying between 54.4 ng/dL and 4.366 ng/mL. The antithyroglobulin antibodies were always negative (<40 UI/mL). During follow-up, additional radiological examinations of the neck ultrasound and chest and abdomen computed

tomography scans revealed no other lesions. Serial ^{131}I whole-body scanning showed only brain activity (Fig. 3) and the patient received a total dose of 1.2 Ci of ^{131}I over the next 10 years. Recombinant thyroid-stimulating hormone (TSH) was used each time to avoid exposure of high TSH for a long time, which could induce metastatic growth.

Because of the persistence of high levels of thyroglobulin, and brain images in MRI images, the patient underwent partial surgical removal of brain metastases, because complete resection was not achievable. Next, the patient was submitted to whole-body radiotherapy (WBRT) with a dose of 44 Gy, followed by gamma knife radiosurgery (GKR). GKR was performed in 2006 and 2008, 15 Gy twice, because of tumor growth. Subsequently, serial MRI scans performed at 6-month intervals revealed partial size reduction of the brain metastases (Fig. 4). The patient received oral dexamethasone 2 mg four times a day, beginning the day before ^{131}I therapy or WBRT, and lasting for 3 months after treatment.

The patient has been followed up for 10 years without change in biochemical tests of liver and kidney function or hemogram. In addition, she has been clinically free of intracranial hypertension and performing well her daily activities.

Discussion

PTC constitutes around 80% of all thyroid malignancies. Based on the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute data, the incidence of PTC has increased significantly over 30 years (1973–2003) (6,7). In general, the prognosis is excellent and the reported survival rates for nonmetastatic lesions are 97.8% at 5 years and 94.9% at 10 years (2). The presence of distant metastases diminishes the survival rates to 37% and 24% at 5 and 10 years, respectively. Lungs are the most common site of distant metastases. Brain metastases are uncommon, comprising 0.1%–5% of all distant metastases, and few reports have been described (1,3,8,9). Risk factors for distant metastasis of PTC include male sex, advanced age, histological grade, and extra-thyroidal invasion at the onset. Other risk factors are completeness of surgical resection of the primary tumor and

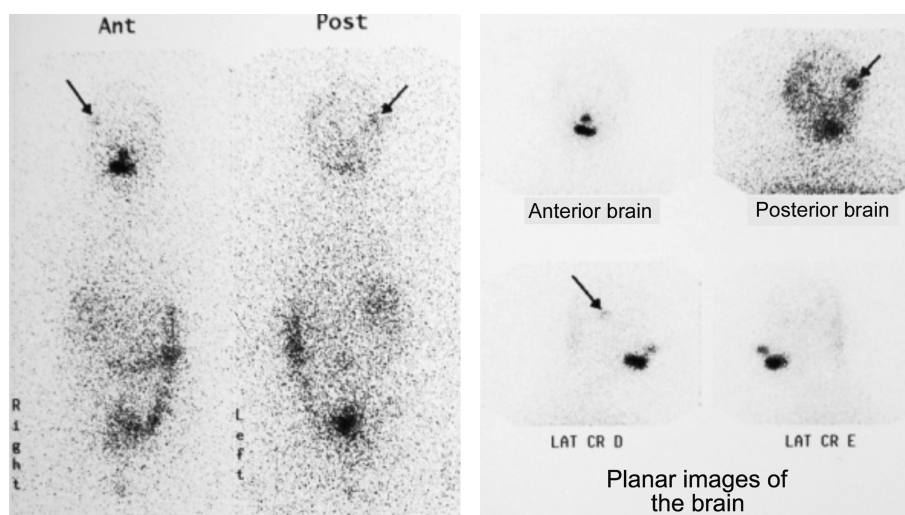


FIG. 2. The first whole-body ^{131}I scan showing evidence of intracranial metastases and cervical uptake (2001). Arrows show metastatic lesions.

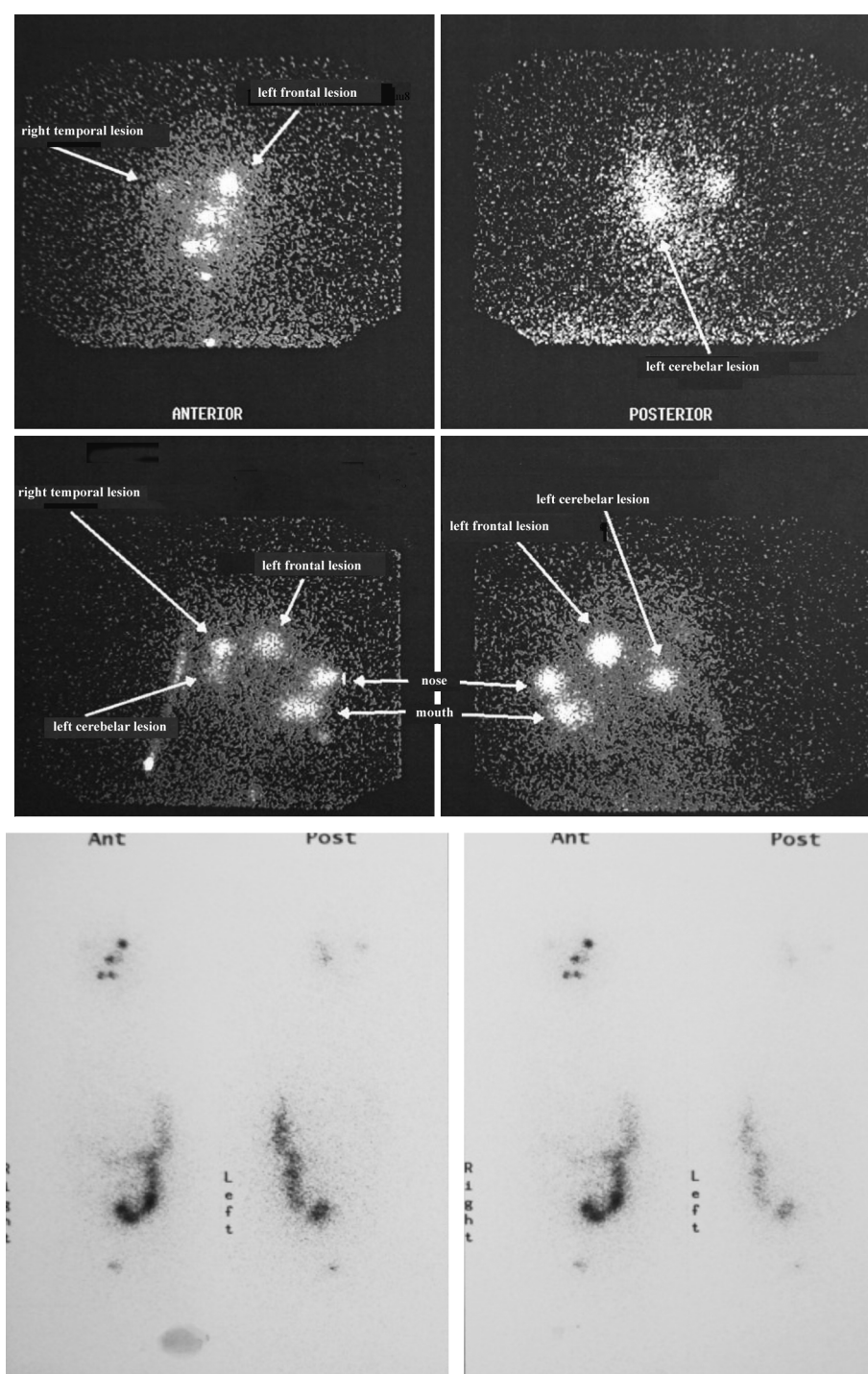


FIG. 3. Whole-body ^{131}I scan showing brain uptake (2003).

nuclear DNA content (1). In addition, the reported survival interval ranges from 14 months to 7 years and all patients survived for at least 1 year (5).

The optimal management of PTC consists of total or near total thyroidectomy and ablation of the thyroid remnants with ^{131}I . The presence of brain metastasis is a negative prognostic factor; therefore, treatment must be tailored to the individual patient. Current guidelines are for surgery, when feasible, as the first option, followed by radioiodine or

external radiotherapy (10,11). Several treatment modalities have been used in a limited number of patients with intracranial metastatic PTC, including surgical resection for accessible lesions, external beam radiation, GKR, and radioiodine therapy (1,12).

WBRT has been commonly used in the management of patients with incomplete resection of brain tumors. The use of GKR has not been well defined for this pathology and only scattered data have been reported (13). However, it is

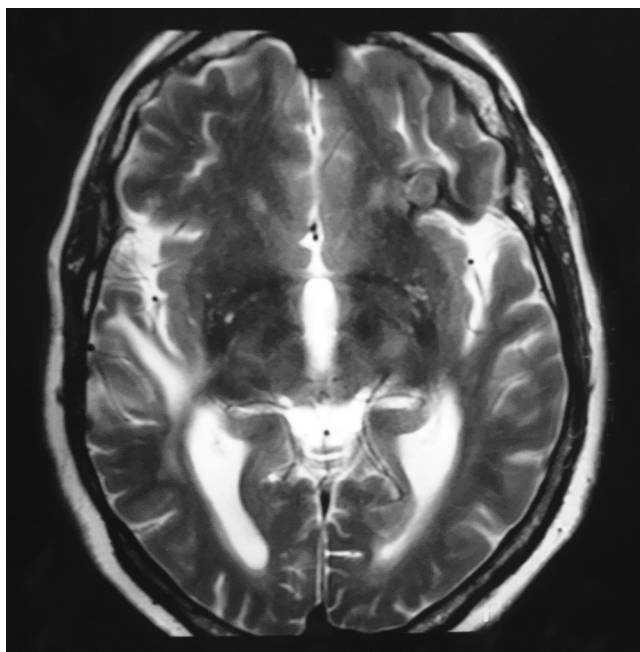


FIG. 4. Magnetic resonance imaging showing partial reduction of brain metastases (2009).

minimally invasive and thus enhances tumor control. It has also been suggested that the combined use of WBRT and GKR in comparison to each modality alone improves tumor management (1).

The role of ^{131}I therapy in the management of DTC is well established (14). To date, chemotherapy has not been recommended in patients with brain metastasis from thyroid carcinoma (1,12,15,16). Given the susceptibility that small brain tissue growth can cause significant symptoms, the use of recombinant TSH stimulation of ^{131}I uptake (instead of a several weeks of thyroid hormone withdrawal) is a reasonable approach, especially for patients with tumors localized near vital regions (12).

The most frequent early side effect is acute radiation sickness. This usually occurs within 12 hours of ^{131}I administration and has been reported in up to 73% of cases (17). Another common side effect is sialoadenitis, which occurs shortly after treatment and lasts for several days. Brief, asymptomatic bone marrow suppression may arise within the first month of treatment. Permanent or severe marrow suppression has been reported when the blood radiation dose was high, but has not been observed when the radiation dose to the blood was less than 200 rad (17). Finally, some patients report pain in metastases following treatment. This presumably is due to radiation-induced swelling and is analogous to radiation thyroiditis (17). Although our patient received 1.2 Ci ^{131}I therapy (44.4 GBq), she did not have any significant pain.

External beam radiation for cerebral metastases can also cause complications such as cerebral edema and transtentorial herniation (18). Steroids have been shown to decrease both the amount of radiation-induced brain edema of ^{131}I therapy and external beam therapy (18,19). How steroids reduce brain edema associated with brain metastases is unclear. It appears that steroids stabilize the capillary endothelial membrane, thus preventing serum proteins and other substances from

crossing it, or they prevent the release of enzymes by the lysosomes, which produce deleterious effects on adjacent brain tissue (17,20). Some authors recommend prophylactic glycerol rather than corticosteroids, because of the possibility of decreased iodine uptake from corticosteroids (12,17) and caution should be taken to prevent rapid worsening of tumor growth during treatment.

Conclusion

To our knowledge only a limited number of studies focused on PTC with brain metastases. Although there has been a general consensus that brain metastases are associated with poor prognosis, here we report, for the first time, a patient who survived for 10 years. This was achieved with resection of surgically accessible lesions associated with high doses of ^{131}I therapy, whole-brain radiation external therapy, and the GKR.

Although guidelines for clinical practice cannot be derived from a report, it illustrates how four different modes of treatment can be used to promote asymptomatic and prolonged survival.

Acknowledgments

This work was partially supported by grants from CAPES, CNPq, and FAPEMIG (Brazil).

Disclosure Statement

The authors declare that no competing financial interests exist.

References

1. Cha ST, Jarrahy R, Mathiesen RA, Suh R, Shahinian HK 2000 Cerebellopontine angle metastasis from papillary carcinoma of the thyroid: case report and literature review. *Surg Neurol* 54:320–326.
2. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP 1977 Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine (Baltimore)* 56:171–196.
3. Goolden AWG, McLaughlin JE, Valentine AR, Pease C 1990 Solitary cerebral metastasis from a papillary carcinoma of the thyroid. *Postgrad Med J* 66:127–129.
4. Chiu AC, Delpassand ES, Sherman SI 1997 Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab* 82:3637–3642.
5. Fujita T, Ogasawara Y, Doihara H 2009 Solitary cranial metastasis of thyroid carcinoma 13 years after primary surgery: report of a case. *Surg Today* 39:44–47.
6. Albores-Saavedra J, Henson DE, Glazer E, Schwartz AM 2007 Changing patterns in the incidence and survival of thyroid cancer with follicular phenotype—papillary, follicular, and anaplastic: a morphological and epidemiological study. *Endocrinol Pathol* 18:1–7.
7. Davies L, Welch HG 2006 Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 295:2164–2167.
8. Hoie J, Stenwing AE, Kullmann G, Lindegaard M 1988 Distant metastases in papillary thyroid cancer: a review of 91 patients. *Cancer* 61:1–6.
9. Dinneen SF, Valmaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, Hay ID 1995 Distant metastasis in papillary thyroid

- carcinoma: 100 cases observed at one institution during 5 decades. *J Clin Endocrinol Metab* **80**:2041–2045.
10. Coelho SM, Carvalho DP, Vaisman M 2007 New perspectives on the treatment of differentiated thyroid cancer. *Arq Bras Endocrinol Metabol* **51**:612–624.
 11. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **19**:1167–1214.
 12. McWilliams RR, Giannini C, Hay ID, Atkinson JL, Stafford SL, Buckner JC 2003 Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. *Cancer* **98**:356–362.
 13. Kim In-Y, Kondziolka D, Niranjana A, Flickinger JC, Lunsford LD 2009 Gamma knife radiosurgery for metastatic brain tumors from thyroid cancer. *J Neurooncol* **93**:355–359.
 14. Maxon HR 3rd, Smith HS 1990 Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. *Endocrinol Metab Clin North Am* **19**:685–718.
 15. Masiukiewicz US, Nakchbandi IA, Stewart AF, Inzucchi SE 1999 Papillary thyroid carcinoma metastatic to the pituitary gland. *Thyroid* **9**:1023–1027.
 16. Ogawa Y, Sugawara T, Seki H, Sakuma T 2006 Thyroid follicular carcinoma metastasized to the lung, skull, and brain 12 years after initial treatment for thyroid gland-case report. *Neurol Med Chir (Tokyo)* **46**:302–305.
 17. Datz FL 1986 Cerebral edema following iodine-131 therapy for thyroid carcinoma metastatic to brain. *J Nucl Med* **27**:637–640.
 18. Young DF, Posner JB, Chu F, Nisce L 1974 Rapid-course radiation therapy of cerebral metastases: results and complications. *Cancer* **34**:1069–1076.
 19. Nisce LZ, Hilaris BS, Chu FC 1971 A review of experience with irradiation of brain metastasis. *Am J Roentgenol Radium Ther Nucl Med* **111**:329–333.
 20. Holmquest DL, Lake P 1976 Sudden hemorrhage in metastatic thyroid carcinoma of the brain during treatment with iodine-131. *J Nucl Med* **17**:307–309.

Address correspondence to:
 Elizabete R. Miranda, M.D., M.Sc.
 Department of Medicine
 Universidade Federal de Minas Gerais
 Rua Timbiras 832/501
 Belo Horizonte
 Minas Gerais 30140060
 Brazil

E-mail: elizabetemiranda@medicina.ufmg.br

