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(CASE REPORT)

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Brain metastasis as the initial presentation of papillary thyroid carcinoma, tall cell variant: Case report and brief literature review

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Abstract

Brain metastasis as the initial manifestation of papillary thyroid carcinoma (PTC) is exceedingly rare. We report a 49-year-old female who presented with progressive headaches, confusion, and right-sided weakness. A brain MRI showed a single ring-enhancing lesion in the left parietal region, accompanied by a noticeable mass effect. This finding raised concern for either primary brain cancer or a metastatic tumor from an unknown source. Craniotomy with gross total resection was performed, and pathology revealed metastatic PTC, tall-cell variant (TCV), which was later confirmed by thyroglobulin and TTF-1 immunohistochemistry (IHC). On further evaluation, a primary thyroid tumor was found, and staging revealed pulmonary involvement. The patient underwent total thyroidectomy with central neck dissection, which was followed by radioactive iodine therapy, adjuvant brain radiotherapy, and TSH suppression. Despite all treatments, her condition progressed, and she died 18 months after diagnosis. This case highlights the importance of considering PTC in the differential diagnosis of brain lesions, even in the absence of thyroid-related symptoms, while focusing on the aggressive treatment clinical course of PTC. This article further discusses the background and pathogenesis of this condition while comparing the case with the current literature.

Keywords: Papillary thyroid carcinoma; Tall cell variant; Aggressive; Brain metastasis; Immunohistochemistry.

1. Introduction

PTC is the most common thyroid malignancy worldwide and accounts for 85% of newly diagnosed cases. Histology shows intranuclear cytoplasmic inclusions, nuclear grooves, and laminated calcifications. [1,2,3] This variant of thyroid carcinoma is typically indolent, spreading to the lymph nodes, and maintains a favorable prognosis. Despite this carcinoma's high prevalence, distant metastasis generally occurs to the lungs or bones, with a minority of less than 6% of cases metastasizing to the brain. [1,2] TCV of PTC is the most aggressive variant, characterized by tall cells occupying ≥ 30% tumor and well-developed PTC nuclear features. TCV usually requires more aggressive treatment and closer disease surveillance. [2]

The pathophysiology involves hematogenous spread and molecular alterations that advance tumor invasion. [3] The rarity of this clinical presentation demonstrates challenging diagnostic considerations and unusual characteristics in involved patients, such as neurological deficits, leading to deferred diagnostic probability. [4] Imaging modalities use

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ultrasounds, fine-needle aspiration (FNA) biopsy, and computed tomography scans, as well as surgical resection and radioactive iodine therapy. [3]

We report this case to emphasize the complexity of an aggressive variant of papillary thyroid carcinoma (PTC) and to contribute to the medical literature. Early identification of metastasis requires further investigation. Evidence-based interventions can help improve clinical recognition, guide therapeutic management, and enhance patient outcomes.

2. Clinical Presentation

2.1. Clinical Presentation and Radiological Findings

A 49-year-old woman presented to the emergency department with a three-week history of progressive headaches, intermittent episodes of confusion, and mild right-sided weakness. She also reported subtle changes in her gait and balance over the preceding two months, which she had initially attributed to fatigue. There was no prior history of malignancy, thyroid disease, or significant family history of cancer. She was otherwise healthy, with no tobacco use and no known toxic exposures. Review of systems was unremarkable for weight loss, neck swelling, dysphagia, or voice changes.

On physical examination, the patient was alert but mildly disoriented. Vital signs were within normal limits. Neurological assessment revealed mild right hemiparesis with brisk deep tendon reflexes on the right side and a right-sided pronator drift. Cerebellar signs were absent. Cranial nerve examination was intact. Notably, neck examination was unremarkable, with no palpable thyroid enlargement, nodularity, or cervical lymphadenopathy. No other peripheral lymphadenopathy or hepatosplenomegaly was detected.

Initial blood work was largely within normal limits. A complete metabolic panel, complete blood count, and coagulation studies were unremarkable. TSH, free T4, and free T3 levels were normal, ruling out thyroid causes. Tumor markers, including CEA and CA 19-9, were mildly elevated but non-specifically so. Thyroglobulin level was not ordered at the time of initial presentation, as thyroid pathology was not yet suspected.

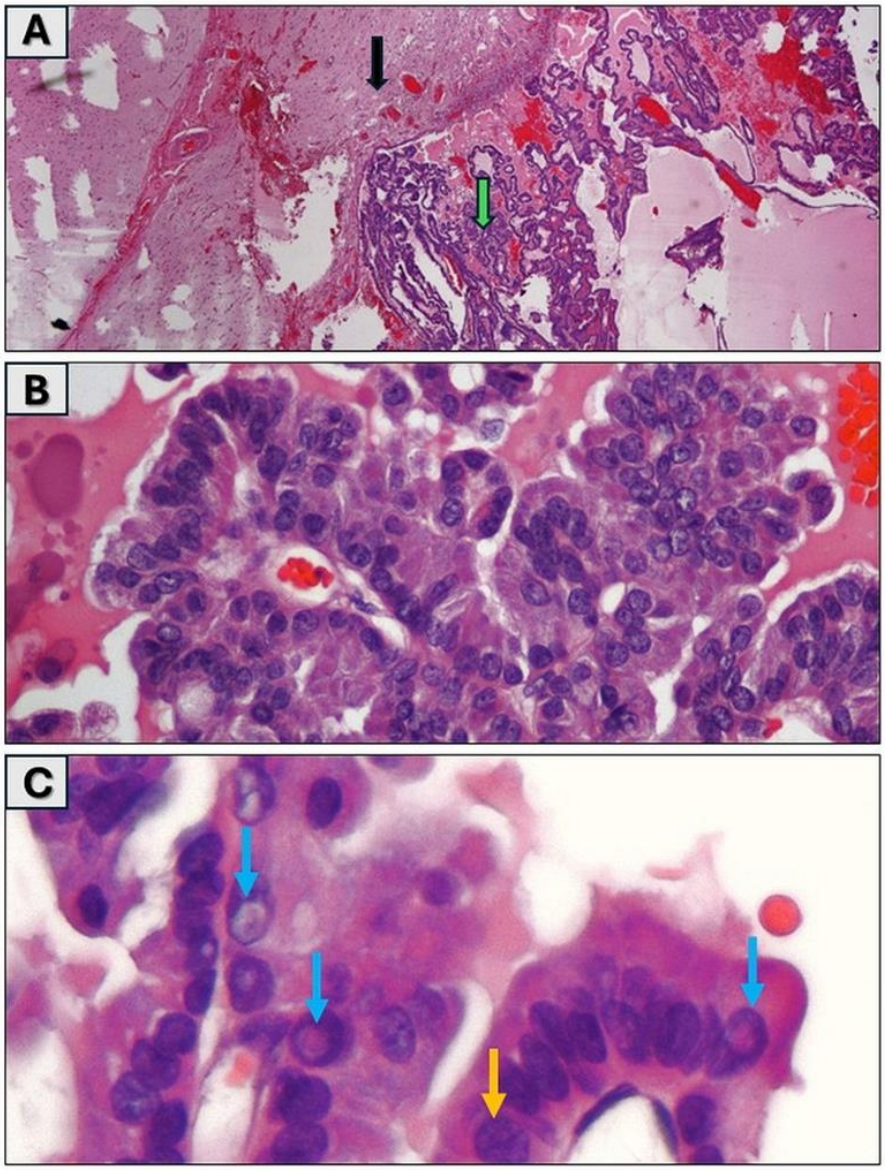
Urgent contrast-enhanced MRI of the brain revealed a solitary, well-circumscribed, ring-enhancing mass measuring 3.2 × 2.8 cm in the left parietal lobe, associated with significant surrounding vasogenic edema and mild midline shift. The radiological appearance raised concern primarily for a high-grade glial tumor or solitary brain metastasis. Whole-body CT imaging was performed as part of the metastatic workup. No primary lesion was identified in the chest, abdomen, or pelvis on initial staging CT. Thyroid imaging was not specifically included in the primary workup protocol. Two small sub-centimeter pulmonary nodules were noted incidentally but deemed indeterminate and below the size threshold for definitive characterization at that time.

Differential diagnosis included glioblastoma multiforme, solitary brain metastasis from an occult primary, primary CNS lymphoma, and brain abscess. The solitary nature of the lesion, its imaging characteristics, the patient's age, and the absence of an identified systemic primary led the oncology and neurosurgery teams to weigh the options of stereotactic biopsy and surgical excision carefully.

2.2. Tumor Board Discussion and Management

The case was formally reviewed at the multidisciplinary tumor board. Two primary management options were debated: stereotactic needle biopsy versus surgical excision with curative intent. Arguments favoring biopsy included the desire to obtain tissue diagnosis with minimal risk prior to committing to open craniotomy. Arguments favoring excision emphasized the mass effect causing symptomatic edema, the technical resectability of the lesion, the absence of a primary, and the potential dual benefit of decompression and tissue diagnosis. After deliberation, the tumor board reached consensus in favor of surgical excision. The rationale was that resection would both relieve the patient's neurological symptoms and provide a sufficient tissue specimen to guide definitive pathological diagnosis and subsequent treatment planning.

The patient underwent left parietal craniotomy with gross total resection of the lesion. The intraoperative frozen section was consistent with metastatic carcinoma. Final histopathological analysis demonstrated metastatic papillary thyroid carcinoma, tall cell variant, characterized by elongated follicular cells with height-to-width ratios exceeding three, abundant eosinophilic cytoplasm, and nuclear features classic of papillary thyroid carcinoma (Figure 1A, B, C). IHC evaluation demonstrated positive staining for thyroglobulin, TTF-1, and CK19, supporting the thyroid origin of the metastatic lesion.



1A: Low power view showing metastatic papillary carcinoma (Green arrow) to the brain tissue (Black arrow) (H&E, X20).; 1B: Intermediate power view showing papillary architecture of thyroid carcinoma with tall cell features (H&E, X40). 1C: High-power view showing nuclear features of thyroid papillary carcinoma with nuclear grooves (yellow arrow) and intranuclear inclusions (blue arrows) (H&E, X60)

Figure 1 Microscopic findings of metastatic papillary thyroid carcinoma to the brain

2.3. Discovery of Primary, Pulmonary Metastases & Management

After confirming the pathology, a targeted search for the thyroid primary was performed. Thyroid ultrasound revealed multiple hypoechoic nodules with microcalcifications, the largest measuring 1.4 cm. Ultrasound-guided FNA biopsy confirmed PTC, tall cell variant. Repeat staging with PET-CT demonstrated FDG-avid uptake in the thyroid gland and in two bilateral pulmonary nodules, now definitively characterized as metastatic disease. The lung nodules noted incidentally on the initial CT were reclassified accordingly.

The patient subsequently underwent total thyroidectomy with bilateral central neck dissection. Final surgical pathology confirmed the tall cell variant of papillary thyroid carcinoma with extrathyroidal extension. There was no evidence of regional lymph node metastasis. Postoperative management included high-dose radioactive iodine (RAI) ablation therapy targeting residual thyroid tissue, known pulmonary metastases, and the operative bed. External beam radiation therapy was administered to the surgical brain site. TSH suppression with high-dose levothyroxine was maintained throughout the post-treatment course.

2.4. Surveillance, Recurrence, Unfavorable Outcome, and Final Course

The patient entered an active surveillance protocol consisting of serum thyroglobulin monitoring, RAI whole-body scans, and cross-sectional imaging at three-month intervals. For several months, clinical and biochemical stability was maintained, with thyroglobulin levels declining. However, approximately eleven months following the initial brain metastasis diagnosis, surveillance imaging demonstrated enlargement of the existing pulmonary nodules and the appearance of new lytic osseous lesions involving the thoracic vertebrae and right iliac wing. Bone biopsy confirmed metastatic papillary thyroid carcinoma.

The disease thereafter followed an aggressive and unfavorable course. Approximately sixteen months following the initial presentation and seven months after bone metastases were documented, further new bone lesions emerged, signifying continued skeletal progression despite systemic therapy. The patient was transitioned to best supportive care, with palliative radiation directed at symptomatic skeletal lesions. She experienced increasing pain, functional decline, and eventually developed malignant hypercalcemia. She passed away eighteen months after the initial diagnosis of brain metastasis, having never experienced a sustained disease-free interval. The case exemplifies the exceptionally aggressive biological behavior of the tall cell variant, which, even in the context of multimodal therapy, carried a markedly worse prognosis than conventional papillary thyroid carcinoma.

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

PTC is the most prevalent type of endocrine malignancy. It accounts for 80-85% of all thyroid cancers. [4,5] It has an annual incidence rate of 10-15 per 100,000 people worldwide and mostly affects females compared to males. [4,5] The typical age of onset of individuals aged between 30s and 50s is mostly associated with favorable long-term survival of over 90% at 10 years. [5] Even so, considerable clinicopathologic heterogeneity is evident among histologic subtypes, as outlined in the 2022 WHO classification of PTCs, which include classical, tall cell, follicular, columnar, and hobnail variants. [4,6]

TCV represents a high-risk subtype, defined by ≥30% tall cells with a height at least three times their width and abundant eosinophilic cytoplasm. TCV accounts for about 1-13% of PTC cases, with the average age of affected patients being 50 years [7]. It is characterized by aggressive behavior, with elevated rates of extrathyroidal extension, metastasis, and vascular involvement, ultimately producing worse clinical outcomes compared with classical PTC. [7,8]

Although metastasis to regional cervical lymph nodes occurs through the lymphatic system, the aggressive nature of the TCV tumor facilitates hematogenous dissemination to sites such as the lungs and bones. [8,9] metastasis to the brain, on the other hand, is exceedingly uncommon and occurs in about 0.1-1.4% of PTC cases. [5] Additionally, it manifests during advanced stages of the disease. TCV may show atypical metastatic characteristics, such as early CNS involvement. These findings reveal that it is crucial to examine brain metastasis as a potential indicator of initial thyroid malignancy incidence.

3.2. Pathogenesis, Pathophysiology

PTC typically arises from follicular thyroid epithelial cells. Tumorigenesis is attributed to continuous activation of intracellular proliferation and differentiation. The mitogen-activated protein kinase (MAPK) pathway plays the main role. It is triggered by BRAF V600E mutations, RAS mutations, and RET/PTC rearrangement. [4,10] The TCV possesses a high frequency of BRAF V600E mutations, which are usually accompanied by TERT promoter mutations. These predict more aggressive behavior, elevated recurrence, and disease-specific cancer mortality. [10,11]

The molecular alterations lead to dedifferentiation by inhibiting thyroid-specific genes associated with iodine metabolism. In effect, it contributes to reduced sensitivity to RAI avidity and elevated therapeutic resistance. [10] At the same time, the stimulation of the epithelial–mesenchymal transition (EMT) pathway increases cell motility, vascular dissemination, and invasiveness. [11] Although conventional PTC usually metastasizes via the lymphatic system, TCV shows greater vascular invasion. This results in hematogenous metastasis to distant organs, such as the lungs and bones, and, although rare, even the brain. [8]

Metastasis to the brain typically occurs via hematogenous spread, illustrative of advanced tumor biology that can breach the blood-brain barrier. Neurological symptoms emerging from such pathology occur by means of mass effect, focal cerebral cortex disruptions, and vasogenic edema as evidenced by intracranial lesions. From a histopathologic

perspective, these cellular alterations are indicative of the classic nuclear morphology of PTC and elongated eosinophilic cell structures in TCV, reflecting increased aggressiveness and a less differentiated phenotype. [4]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

The present case shared several features with previously reported brain metastases from PTC, while also illustrating an unusually aggressive clinical trajectory. Brain metastasis from differentiated thyroid carcinoma has been consistently described as rare and prognostically unfavorable, with reported median survival after brain metastasis ranging from approximately 15 to 25 months in contemporary series. [12,13] Similar to published cohorts, our patient presented with nonspecific neurological symptoms, including headache, confusion, gait disturbance, and focal weakness, and the brain lesion was initially radiologically indistinguishable from a primary glial tumor or metastasis from a more common occult primary. [12,13,15]

A particularly close parallel existed with the series by Tahmasebi et al., in which brain metastasis was the first clinical manifestation in three of nine patients with PTC, and two of these patients had the tall cell variant. [16] This supported the observation that aggressive PTC variants may metastasize intracranially earlier and more unexpectedly than classic PTC. Our case also resembled reports in which solitary or limited brain lesions were treated surgically, because resection provided both decompression and definitive tissue diagnosis. [13,14] However, it differed from many cases in that the thyroid gland was clinically silent, there was no palpable cervical disease, and central neck dissection showed no regional nodal metastasis despite synchronous pulmonary disease and subsequent osseous progression. In the 2023 case series by Ha et al., most patients had known differentiated thyroid carcinoma before brain involvement, and some metastases were detected during systemic imaging rather than as the first manifestation. [14] In contrast, our case emphasized that tall cell PTC could declare itself first through symptomatic brain metastasis and then progress rapidly despite total thyroidectomy, radioactive iodine, brain-directed radiation, and TSH sup

4. What Have We Learned from This Case?

This case reinforced the point that a solitary enhancing brain mass in an adult should not be presumed to represent a glioma when the clinical context remains incomplete. The absence of thyroid symptoms, normal thyroid function tests, and a nonpalpable neck examination did not exclude an occult aggressive thyroid malignancy. Progressive headache, confusion, gait change, focal weakness, vasogenic edema, and unexplained small pulmonary nodules should therefore be regarded as red flags that justify a broad metastatic workup and early tissue diagnosis.

The practical lesson was that management should be multidisciplinary from the outset. In this patient, surgical excision was justified not only for symptom relief and mass effect, but also because it yielded adequate tissue for histology and immunohistochemistry, allowing recognition of metastatic tall cell PTC. Published data similarly suggested that selected patients with brain metastases from differentiated thyroid cancer may benefit from aggressive local therapy, particularly neurosurgery or stereotactic approaches, when performance status is favorable. [13,14] The case also underscored the need for close post-treatment surveillance, because tall cell PTC carries early mortality risk and may progress through lung and bone metastases even after apparently appropriate multimodal therapy.

Abbreviations

- Papillary thyroid carcinoma (PTC);
- Tall cell variant (TCV);
- Immunohistochemistry (IHC);
- Radioactive iodine (RAI)

5. Conclusion

We report this case to demonstrate an uncommon and clinically important presentation of PTC, tall cell variant: symptomatic brain metastasis as the initial manifestation of an otherwise occult thyroid primary. The case adds value by showing that aggressive thyroid carcinoma may be present without thyroid-related symptoms, without abnormal thyroid function, and without clinically evident cervical nodal disease. It also highlights the diagnostic importance of considering thyroid origin in metastatic carcinoma to the brain, particularly when supported by IHC for thyroglobulin and TTF-1.

The unfavorable outcome, despite gross total resection of the brain lesion, thyroidectomy, radioactive iodine, external beam radiation, and TSH suppression, illustrates the biologic aggressiveness of the tall cell variant. For clinicians, the central message is that unexplained neurological symptoms with a solitary enhancing brain mass should prompt timely tissue diagnosis and broad oncologic evaluation, including consideration of thyroid carcinoma. For the medical community, this case contributes to the limited literature on tall cell PTC presenting first with brain metastasis. It reinforces the need for vigilant surveillance and individualized multidisciplinary management.

Compliance with ethical standards

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Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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