AACE Clinical Case Rep. 8 (2022) 131–134

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Incidental Solitary Adrenal Metastasis as the Initial Manifestation of a Solid Variant of Papillary Thyroid Carcinoma, With Emphasis on Pathologic Diagnosis and Clinical Management

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ARTICLE INFO

Article history:
Received 13 October 2021
Received in revised form
1 January 2022
Accepted 5 January 2022
Available online 13 January 2022

Key words:
adrenal incidentaloma
papillary thyroid cancer
solid variant of papillary thyroid cancer
papillary thyroid cancer metastatic to the adrenal gland

ABSTRACT

Objective: Distant metastases from papillary thyroid carcinoma (PTC) are relatively rare and may be associated with a poor prognosis. The adrenal gland is a highly unusual site of metastasis in the natural course of PTC. Herein, we describe a case of an incidentally detected metastatic solid variant of PTC in the adrenal gland of an asymptomatic patient as the initial presentation.
Case Report: A 67-year-old male patient was evaluated for a 4.7-cm adrenal incidentaloma discovered during a workup for nephrolithiasis. Biochemical evaluation revealed a nonfunctioning adrenal mass. The patient underwent adrenalectomy, which revealed metastatic PTC. A subsequent thyroid ultrasound revealed an isthmic nodule. Fine needle aspiration of the nodule was cytologically suspicious for a follicular neoplasm, and gene expression analysis revealed an *HRAS* c.182A>G sequence variation. The patient subsequently underwent total thyroidectomy, which revealed a 1.2-cm solid variant of PTC in the thyroid isthmus. Postoperatively, the patient underwent radioactive iodine ablation.
Discussion: Our case illustrates an exceedingly rare and challenging situation—a metastatic solid variant of PTC in the adrenal gland of a patient with no prior history of PTC. When confronted with a PTC in the adrenal gland in the absence of a previously identified primary tumor, our experience suggests that the next step in management should be total thyroidectomy followed by radioactive iodine ablation.
Conclusion: A solid variant of PTC is a rare cause of an incidentally detected adrenal lesion. Multidisciplinary care team coordination is essential for accurate diagnosis and treatment plan formulation.

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for 80% to 93% of thyroid tumors in contemporary case series.[1] The majority of patients with PTC follow an indolent clinical course with an overall excellent prognosis and a life expectancy similar to the general population, with 5-year survival rates exceeding 98%.[2] Distant metastases have been reported in 10% to 15% of patients and are recognized as an unfavorable prognostic pathologic feature by the American Thyroid Association management guidelines, with the lungs and bones representing the most common sites of disease involvement.[3] The adrenal gland is a highly unusual site of PTC metastasis that has been described in several case reports of patients with a known prior history of PTC, in whom the metastasis was detected during postoperative surveillance.[4-7] Here, we report an exceedingly rare clinical scenario, in which a 67-year-old man who had no prior history of thyroid carcinoma or imaging evidence of thyroid nodules presented with an incidental adrenal mass, which led to a pathologic diagnosis of metastatic thyroid carcinoma based on morphologic and immunophenotypical features. Later, he was

Abbreviations: CT, computed tomography; PTC, papillary thyroid carcinoma; PTH, parathyroid hormone.

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https://doi.org/10.1016/j.aace.2022.01.002

diagnosed with a solid variant of PTC of the thyroid isthmus. To the best of our knowledge, this is the first case of adrenal metastasis of a solid variant of PTC that was discovered during the workup and management of an adrenal incidentaloma.

Case Report

The patient is a 67-year-old Caucasian man who initially presented to the emergency department with severe flank pain and hematuria. He underwent a noncontrast computed tomography (CT) scan of his abdomen/pelvis, which was diagnostic for nephrolithiasis. His laboratory workup was notable for a serum calcium level of 11.2 mg/dL (normal range, 8.4-10.2 mg/dL). Additionally, his CT scan showed an incidental 4.7-cm irregular heterogeneous mass in the right adrenal gland, with indeterminate imaging criteria. Of note, his kidney stone did not pass spontaneously and required lithotripsy. Subsequently, he was referred to our high-volume endocrine surgery clinic for evaluation of suspected primary hyperparathyroidism and a right adrenal incidentaloma.

With regard to his hyperparathyroidism workup, an elevation of the serum calcium level (10.9 mg/dL) was again observed, with a concordant elevation of his parathyroid hormone (PTH) level of 111.5 pg/mL (normal range, 15-65 pg/mL). His 25-hydroxyvitamin D level was within normal limits at 35.9 ng/mL. Ultrasound and technetium-99m sestamibi scan demonstrated a left inferior parathyroid adenoma. With regard to his adrenal lesion, a biochemical evaluation revealed a nonfunctioning adrenal mass. An adrenal protocol CT scan (noncontrast phase, portal venous phase, 15-minute delayed phase) redemonstrated an indeterminate right adrenal mass, measured at 4.7 × 4.6 × 3.8 cm (Fig. 1 *A* and *B*). Central fluid was noted, possibly representing necrosis. There was no internal fat density. Adrenalectomy was recommended to the patient, given the suspicious clinical features.

In the context of the adrenal mass being nonfunctional and having indeterminate, albeit suspicious clinical features, the patient wished to address his hyperparathyroidism first to minimize his risk of experiencing a recurrent kidney stone. He underwent resection of a left inferior parathyroid adenoma. Pathologic examination revealed benign parathyroid tissue (Fig. 2 *A*), and the surgery resulted in a clinical and biochemical cure with normalization of his PTH level to 26.8 pg/mL intraoperatively. Nine months after his surgery, the patient's PTH and serum calcium levels were 30.9 pg/mL and 9.1 mg/dL, respectively.

Six weeks after his parathyroidectomy, the patient returned for a right adrenalectomy. The surgery was started laparoscopically; however, intraoperatively, the superior margin of the adrenal gland appeared to be adhered to the right lobe of the liver, and the procedure was converted to an open surgery. Ultimately, a small rim of adherent liver was left on the superior portion of the adrenal gland. The remainder of the surgery proceeded without complication, and the patient was discharged home on postoperative day 4.

A microscopic examination of the adrenal lesion revealed a sheet of tumor cells (Fig. 2 *B*) with eosinophilic cytoplasm and open chromatin (Fig. 2 *C*). Occasional nuclear grooves were seen. The cells had diffuse and strong immunoreactivity for thyroglobulin, TTF-1, and PAX8, strongly supporting their being of thyroid origin (Fig. 2 *D*). The cells' immunonegativity for adrenal cortical (SF-1, inhibin, calretinin, D2-40, and melan A), melanotic (S100, SOX10, and HMB45), and neuroendocrine markers (chromogranin and synaptophysin) ruled out a primary adrenal tumor or a metastasis from melanoma or a neuroendocrine tumor. Given the immunoprofile of the tumor cells, their most likely source seemed to be a metastatic carcinoma from the thyroid gland. Notably, the patient had no palpable thyroid nodules on physical examination, and he had undergone a thyroid ultrasound for parathyroid localization

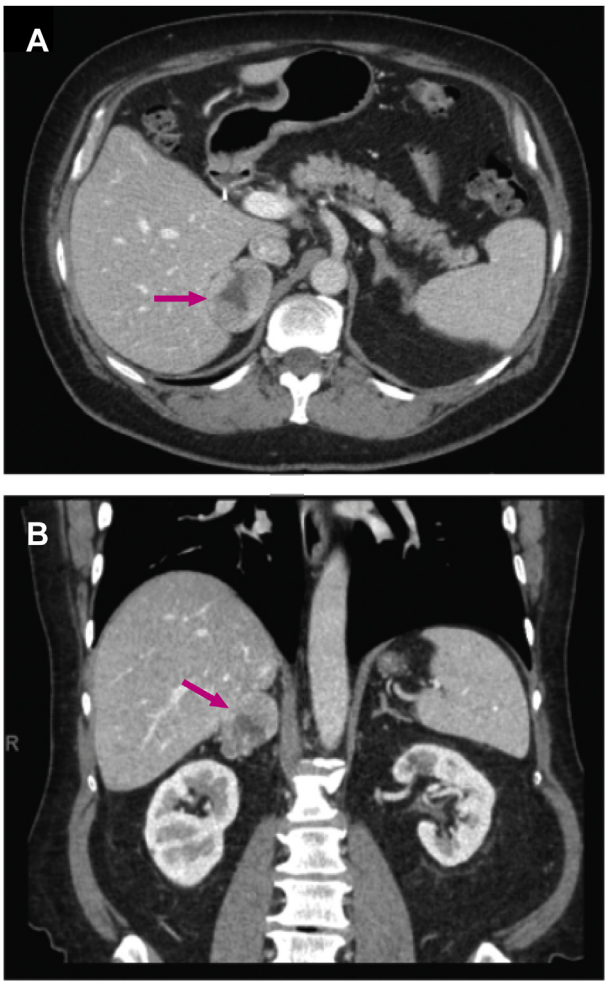

Fig. 1. Contrast-enhanced computed tomography scan shows an adrenal mass with central fluid, possibly representing necrosis, and no internal fat density. *A*, Axial plane image of the right adrenal gland lesion (pink arrow). *B*, Coronal plane image depicting the right adrenal gland lesion adherent to the liver (pink arrow).

prior to his parathyroidectomy, which had not revealed any suspicious thyroid nodules. A subsequent CT scan of the chest and whole body F-18-fluorodeoxyglucose positron emission tomography/CT imaging demonstrated no evidence of other sites of metastatic disease. In light of his surprising pathologic findings, the thyroid ultrasound was repeated, which revealed 2 nodules (Thyroid Imaging Reporting and Data System score of 4) in the right thyroid lobe, which were biopsied. Both biopsies were benign. Two months later, the ultrasound was repeated by the patient's endocrinologist, which revealed a 1.13 × 0.77 × 0.62-cm isthmic nodule that was solid and hypoechoic with irregular margins and microcalcifications. The nodule was assigned a Thyroid Imaging Reporting and Data System score of 5. Needle aspiration biopsy was cytologically suspicious for a follicular neoplasm. A corresponding gene expression analysis of the biopsied cells was suspicious and revealed an *HRAS* c.182A>G sequence variation. The decision was then made to proceed with total thyroidectomy. The patient's preoperative thyroglobulin level was 28 ng/mL, and thyroglobulin antibodies were undetectable. Subsequently, he underwent an uncomplicated total thyroidectomy. Histopathology confirmed a 1.2-cm solid variant of PTC with angioinvasion located in the isthmus, showing similar morphologic characteristics to the adrenal lesion (Fig. 2 *E*), and a separate 2-mm conventional papillary microcarcinoma in the right thyroid lobe (Fig. 2 *F*). One benign

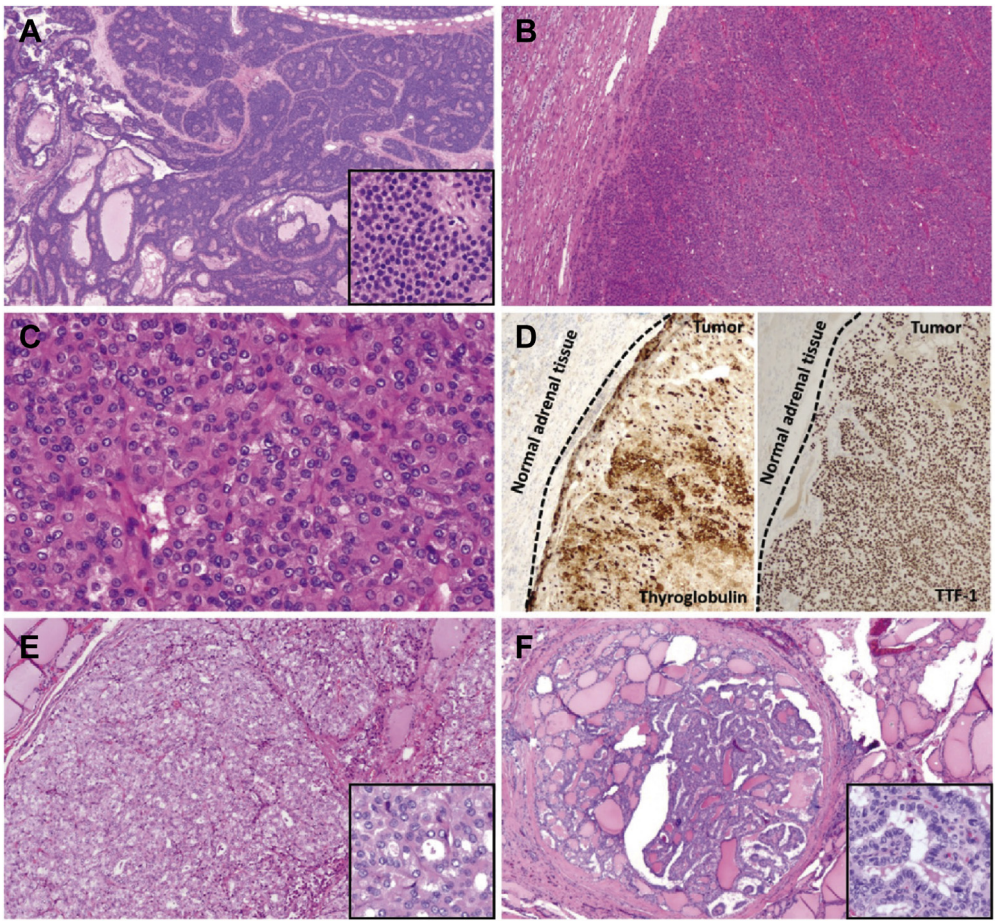

Fig. 2. Pathologic findings of 3 lesions in a 67-year-old male patient. *A*, The left inferior parathyroid gland shows benign parathyroid tissue (magnification ×40; inset magnification ×200). *B*, The adrenal mass demonstrates a well-demarcated tumor composed of a sheet of tumor cells (magnification ×40). *C*, At a high magnification (×200), the eosinophilic cytoplasm, open chromatin, and occasional nuclear grooves of the sheet are readily visible. *D*, Diffuse and strong positivity for thyroglobulin (cytoplasmic) and TTF-1 (nuclear) supports a thyroid origin (magnification ×100). Total thyroidectomy reveals a solid variant of papillary thyroid carcinoma with angioinvasion in the thyroid isthmus, showing similar morphologic characteristics as the adrenal lesion (*E*) and a separate conventional papillary microcarcinoma in the right thyroid lobe (*F*) (magnification ×40; inset magnification ×200).

lymph node was removed. The patient's postoperative thyroglobulin level was 0.1 ng/mL, and thyroglobulin antibodies were undetectable. A whole body iodine-131 scan performed 5 days after the administration of 184-mCi I-131 showed uptake in the thyroid bed only, corresponding to the thyroid remnant. No further distant metastases were seen. The 6-month postoperative laboratory results showed an undetectable serum thyroglobulin. He has been treated with thyroid hormone suppression to <0.1 mU/L and monitored every 3 months with a thyroglobulin level and every 6 months with a neck ultrasound.

Discussion

Our case illustrates an exceedingly rare and challenging situation: a metastatic solid variant of PTC in the adrenal gland of a 67-year-old man with no prior history of PTC or imaging evidence of thyroid nodules at the time of diagnosis. We were able to render the correct diagnosis because of our high degree of clinical suspicion coupled with careful clinicoradiological correlation and a thorough pathologic examination. Moreover, to the best of our knowledge, this is the first report of a solid variant of PTC with an associated *HRAS* sequence variation. This is particularly notable because *RAS*-mutated thyroid tumors are most often associated with follicular neoplasms.[8,9] Although there is a paucity of genetic data for patients with a solid variant of PTC, to our knowledge, only 1 *RAS*-mutant solid variant of PTC has been previously reported; in that case, *NRAS* was mutated.[10]

PTC is the most common thyroid cancer, which predominantly affects women and has a typically indolent clinical course. Distant metastasis in PTC is an unusual occurrence; when it occurs, it most commonly affects the lungs and bones. In a study of 1038 consecutive patients treated at the Memorial Sloan Kettering Cancer Center over a 55-year period, 44 (4%) patients had distant metastases at their initial examination, and the incidence was reportedly highest in patients aged >45 years with follicular thyroid carcinoma.[11] Several case reports have described PTC metastasizing to the adrenal gland; however, in each of these cases, the adrenal lesion was detected during postoperative surveillance in patients with a known history of PTC. A solid variant of PTC is rare and poorly characterized and has been predominantly described in children with a history of radiation exposure. This variant is associated with a slightly higher frequency of distant metastases and a less favorable prognosis than classical PTC.[12,13]

When presented with the pathology of thyroid tissue in the adrenal gland without an identified primary thyroid cancer, there are 3 possibilities. The patient has the following: (1) a metastatic thyroid malignancy, (2) benign ectopic thyroid tissue (also known as a thyroid rest) of the adrenal gland (ie, thyroid parenchyma

present outside the orthotopic position of the thyroid gland), or (3) a malignancy derived from ectopic thyroid tissue. An ectopic thyroid results from a failure of the thyroid to descend from the thyroid anlage region to its final location anterior to the trachea, which can present at any position from the foramen caecum at the base of the tongue to the mediastinum, with the lingual area being the most common location.[14] The other possible locations of an ectopic thyroid include the head and neck, axilla, heart and ascending aorta, thymus, gastrointestinal system, and adrenal gland. The prevalence of ectopic thyroid is 1 case per 100 000 to 300 000 healthy individuals; however, it has been reported to occur in 1 per 4000 to 8000 patients who have thyroid disease.[15,16] Several case reports have described benign ectopic thyroid tissue in the adrenal gland; however, in our case, malignant cells were clearly observed.[17-21] Malignant transformation of ectopic thyroid tissue has been described in case reports and should be considered when making a differential diagnosis in unusual situations such as ours.[22] However, considering the low prevalence of ectopic thyroid as well as the adrenal gland being a rare location of an ectopic thyroid, a thyroid carcinoma arising from ectopic thyroid tissue should be considered only after a primary thyroid lesion has been confidently ruled out.

A notable challenge in this case was that the thyroid nodule harboring carcinoma was not identified on the first 2 thyroid ultrasound studies. The ultrasounds were performed 8 months and 2 months prior to the diagnostic biopsy, and the isthmic nodule was not identified on either of the first 2 studies. There are several possible reasons for this occurrence. The indication for the first ultrasound was preoperative parathyroid adenoma localization; as such, the technician and radiologist may have overlooked the suspicious thyroid nodule while focusing on identifying parathyroid pathology. Additional possibilities, which are not mutually exclusive, include growth of the thyroid nodule between the ultrasound studies and the operator-dependent nature of ultrasound examinations. Given the patient's prior parathyroidectomy, total thyroidectomy required reoperative neck surgery, rendering the patient at higher risk for operative complications. As such, it was believed that a diagnosis of a primary PTC should be confirmed in the preoperative setting. However, because malignancy arising from ectopic thyroid tissue in the adrenal gland is extremely rare, it would also have been reasonable to have proceeded directly to total thyroidectomy after the adrenal pathology findings were identified, without intervening thyroid ultrasound, needle aspiration biopsy, and molecular testing.

Conclusion

In conclusion, to the best of our knowledge, this is the first report of a metastatic solid variant of PTC presenting as an adrenal incidentaloma and the first case of an *HRAS*-mutated solid variant of PTC. When confronted with the highly unusual situation of having PTC in the adrenal gland in the absence of an identified primary tumor, our experience suggests that the next step in management should be total thyroidectomy. This is similar to the management of patients with metastatic PTC to other sites, such as the lung or bone, at the time of diagnosis—which typically includes total thyroidectomy followed by radioactive iodine ablation.[23] Even when it is unclear whether the patient has a metastatic PTC or a malignant transformation of a thyroid rest, total thyroidectomy offers the benefit of treating, or definitively ruling out, a primary thyroid tumor. During the follow-up, residual malignant tissue can be ablated with radioactive iodine, and the thyroglobulin levels can be followed postoperatively. Ultimately, multidisciplinary care team co-ordination was critical in accurately diagnosing and formulating a treatment plan for this patient.

Acknowledgment

We thank Dave Primm of the UT Southwestern Department of Surgery for help in editing this article. Dr Karalis was supported by a Physician-Scientist Institutional Award from the Burroughs Wellcome Fund (award No. 1018897).

Disclosure

The authors have no multiplicity of interest to disclose.

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