Autopsy Case Reports

Article / Clinical Case Report

Multifocal papillary carcinoma of the thyroid with heterotopic ossification and extramedullary hematopoiesis associated with a lipomatous follicular nodule

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How to cite: Xavier-Júnior JCC, Camilo-Júnior DJ, Conrado-Neto S, Lippe ACSC, Mattar NJ. Multifocal papillary carcinoma of the thyroid with heterotopic ossification and extramedullary hematopoiesis associated with a lipomatous follicular nodule. Autops Case Rep [Internet]. 2019;9(2):e2018083. https://doi.org/10.4322/acr.2018.083

ABSTRACT

Heterotopic ossification has been described in papillary thyroid carcinoma in association with high incidence of extrathyroidal invasion, multifocality, lymph node metastasis, and older age. Nevertheless, it has not been described as a specific subtype of papillary thyroid carcinoma, because of its rarity. We described the case of an 80-year-old female patient, with familial history of papillary thyroid carcinoma. In the annual screening examination, she was diagnosed with thyroid nodules. The patient was submitted to a thyroidectomy because the fine needle aspiration cytology was positive for malignancy according to the Bethesda classification. The surgical specimen analyses showed a multifocal papillary carcinoma with one major lesion in the left lobe measuring 0.9 cm, and two small lesions (0.4 cm and 0.2 cm) in the right lobe. Only the biggest lesion in the right lobe had the osteoid matrix with rare osteoclasts and fat metaplasia with progenitor cells. There was perineural invasion, but vascular invasion was not identified. The margins were free and there was no extrathyroidal extension. In the left lobe there was an oncocytic nodule and a lipomatous follicular nodule. In recent years there has been a significant increase in the diagnosis of thyroid cancer, mainly because of the finding of microcarcinomas as a result of many requests for cervical image exams. Future studies may define (i) whether papillary thyroid carcinoma with heterotopic ossification is a true histological variant; (ii) the causes of that alteration; and (iii) eventual follow-up implications.

Keywords
Thyroid Gland; Thyroid Neoplasms; Ossification, Heterotopic; Carcinoma, Papillary

INTRODUCTION

Over the last 20 years, there has been a significant increase in the diagnosis of thyroid cancer, mainly due to the discovery of microcarcinomas[1] as a result of excessive requests for cervical image exams.[2] Among the different subtypes of thyroid cancer, papillary thyroid carcinoma (PTC) is the most frequent.

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There are many variants of PTC, but PTC with intratumoral heterotopic ossification (IHO) has not been defined as a singular one.[3] The main risk factor for the development of thyroid cancer is previous radiant exposure.[2,3]

In the latest estimate (2016) from the Brazilian Cancer National Institute (INCA – Instituto Nacional do Cancer José Alencar Gomes da Silva) approximately 7,000 new cases of thyroid cancer were expected, and it was the eighth most frequent malignant neoplasia among women.[2]

We describe a multifocal PTC with IHO and extramedullary hematopoiesis (EMH) associated with a lipomatous colloid nodule in a patient with multinodular goiter. We believe that collectively all these 4 findings in a single case wasn't described in the English language, based on literature research on PUBMED using the uniterms "papillary thyroid carcinoma" and/or "heterotopic ossification" and/or "extramedullary hematopoiesis" and/or "lipomatous thyroid nodule".

CASE REPORT

An 80-year-old female patient sought medical care because she was incidentally found to have a thyroid nodule during an annual screening exam. Both of her sons had been previously been diagnosed with papillary thyroid carcinoma. The patient's thyroid hormone levels were normal: TSH: 3.1 Um/L (0.3-4.0 mU/L); freeT4: 1.04 (0.7-1.8 ng/dL). The cervical ultrasound revealed a multinodular goiter with coarse calcification in the right lobe. In the left lobe, two well-defined nodules (one with 7.2 mm and the other with 11.9 mm), and one irregular outline lesion measuring 9.9 mm, which did not fit all the benign criteria, were found. The results of the fine needle aspiration of the irregular lesion in the left lobe revealed it to be malignant and consistent with papillary carcinoma (category VI of the Bethesda system).[4] The aspiration sample provided a hypercellular smear with widely oncocytic changes. It was also identified nuclear grooves and rare pseudo nuclear inclusions (Figure 1). No colloid was present in this sample.

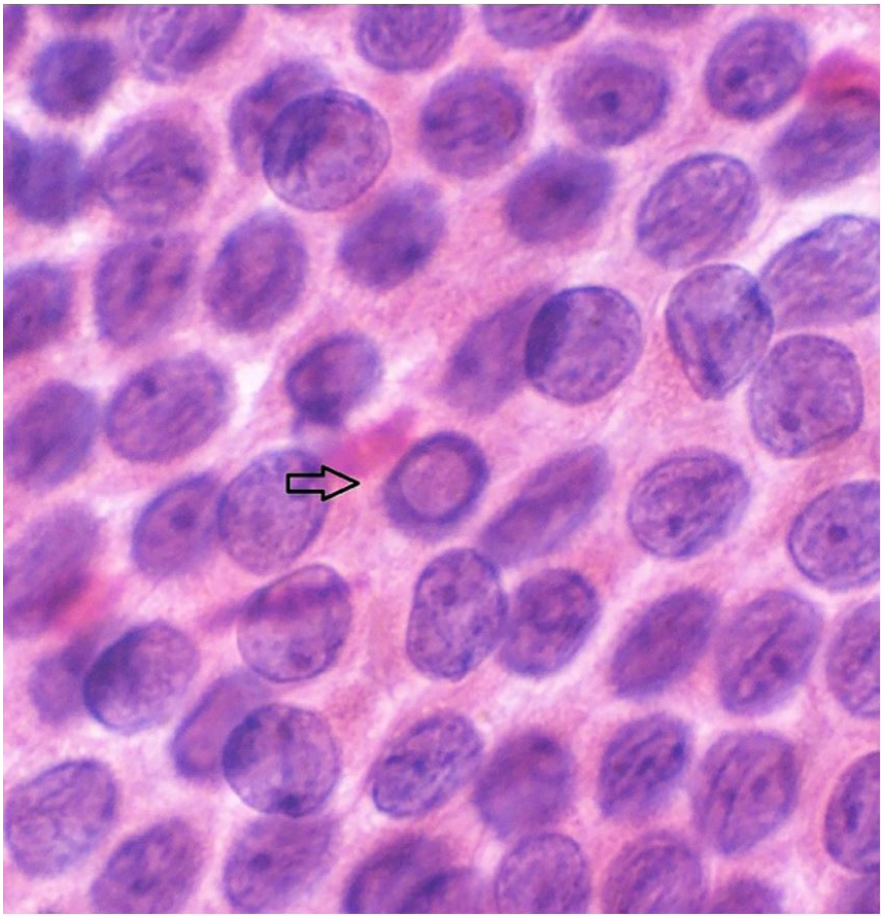

Figure 1. Photomicrograph of the fine needle aspiration smear. Nuclear grooves and a pseudo inclusion (arrow) (H&E, 1,000X).

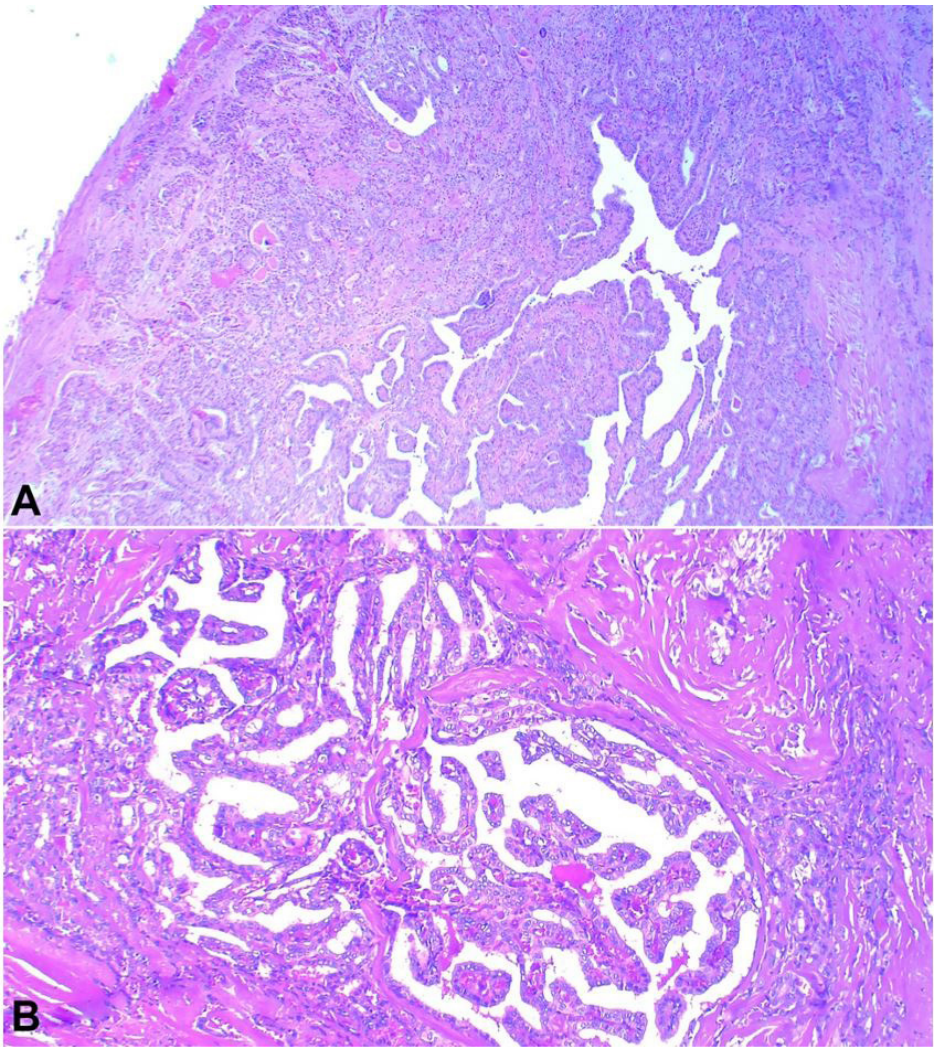

Figure 2. Photomicrograph of the surgical specimen. **A –** Low power view of papillary thyroid carcinoma in the left thyroid lobe (H&E,40X); **B –** Panoramic view of the smaller lesion in the right lobe with a papillary architecture of a microcarcinoma of PTC (H&E, 100X).

Patient subsequently underwent thyroidectomy. During surgery no suspicious cervical lymph nodes were identified.

At gross analyses, the surgical specimen weighed 17 g. The right lobe measured 4.3 × 2.0 × 1.5 cm, the isthmus 3.0 × 1.5 × 0.8 cm, and the left lobe 4.5 × 2.0 × 1.5 cm. There was a multifocal PTC (Figures 2 to 4) with one major lesion in the left lobe measuring 0.9 cm, and two small lesions in the right lobe measuring 0.4 cm and 0.2 cm. Only the largest lesion in the right lobe showed IHO with EMH. All lesions showed nuclear features of PTC, and a predominant follicular pattern with areas of classical subtype.

The IHO was characterized by an osteoid matrix (Figure 4A) with rare osteoclasts (Figure 4B) and EMH was characterized by fat metaplasia with progenitor cells

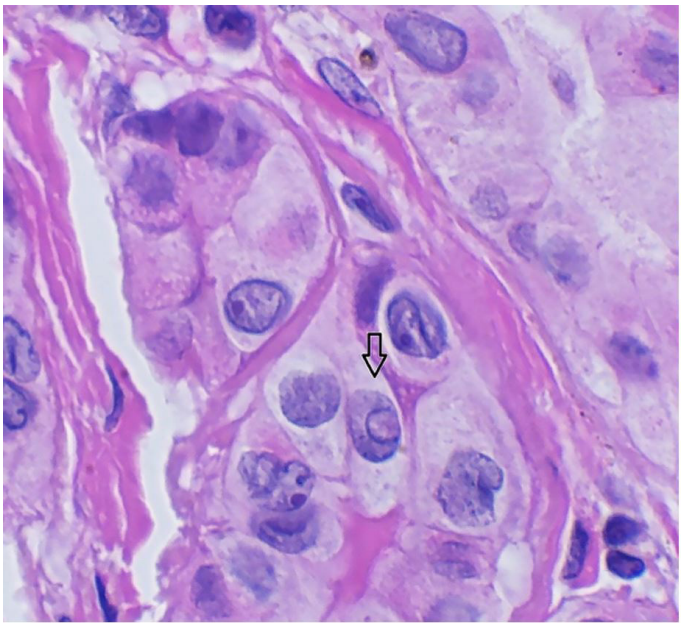

Figure 3. High magnification photomicrograph of the surgical specimen. Note the pseudo inclusion (H&E,1000X).

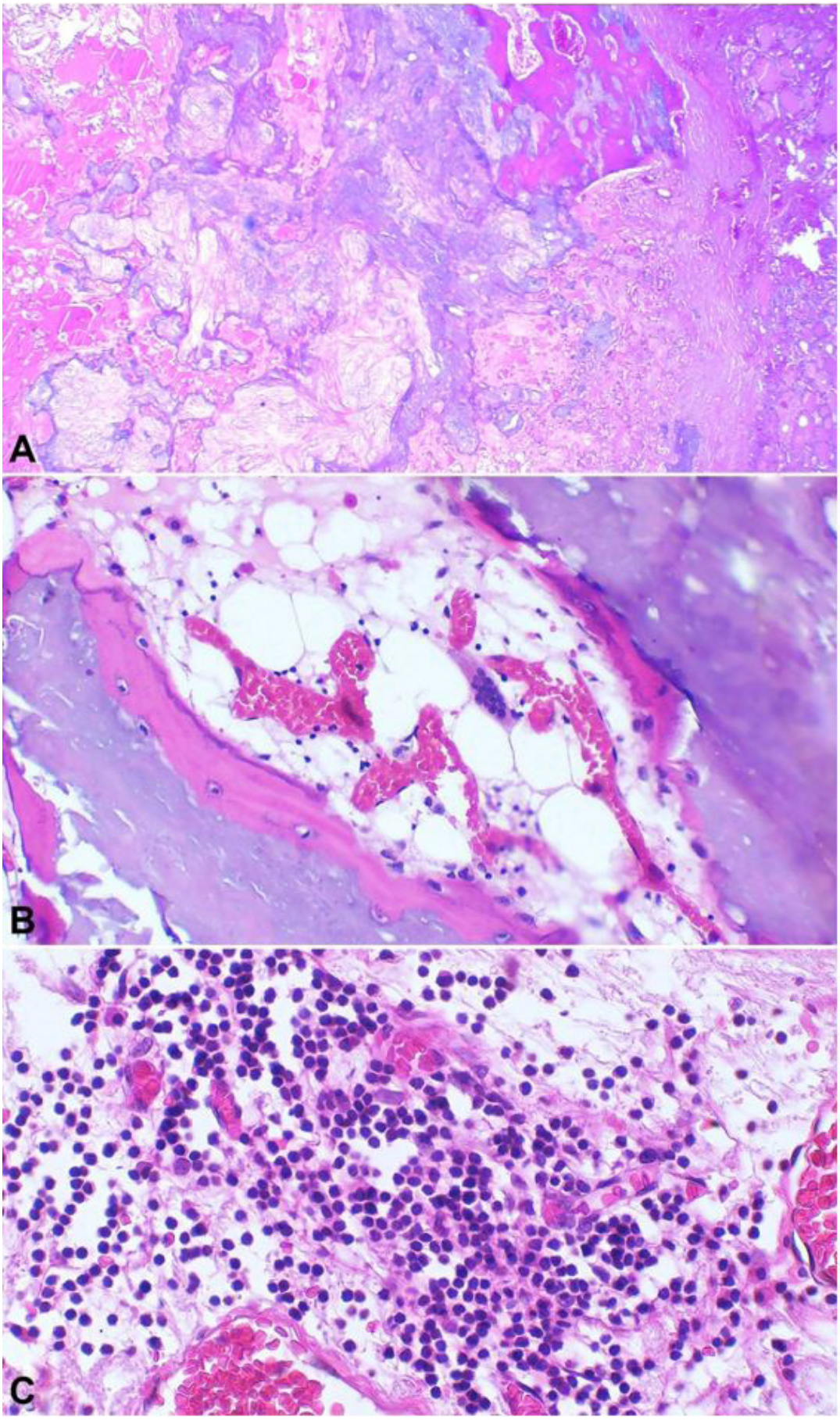

Figure 4. Photomicrographs of the surgical specimen. **A –** Panoramic view of the 0.4 cm lesion in the right lobe (H&E, 40X); **B –** Intratumoral heterotopic ossification. Note the osteoclast (H&E, 400X); **C –** Progenitor bone marrow cells (H&E, 400X).

(Figure 4C). IHO was identified in both right lobe nodules while EMH was present in only the larger (0.4 cm) nodule.

There was perineural invasion (Figure 5), but vascular invasion was absent. The margins were free of neoplasia and there was no extrathyroidal extension. In the left lobe there was a lipomatous follicular nodule (Figure 6). The lipomatous follicular nodule can be described as a non-capsulated follicular proliferation among mature adipose cells. In this setting, there was good correlation among the ultrasound and the histological analyses.

The patient's outcome was uneventful and she was referred to the nuclear medicine service because of the multifocality and the perineural invasion.

DISCUSSION

Heterotopic ossification has been described in up to 20% of papillary thyroid carcinomas[5-7] and is associated with a high incidence of extrathyroidal extension,[6,7] multifocality, lymph node metastasis,[7] and older age,[6]; however, it does not seem to influence the survival rate.[5] In our case, the patient was 80 years old and the tumor was multifocal, but there was neither extrathyroidal extension nor lymph node metastasis.

The cervical ultrasound examination lacks a pathognomonic finding of malignancy in thyroid nodules.[8] The finding of coarse calcification is frequently associated with benign nodules in multinodular goiter.[8]

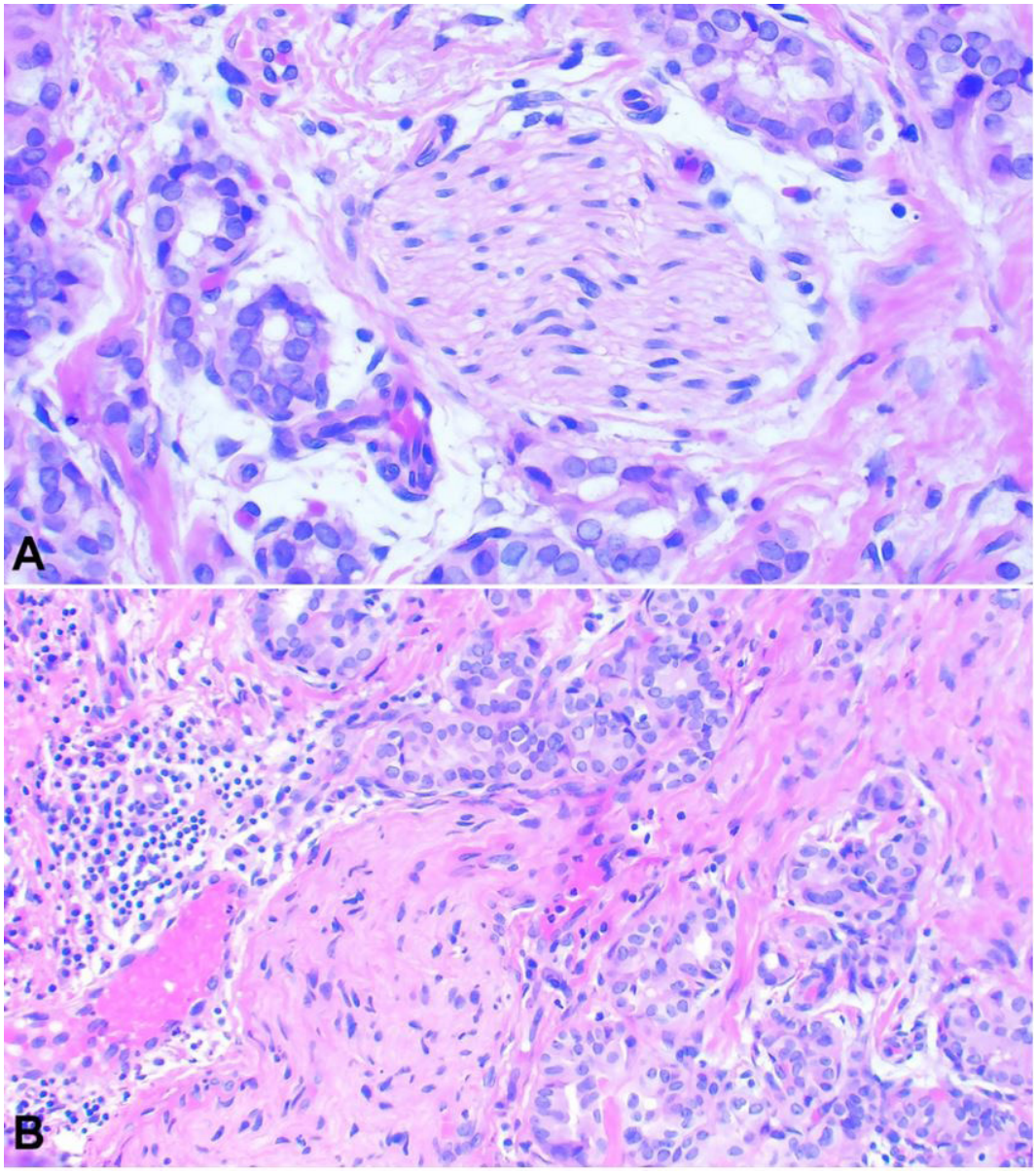

Figure 5. A, B – Photomicrograph of the surgical specimen showing the neoplastic follicles surrounding the nerves in two different areas (H&E, 200X).

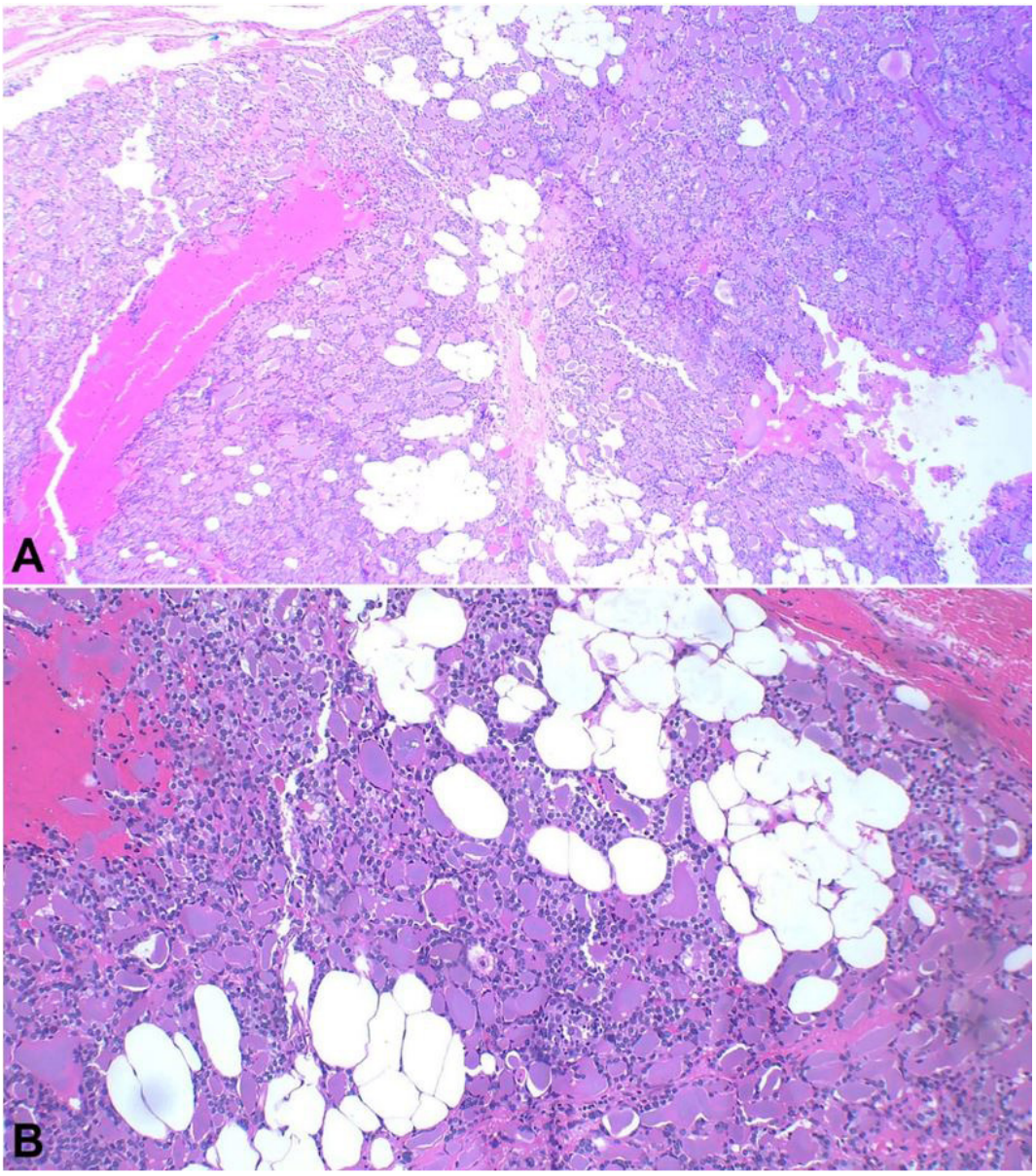

Figure 6. Photomicrograph of the surgical specimen showing the follicular lipomatous nodule. **A –** H&E, 40X; **B –** H&E,100X.

Nevertheless, our patient presented IHO with EMH in association with malignancy. Therefore, coarse calcification can be associated with IOH and EMH as described. IOH and EMH can be present in malignant and benign thyroid nodules.[9,10]

A possible explanation for IHO in thyroid nodules is increased bone morphogenetic proteins (BMP)—a group of proteins associated with ectopic bone formation inducing local ossification.[5,9] Na et al.[6] described an activin-receptor-like kinase (ALK) 1 expression associated with PTC with bone formation compared with normal thyroid tissue and PTC without bone formation. Another possible hypothesis is the role of ALK1 as a cellular receptor for BMP, inducing osteogenesis.[6]

Extramedullary hematopoiesis is defined by the presence of immature hematopoietic cells in sites other than bone marrow, which is extremely rare in the thyroid gland. [11] There are some theories considering EMH as a possible result of heterotopic bone formation arising in long-standing dystrophic calcifications.[12]

Our case is the first case describing multifocal PTC with IHO, EMH, and a follicular lipomatous nodule in a single patient.

Follicular lipomatous nodule or adenolipoma is defined as by the presence of thyroid follicles

intermingled with mature adipose tissue.[3,12] Usually, it is an incidental finding.[13] In our case, since there was no fibrous capsule, it was called a follicular nodule with adipose metaplasia. Lipoadenomas are related to Cowden syndrome and previous radiation exposure,[3] which were not present in this case. Besides that, a fat component can be found in benign and malignant thyroid lesions.[12,14]

The last WHO classification of endocrine tumors did not describe the PTC with IHO as a specific category,[3] probably because it is a rare phenomenon without well-known prognostic significance. Since IHO and EMH are rarely described and are underestimated, future studies might define (i) if it is a true histological variant of PTC; (ii) the underlying mechanism and pathogenesis of this entity; and (iii) the management and prognostic implications.

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The authors retain an informed consent signed by the patient authorizing the use of data and images in this case report.

Author contributions: Xavier-Júnior JCC was the pathologist in charge of the histological report and wrote the manuscript. Camilo-Júnior DJ reviewed the manuscript and the pathological analysis. Conrado-Neto S was the head and neck surgeon. Lippe ACSC and Mattar NJ reviewed the manuscript.

Conflict of interest: None

Financial support: None

Submitted on: January 14th, 2019
Accepted on: March 12th, 2019

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