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Papillary Thyroid Carcinoma With Cystic Changes in a Patient With Prior History of Toxic Nodule

Gliceida Maria Galarza Fortuna, MD[1], Paola Rios, MD[1], Ailyn Rivero, MD[1], Gabriela Zuniga, MD[1], Kathrin Dvir, MD[1], Michael M. Pagacz, MD[1], and Alex Manzano, MD[1]

Abstract

Thyroid nodules are palpable on up to 7% of asymptomatic patients. Cancer is present in 8% to 16% of those patients with previously identified thyroid nodules. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 85% of thyroid cancers. Although most appear as solid nodules on ultrasound imaging, a subset of 2.5% to 6% has cystic components. The presence of cystic changes within thyroid nodules decreases the accuracy of fine needle aspiration (FNA) in the diagnosis of thyroid cancer, given the difficulty of obtaining appropriate cellular content. This becomes a diagnostic and therapeutic challenge. We present a case of a 31-year-old female with a 1-month history of palpitations, fatigue, and night sweats, who underwent evaluation, and was diagnosed with subclinical hyperthyroidism. She presented 4 years later with compressive symptoms leading to repeat FNA, showing Bethesda III-atypia of undetermined significance and negative molecular testing. Thyroid lobectomy revealed PTC with cystic changes. This case is a reminder that patients with hyperfunctioning thyroid nodule should have closer follow-up. It poses the diagnostic dilemma of how much is good enough in the evaluation and management of a thyroid nodule. Early detection and action should be the standard of care.

Keywords

papillary thyroid carcinoma, thyroid cancer, papillary thyroid carcinoma with cystic changes

Introduction

Thyroid nodules are palpable on up to 7% of asymptomatic patients; similarly, radiographic evidence of thyroid gland nodules can be detected by ultrasonography in approximately 19% to 68% of the population. Regardless of the frequency of thyroid nodules, cancer is present in only 8% to 16% of the patients with previously identified thyroid nodules, and is more commonly found in females than males.[1,2]

Fine needle aspiration (FNA) is the gold standard for the evaluation of thyroid nodules with sonographic features suggestive of cancer. The Bethesda System is used for cytopathologic evaluation of FNA and estimates the risk of malignancy of the specimen. Furthermore, next-generation sequencing panels are often used for detection of mutations associated with thyroid cancers in those patients with atypia of undetermined significance/follicular lesion of unknown significance (AUS/FLUS)—Bethesda class III on cytological evaluation.[3]

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 85% of thyroid cancers.[2] These lesions tend to appear as solid nodules on ultrasound imaging; however, cystic components can be seen in approximately 2.5% to 6% of all thyroid cancers. The presence of cystic changes within thyroid nodules decreases the accuracy of FNA in the diagnosis of thyroid cancer given the difficulty of obtaining appropriate cellular content.[4] This becomes a diagnostic and therapeutic challenge.

We report a case of PTC arising from a complex (Bethesda class III) nodule with significant cystic component and negative molecular study of the FNA sample. The patient has prior history of subclinical hyperthyroidism and increased I-123 uptake within the right thyroid lobe; FNA was benign.

Case Presentation

Our patient is a 31-year-old white Hispanic female with pertinent history of subclinical hyperthyroidism with negative

[1]Mount Sinai Medical Center, Miami Beach, FL, USA

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Corresponding Author:
Gliceida Maria Galarza Fortuna, Department of Internal Medicine, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach, FL 33140, USA.
Email: gliceida.galarza@gmail.com

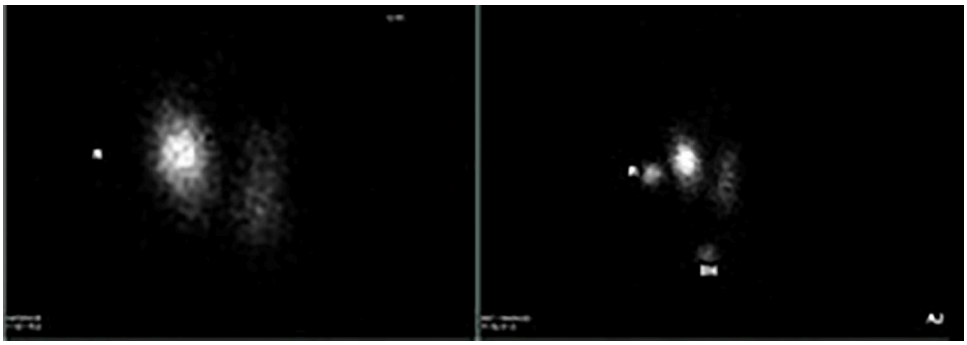

Figure 1. I-123 thyroid uptake imaging showed an asymmetric increased uptake within the right lobe of the thyroid.

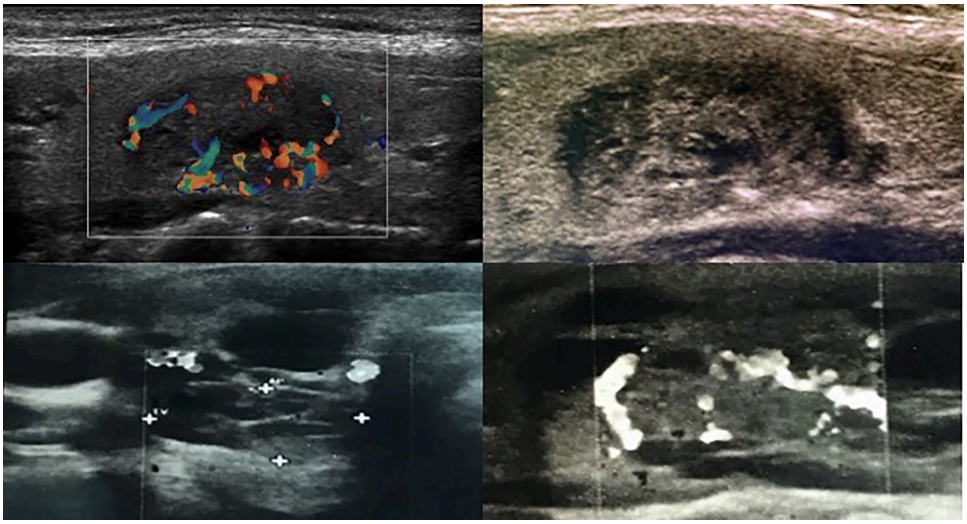

Figure 2. Upper imaging: Thyroid nodule measuring 2.4 cm in greatest dimension. Heterogeneous mixed cystic/solid vascular nodule located in the mid-right thyroid lobe. Lower imaging: 2.1 × 2 × 3.03 cm complex nodule with irregular borders, internal macrocalcifications, and a microcalcification with no evidence of a clear halo.

thyroglobulin antibodies, thyroid-stimulating immunoglobulins, and thyroid peroxidase antibodies. She originally presented to her primary care provider complaining of 1-month history of palpitations, fatigue, and night sweats. Thyroid-stimulating hormone level checked at an urgent care center, 3 days prior, had been below the reference range. Subsequent evaluation and management included I-123 thyroid uptake imaging, which showed an asymmetric increased uptake within the right lobe of the thyroid (Figure 1). Thyroid ultrasound revealed a 2.4-cm heterogeneous mixed cystic/solid vascular nodule located in the mid-right thyroid lobe, corresponding to the focal region of intense uptake noted on the nuclear medicine thyroid uptake study (Figure 2). FNA of the nodule was done, and the cytology showed a benign, BETHESDA II nodule.

Patient was followed-up yearly by physical examination, symptoms survey, and thyroid function test, which were normal. Follow-up thyroid ultrasound, 4 years after the initial presentation, was done due to the presence of compression symptoms. This ultrasound showed a 2.1 × 2 × 3.03 cm (6.4 mL) complex nodule with irregular borders, internal macrocalcifications, and a microcalcification with no evidence of a clear halo and internal vascularity (Figure 2), which corresponded to the nodule seen on I-123 thyroid uptake imaging. FNA was repeated; cytology revealed atypical cells arranged in knobby clusters. Nuclei were poorly visualized, but appeared enlarged with focal chromatin clearing, compatible with a Bethesda III-AUS. A reflex thyroid genomic classifier, Thyrosec, was done with a negative result (low probability of cancer, 3%).

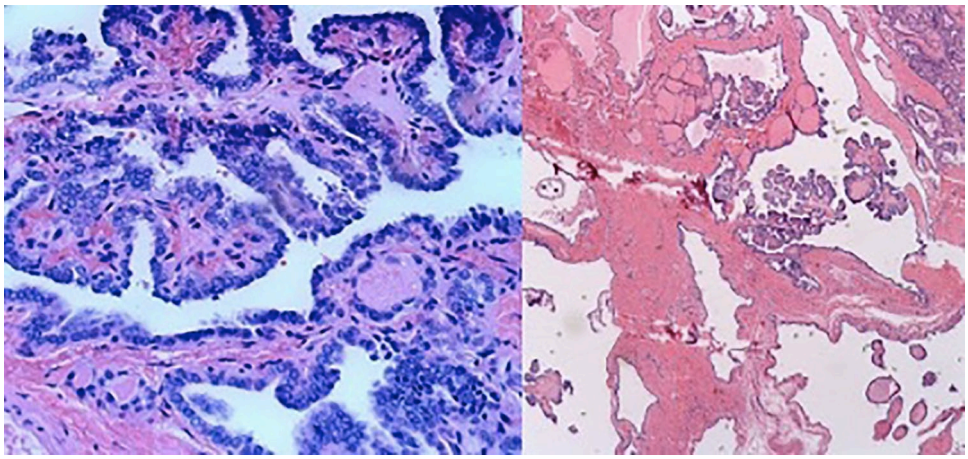

Figure 3. Papillary thyroid carcinoma, classic type with calcifications including psammoma bodies and cystic change.

Given that the thyroid nodule continued to grow, and the patient continued complaining of compressive symptoms in her neck, she was referred to surgical oncology for a right hemithyroidectomy. The pathology report showed PTC, classic type, with calcifications including psammoma bodies and cystic change (2.5 cm) without lymph node involvement (Figure 3).

Discussion

Ultrasound imaging is routinely done on thyroid nodules to assess the need of FNA as a diagnostic study. Benign lesions often appear as isoechoic or hyperechoic nodules with well-defined margins and variable degree of vascularity on Doppler; a hypoechoic surrounding shadow is often seen. Malignant thyroid nodules, on the other hand, are typically associated with marked hypo-echogenicity, irregular margins without a halo, microcalcifications, intranodular vascularity greater than peripheral vascularity, and taller greater than width. Similarly, PTC often presents as a nodule with calcification, irregular shape, and heterogeneous internal echogenicity.[5] Ultrasound is an important tool for the classification of thyroid nodules; however, FNA remains the gold standard for diagnosis.

When a thyroid nodule is found and measures more than 1 cm, a thyroid-stimulating hormone level should be obtained. If it is low, a radionuclide thyroid uptake scan should be ordered to study if the nodule is a hyperfunctioning "hot" nodule, characterized by increased thyroid nodule uptake relative to its surroundings. The nodule can also be isofunctioning, or nonfunctioning. If the nodule is hyperfunctioning, no FNA is necessary, considering hyperfunctioning nodules rarely are malignant.[2] Mirfakhraee et al[6] described the prevalence of malignancy on hyperfunctioning nodules as 3.1%. They found that follicular thyroid carcinoma and Hurthle cell carcinoma were more prevalent in "hot nodules" than in all nodules.[6] Giles et al[7] described the incidence of thyroid carcinoma in patients with toxic nodule to be 12% and 6.4% in toxic multinodular goiter. However, the incidence could be even higher given that the majority ended in radioiodine treatment.[7] The decision of FNA biopsy in hyperfunctioning nodules may be considered based on high suspicious sonographic features as in the presented case. Extrapolating from the latter point, the clinician should be aware that a "hot nodule" can harbor malignancies.

Furthermore, malignant thyroid nodules are often described as having a solid internal content. Na et al[8] in 2016 published a study in which they correlated the risk of malignancy of different thyroid nodules with the features of their internal content. In their research, minimally cystic nodules and partially cystic nodules had a risk of malignancy of approximately 3.3%. A nodule was described as minimally cystic if an anechoic cystic portion was identified within the nodule, and partially cystic if the anechoic portion composed more than 10% of the nodule's volume.[8]

Papillary thyroid carcinoma is more often associated with cystic lesions than any other thyroid cancers. Given the low cellularity associated with this cystic lesion, and the degenerative changes often associated with these cystic areas, diagnosing thyroid cancer by FNA from a lesion with a high cystic content is often difficult.[4,9] Some radiographic characteristics, such as the presence of microcalcifications within the solid portion of a partially cystic thyroid nodule, and eccentric configuration of the nodule should raise concern for a thyroid malignancy. Previous research has estimated a prevalence of cystic changes on approximately 1.3% to 6% of PTC.[4]

FNA is indicated on nodules measuring 1 cm or larger with high or intermediate suspicion characteristics on

ultrasound, 1.5 cm or larger with low-suspicion pattern, and last, 2 cm or larger with very low suspicion pattern on ultrasound.[1] The Bethesda System for Reporting Thyroid Cytopathology is a standardized reporting system for thyroid FNAs. This system has 6 different categories ranging from I, nondiagnostic or unsatisfactory, to VI, classified as malignant. Lesions reported as benign on this system have a 0% to 3% risk of malignancy. On the other hand, AUS/FLUS, Bethesda class III, have a 6% to 18% risk of malignancy.[10]

If a nodule is Bethesda II, the false-negative rate is low. Glynn et al[11] studied 400 patients, 63% were benign thyroid nodules and the negative predictive value of an initial benign cytology was 99%. However, in the case presented in this article, the patient had a cytology classified as Bethesda II, and 4 years later, FNA was Bethesda III, and her histology was positive for PTC. Therefore, the American Thyroid Association recommends follow-up for benign nodules with benign FNA cytology and low to intermediate suspicious characteristics with ultrasound every 12 to 24 months. FNA should be repeated if there is evidence of new suspicious sonographic evidence, or if there is increase in size of 20% in at least 2 nodule dimensions.[2]

Molecular testing/analysis is often part of the usual management of thyroid nodules with FNA result of AUS/FLUS.[1] ThyroSeq v2 is a large multigene, DNA sequencing panel used to identify driver mutations associated with thyroid cancer in nodules classified as AUS/FLUS. This next-generation sequencing test is able to detect up to 56 genes associated with thyroid cancer. Several studies have been done to assess the sensitivity and specificity of this molecular study to detect thyroid cancer. Nikiforov et al[3] designed a prospective study to determine if this multigene next-generation sequencing assay provides any benefit in the diagnosis of AUS/FLUS nodules. In this study, they proved that ThyroSeq v2 has a 90.9% sensitivity and 92.1% specificity in detecting thyroid cancer with an overall accuracy of 91.8%.[3]

Most patients with a negative result on the DNA sequencing test do not opt for thyroidectomy. Indications for thyroidectomy on ThyroSeq-negative nodules include enlarging nodules, compressive symptoms, and/or patient's preference. In our case ThyroSeq was a false negative with a low risk of malignancy per the test. However, patient went for a lobectomy due to symptoms and ultrasound thyroid nodule appearance. Moreover, Taye et al designed a study to determine the clinical performance of ThyroSeq v2 in thyroid nodules with a Bethesda classification of AUS/FLUS. In their study, 23% of patients with a negative ThyroSeq v2 result underwent thyroid resection, of the 23 resected specimens, 1 had a final surgical pathology showing PTC—oncocytic variant, for a false-negative rate of only 4%.[12] Even with negative molecular test results, the clinician should consider all the patient risks for thyroid cancer as the thyroid ultrasound high-risk features for malignancy.

Conclusion

Cystic papillary carcinoma is a variant of PTC, which continues to be a diagnostic challenge due to its hypocellular features. Previous studies have shown that only 0.2% of cystic PTC have been diagnosed by FNA.[13] This case serves as a multifaceted reminder that a diagnosis of autonomously functioning thyroid nodules should not be the end of a patient's evaluation, as we now know, more and more, that it can be a risk factor for tumorigenesis. Furthermore, this case poses the significant dilemma of how much is good enough. In the evaluation and management of a thyroid nodule, early detection of tissue that could potentially have more serious consequences for the patient in the long run should be the standard of care, and failing to do so should be something we aim to avoid. This case is a call to review the optimal recommendations that physicians provide for patients similar to the one presented in this article.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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ORCID iD

Gliceida Maria Galarza Fortuna https://orcid.org/0000-0002-1084-953X

References

1. Burman KD, Wartofsky L. Clinical practice. Thyroid nodules. *N Engl J Med*. 2015;373:2347-2356.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26:1-133.
3. Nikiforov YE, Carty SE, Chiosea SI, et al. Impact of the multi-gene thyroseq next-generation sequencing assay on cancer diagnosis in thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance cytology. *Thyroid*. 2015;25:1217-1223.

4. Kim JY, Kim E, Lee HS, Kwak JK. Conventional papillary thyroid carcinoma: effects of cystic changes visible on ultrasonography on disease prognosis. *Ultrasonography*. 2014;33: 291-297.
5. Dighe M, Barr R, Bojunga J, et al. Thyroid ultrasound: state of the art. Part 2—focal thyroid lesions. *Med Ultrason*. 2017;19:195-210.
6. Mirfakhraee S, Mathews D, Peng L, Woodruff S, Zigman JM. A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. *Thyroid*. 2013;6:7. doi:10.1186/1756-6614-6-7
7. Giles YS, Tunca F, Boztete H, Kapran Y, Terzioglu T, Tezelman S. The risk factors for malignancy in surgically treated patients for Graves' disease, toxic multinodular goiter, and toxic adenoma. *Surgery*. 2008;144:1028-1037.
8. Na DG, Kim JH, Kim DS, Kim SJ. Thyroid nodules with minimal cystic changes have a low risk of malignancy. *Ultrasonography*. 2016;35:153-158.
9. Mokhtari M, Kumar PV, Hayati K. Fine-needle aspiration study of cystic papillary thyroid carcinoma: rare cytological findings. *J Cytol*. 2016;33:120-124.
10. Cibas E, Ali S. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2017;27:1341-1346.
11. Glynn N, Hannon MJ, Lewis S, et al. Utility of repeat cytological assessment of thyroid nodules initially classified as benign: clinical insights from multidisciplinary care in an Irish tertiary referral centre. *BMC Endocr Disord*. 2016; 16:45.
12. Valderrabano P, Khazai L, Leon ME, et al. Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology. *Endocr Relat Cancer*. 2017;24:127-136. doi:10.1530/ERC-16-0512
13. Yang GCH, Stern CM, Messina AV. Cystic papillary thyroid carcinoma in fine needle aspiration may represent a subset of the encapsulated variant in WHO classification. *Diagn Cytopathol*. 2010;38:721-726. doi:10.1002/dc.21282