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Low-Risk Papillary Thyroid Carcinoma Recurring as a Single Brain Metastasis: A Case Report and Literature Review

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Abstract

Background: Brain metastases from papillary thyroid carcinoma are infrequent occurring in 0.15% to 1.3% of patients, and they are generally accompanied by synchronous metastases in other sites and in isolation are even less frequent; the information about their management is limited and it has been based mainly on retrospective studies, experiences, case reports, and management guidelines of brain metastasis of other cancers. **Aim:** We report this case with the objective of describing how unpredictable the behavior of thyroid cancer can be despite being classified as low risk of recurrence. **Case Presentation:** A female patient with a diagnosis of papillary thyroid carcinoma classified as low risk who after more than a year of surveillance and without alterations in laboratory and imaging studies, developed a single brain metastasis susceptible to treatment with radioactive iodine (RAI) therapy. **Conclusion:** This case emphasizes the importance of a close follow-up of patients and not to minimize any symptom, no matter how simple it may seem, since cancer has no rules in its evolution.

Keywords

Thyroid Cancer, Papillary Thyroid Carcinoma, Brain Metastasis

1. Introduction

Currently, patients with papillary thyroid carcinoma have a good prognosis with a 10-year survival rate of 90% since most of them are diagnosed in a timely manner [1]-[3]; however, local recurrences occur in 10% to 25% of cases, generally at regional lymph nodes [2] [4], and 4% to 23% will present distant metastases at the time of diagnosis or during the course of the disease, being the most frequent cause of mortality [1] [4]-[10].

The most common sites of metastatic disease are lung (70%) and bone (20%) [4] [5] [11] [12]. Metastases to other sites are infrequent and in isolation occur in 1.85% of cases [4], and the most common sites include liver (0.5% of cases as a single lesion) [5] [9] [13] [14], brain (0.1% to 5%) [5] [15], and adrenal glands (1.7% of cases) [5] [12] [16]; however, isolated metastases have been reported in eye [8], ovary [5], kidney [6], pancreas [7], spleen [4] [7], esophagus [5] [9] [13] [14], mammary glands [8], axillary nodes [17], parotid gland [7], submandibular gland [18], chest wall [19], peritoneum, pericardium, pleura and periportal nodes [20]; and some cases have even been diagnosed as metastatic papillary carcinoma after incidental finding and resection of the single metastasis [6] [18]. As for soft tissues, isolated skin metastases (less than 1% of cases) predominate in the head and neck region, probably due to its rich network of vascular capillaries; however, some authors consider that they could be caused by the implantation of malignant cells in the trajectories of fine needle aspiration biopsies [8]. In striated muscle, isolated metastases most frequently affect the erector spinae muscles; however, single metastases have been reported in the sternocleidomastoid, deltoid, biceps, trapezius and quadriceps [19] [21]-[23]; and finally metastases can also develop in the parapharyngeal space through the connections between the perithyroid lymphatic channels and the retropharyngeal lymph nodes, although they could actually be ectopic thyroid glands or a direct tumor extension from the upper thyroid poles [24].

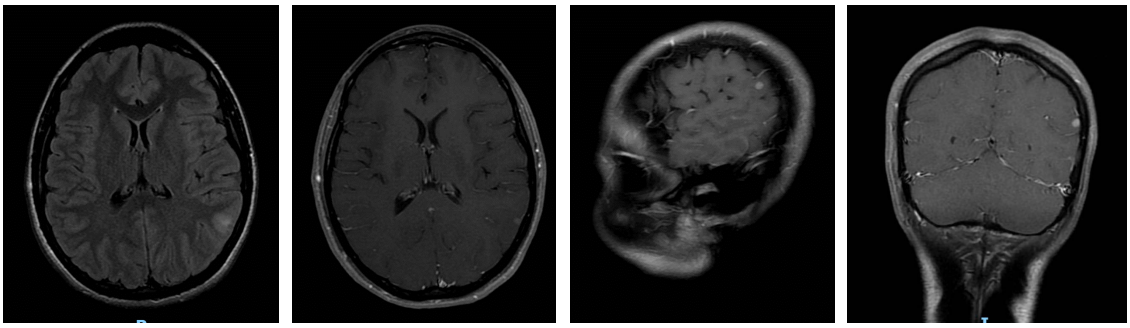
Brain metastases from the different types of thyroid cancers are infrequent occurring in 0.15% to 1.3% of patients with differentiated thyroid carcinoma (papillary/follicular) [15] [25] [26], in 4% of medullary carcinomas, and in 10% of anaplastic carcinomas [11]; they are generally accompanied by synchronous metastases in other sites and in isolation are even less frequent [3] [10] [11] [25]. The information about their management is limited since due to its low frequency their treatment has been based mainly on retrospective studies, experiences, case reports, and management guidelines of brain metastasis of other cancers [1] [10]; in addition, currently there are few series of patients in this scenario that analyze its clinical course and the treatments options [11] [26]. We present the unusual case of a patient with a diagnosis of papillary thyroid carcinoma classified as low risk who after more than a year of surveillance and without alterations in laboratory and imaging studies, developed a single brain metastasis susceptible to treatment with radioactive iodine (RAI) therapy. We report this case with the objective of describing how unpredictable the behavior of thyroid cancer can be despite

being classified as low risk of recurrence.

2. Case Presentation

A 26-year-old female with no relevant pathological history or risk factors for thyroid cancer such as radiation exposure or family history, underwent a neck ultrasound due to the presence of a sebaceous cyst (which was resected by dermatology) with the incidental finding of a left thyroid nodule of 1 × 0.5 × 0.5 cm higher than wide, with microcalcifications and vascularized classified as TIRADS IV, without lateral or central cervical adenopathies of suspicion. A fine needle aspiration biopsy was performed with a Bethesda V cytology report, and thyroid function tests were normal. She underwent total thyroidectomy with histopathological report of unifocal well differentiated papillary carcinoma in the left thyroid lobe, 0.8 × 0.5 cm tumor size, without lymphovascular invasion or perineural invasion, without extrathyroidal extension, and without capsular invasion. The immunohistochemistry report was negative for BRAF V600E and CD34 mutations, agreeing with the low risk factors reported in the histopathological study and being associated with a better prognosis and a lower risk of recurrence. Her postoperative serum calcium was reported at 8.44 mg/dl. Due to the histopathological characteristics and the negative postoperative thyroglobulin levels, she was classified as a low risk disease according to the American Thyroid Association (ATA). Her clinical course was asymptomatic, with an adequate adherence to the suppressive treatment with levothyroxine which was corroborated by suppressed Thyroid-stimulating hormone (TSH) levels, and quarterly surveillance with neck ultrasound, thyroglobulin and antiglobulin antibodies, that were reported within normal parameters. 15 months after surgery she presented intermittent paresthesias in the right pelvic limb; initially they were attributed to a suspected hypocalcemia, however serum calcium and parathormone levels continued in normal ranges, so a brain magnetic resonance imaging (MRI) was performed which revealed a hypointense nodular lesion in T1-weighted image with complete homogeneous nodular enhancement with 4 × 5 mm contrast of cortical localization at the level of the angular gyrus of the left inferior parietal lobe without identifying adjacent meningeal thickening or pathologic deposits in susceptibility weighted imaging (SWI) (**Figures 1(a)-(d)**). Given the previous classification of the disease as low risk, the lack of elevated thyroglobulin and anti-thyroglobulin antibody levels, the absence of suspicious cervical recurrence lesions on ultrasound, that it was a single lesion in an infrequent site, and that the patient did not present any potential factor for the development of metastatic disease, the suspicion of metastasis was low; however, due to the radiological characteristics of the lesion and the new onset symptomatology, a radioactive iodine uptake (RAIU) whole-body scanning (WBS) was performed, which reported an abnormal area of concentration in the skull at the level of the left parietal region in relation to secondary deposit (**Figure 2**). The patient received an ablative dose of radioactive iodine of 150 mCi with previous administration of thyrotropin alfa, continuing with levothyroxine at a suppressive dose and monitoring of thyroglobulin and antibody levels which continued

without elevations, and 6 months later a brain MRI revealed the disappearance of the lesion (Figures 3(a)-(c)). Currently the patient remains on surveillance, asymptomatic and with a disease-free period of 3 years.



(a) (b) (c) (d)

Figures 1. A hypointense nodular lesion with complete homogeneous nodular enhancement after the administration of contrast medium with dimensions of 4 × 5 mm in cortical location at the level of the angular gyrus of the left inferior parietal lobe associated with focal subcortical hyperintensity in Flair of the corresponding gyrus without identifying adjacent meningeal thickening or pathological deposits in SWI.

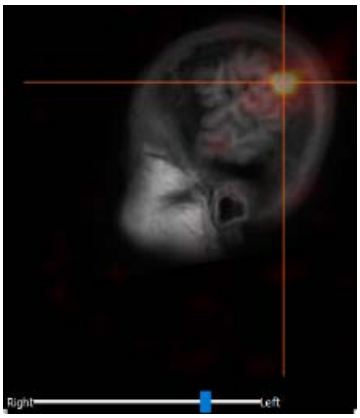
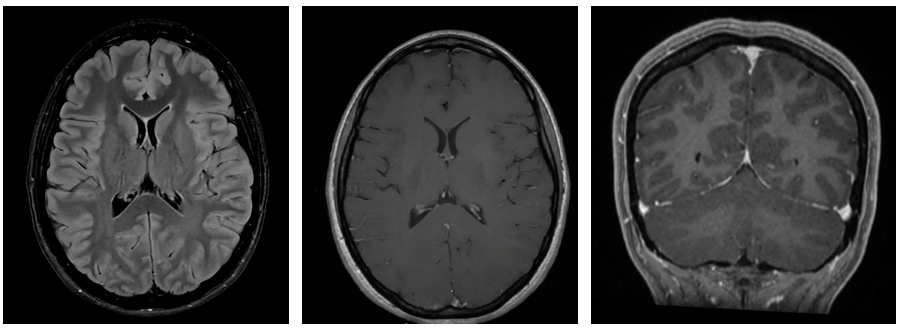


Figure 2. Scarce uptake of radioiodine in sites of physiological distribution in the nasopharyngeal mucosa and liver as well as intestinal and urinary elimination. A focal zone of concentration of the radiotracer is observed at the level of the left parasagittal line of the skull in the topography of the parietal region. No other normal concentration sites are identified.



(a) (b) (c)

Figure 3. CT scan without tumor activity.

3. Discussion

Brain metastases of papillary thyroid carcinoma develop more frequently in the cortex, cerebellum and pituitary gland [3], tend to develop earlier in the follicular type compared to the papillary type [11], and like recurrences in other sites, can develop after long disease-free periods [1]; in our literature review the longest period of time between the diagnosis of the primary tumor and the development of brain metastases was 41 years. Likewise, they seem to be more frequent in women, which agrees with our patient [11] [26], and unlike the reviewed cases in which patients presented synchronous metastases in other sites such as mediastinal nodes, striated muscle, adrenal gland, spleen and lung, our patient only developed a single brain metastasis.

While some patients may present headaches and/or other neurological symptoms (sensory and/or motor disturbances, aphasia, ataxia, seizures) [1] [10] [15] [26], others are asymptomatic for long periods and in up to 15.4% of patients they are discovered incidentally in imaging studies or in RAIU WBS [1] [3] [26] [27]. Our patient presented only sporadic and short-lasting paresthesias in the contralateral pelvic limb as well as a minimal decrease in strength when performing high intensity movements; initially these symptoms were attributed to a hypocalcemia, however serum calcium and parathormone levels did not show decreases.

The ATA estimates the probability of recurrence of papillary thyroid carcinoma based on 3 risk groups; low, intermediate and high [5]. These present a recurrence risk of 3% - 13%, 21% - 36%, and 68% respectively, currently 80% of patients are classified as low risk [5]. In contrast to our patient, in all the cases analyzed brain metastases occurred in patients with intermediate and high risk histopathological criteria such as positive nodes, extra-thyroid extension, elevated postoperative thyroglobulin levels and esophageal invasion, and only one patient presented a similar histopathological report, but with elevated thyroglobulin 4 weeks after total thyroidectomy, for which RAIU WBS was performed that revealed a brain metastasis [25]. We did not find another similar case reporting a single RAI avidity (RAI-A) brain metastasis presented more than 1 year after total thyroidectomy in a patient with low-risk disease and no thyroglobulin elevation.

Recurrences of differentiated thyroid cancer, whether local, regional and/or distant, are generally detected after elevation of serum thyroglobulin and/or antithyroglobulin antibodies, this finding leads to the performance of imaging studies such as ultrasound, tomography, MRI and RAIU WBS [5] [21]. Unlike most of the cases reviewed, our patient never presented elevations of thyroglobulin levels, probably because it was a single metastasis of small dimensions.

In up to 20% of cases of well-differentiated papillary carcinoma, RAIU WBS are negative, requiring 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) for the identification of metastases [15] [19] [26], which in this scenario are related to a more aggressive tumor biology since they are usually less differentiated than the primary tumor [3] [12] [19]. For brain metastases, MRI is considered the most sensitive and specific imaging study

to detect and characterize them [3] [15] [26]; due to the characteristics of the lesion reported in the MRI of our patient, we decided to perform an RAIU WBS which showed RAI-A by the lesion.

In general, patients with metastatic disease due to differentiated thyroid carcinoma can survive for long periods, especially young patients with low tumor burden [28]. However, brain metastases secondary to this cancer tend to be aggressive and are associated with a mortality of 78% and a life expectancy of less than 1 year [15]; besides, the information for their management is limited due to its low frequency and it has been based mainly on retrospective studies, experiences, case reports, and management guidelines of brain metastasis secondary to other cancers [1] [10]. In addition, there are currently few series of patients in this scenario that analyze its clinical course and the treatments options [11] [26].

First-line treatment for metastatic differentiated thyroid carcinoma includes TSH suppression (<0.1 μU/L) and RAI therapy whose administration generally depends on the response rate in tumor activity; despite that, up to one third of patients will present RAIR metastases, either at the time of initial diagnosis when debuting as metastatic disease or during its progression [28]. In this scenario (an advanced refractory thyroid cancer), depending on the characteristics of the disease and its symptomatology, local ablative treatments such as surgery, radiofrequency ablation (RFA), cryoablation, radiotherapy, chemoembolization and ethanol ablation can be used; although these modalities can control symptomatology, postpone the initiation of systemic treatment, avoid possible local complications, and/or be used in a lesion that shows progression during systemic treatment to perpetuate disease control, it should be taken into account that most of the information reported on their success rates is based on their use for other neoplasms [28].

Systemic treatment is indicated for rapidly progressive metastatic disease that is not susceptible to other therapeutic modalities, in tumors located in unfavorable areas, and in symptomatic disease [29]. As conventional chemotherapy, the most widely used drug has been doxorubicin, but its efficacy is currently very limited. The multi-kinase inhibitors (MKIs) sorafenib and lenvatinib have reported progression-free survivals of 10.8 vs. 5.8 months and 18.3 vs. 3.6 months respectively compared to placebos and are currently FDA approved for RAIR progressive disease [28]. Although MKIs can control disease progression and associated symptoms, and even generate partial responses, they also present several adverse effects, and furthermore given the development of resistance mechanisms, many patients eventually require treatment modification based on specific genetic alterations [28] [29].

At the moment, the prognosis and treatment for differentiated thyroid carcinoma brain metastases are determined by several factors including age, tumor grade and size, whether or not it is radioactive iodine-refractory (RAIR), histologic subtype, and the number and location of lesions [12] [15]. Treatment options include surgical resection, stereotactic radiosurgery (SRS), whole-brain radiation

therapy (WBRT), external beam radiation therapy (EBRT), RAI therapy, and MKIs [1] [10] [11] [15] [26] [28] [30]. These treatments can be used as single therapies or in combinations, all are recommended in the ATA, and their choice should be based on the number and size of the lesions, their location, their individual responses to the treatments, and their RAI-A [15] [26].

Local therapies seem to be more effective since they report a higher specific survival of brain metastases [3] [7] [11]; in the series of patients analyzed, survival was higher in those who underwent surgical resection and/or SRS [1]; however, this must be related to the lower tumor burden that makes the patient a candidate for such treatment. In our patient, since it was a single metastasis, of small dimensions, with minimal symptomatology, and since it was RAI-A, we decide to treat it with an ablative dose of RAI that was enough to eradicate it.

Surgical resection seems to be the primary treatment for single or oligometastatic (less than 3 lesions) and symptomatic lesions in patients with good functional status [26]. WBRT should be considered in the presence of multiple disseminated metastases, EBRT can be used for fewer and smaller lesions in patients with a good functional status [28], and SRS is useful for multiple and deep lesions of small dimensions [15] [26]. In cases of high-risk surgery or incomplete resections, radiosurgery and/or radiotherapy can be considered as options [15]. Regarding the use of MKIs in RAIR progressive disease, although the potential risk of intracranial bleeding secondary to the anti-angiogenic effect must be considered, this appears to be limited [11].

Regarding the mutational profiles, these are used in advanced papillary thyroid carcinoma, generally RAIR, with the aim of identifying molecular targets. BRAF V600E constitutes the most common oncogene mutated occurring in 40% to 60% of papillary carcinomas and up to 33% of poorly differentiated carcinomas [31]. This mutation causes a reduction in the expression of genes responsible for the uptake of radioiodine treatment and it has been reported a significant association with adjacent structures invasion, lymph node metastases, and with a worse survival due to a faster rate of growth, spread and a higher risk of death [32] [33]. Our patient's immunohistochemistry was reported negative for BRAF V600E mutation.

4. Conclusion

As previously mentioned, we did not find any cases of patients with brain metastases secondary to papillary thyroid carcinoma similar to our patient; all histopathological reports of thyroidectomies in the reviewed cases reported the presence of intermediate and high risk factors in the primary tumor, and about the clinical presentations, metastases presented as synchronous disease, both as recurrence and initial disease; on the other hand, in a few cases the single metastatic lesion was initially detected in the brain as well as in other organs and after its resection, the diagnosis of papillary thyroid carcinoma was reached. These facts emphasize the importance of a close follow-up of patients and not to minimize

any symptom, no matter how simple it may seem, since cancer has no rules in its evolution; likewise, it should be kept in mind that, just as in patients classified as high risk and high intermediate risk (higher risk features) by ATA, in patients like ours with a history of metastatic disease, routine diagnostic WBS is recommended during surveillance. Finally, treatment for brain metastases from papillary thyroid carcinoma should be individualized and should be based on factors such as the time of presentation (initial disease or recurrence), the disease-free survival period between cure and metastasis development, if the lesions are RAI-A or RAIR, the location, number, and extent of metastases, the presence or absence of synchronous metastases, and the functional status of the patient, and it must be a multidisciplinary approach.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

Radioactive Iodine	RAI
American Thyroid Association	ATA
Thyroid-stimulating hormone	TSH
Magnetic Resonance Imaging	MRI
Susceptibility Weighted Imaging	SWI
Radioactive Iodine Uptake	RAIU
Whole-Body Scanning	WBS
RAI Avidity	RAI-A
18F-fluorodeoxyglucose positron emission tomography-computed tomography	18F-FDG PET-CT
Radioactive Iodine-Refractory	RAIR
Radiofrequency Ablation	RFA
Multi-kinase Inhibitors	MKIs
Stereotactic Radiosurgery	SRS
Whole-brain Radiation Therapy	WBRT
External Beam Radiation Therapy	EBRT