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A rare presentation: A case report of osseous metaplasia and mature bone formation in a follicular adenoma of the thyroid

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ABSTRACT

INTRODUCTION: Cases of multinodular goiter, thyroid hyperplasia, follicular adenoma, papillary thyroid carcinoma, and anaplastic thyroid carcinoma have been reported with histopathologic findings of osseous metaplasia (OM), bone marrow metaplasia (BMM), ectopic bone formation (EBF), ossification, and extramedullary hematopoiesis (EMH). To date no report of a follicular adenoma with OM and mature EBF in the absence of EMH has been reported in the English language.
PRESENTATION OF CASE: 63-year-old woman with an incidental finding of thyroid nodule unable to be biopsied. One area was found to contain OM with mature EBF and without vascular invasion. The surrounding tissue was unremarkable, and no malignancy was found.
DISCUSSION: Ectopic bone formation and osseous metaplasia in a thyroid nodule has an extensive differential diagnosis, from thyroid related pathologies to parathyroid causes, congenital syndromes, and hamartomas. A common theory amongst these is the role of basic fibroblast growth factor (bFGF) and bone morphogenetic protein-2 (BMP-2), signaling factors involved in cellular proliferation and growth.
CONCLUSION: This is the first case report of a follicular adenoma with OM and EBF in the absence of EMH. In this case, this adenoma was an incidental finding and the patient had no symptoms or accompanying laboratory abnormalities. Her benign presentation underscores the importance of awareness of the more common changes a thyroid nodule can undergo, such as hemorrhagic, cystic, and fibrotic changes, as well as the rarer changes of calcification with eventual ossification.

1. Introduction

Thyroid nodules are common amongst the general population, with estimates placing the prevalence up to 6% upon physical exam examination and palpation, and up to 85% on autopsy examination [1]. These nodules can undergo hemorrhagic, cystic, and fibrotic changes, and rarely will calcify or ossify. Cases of multinodular goiter, thyroid hyperplasia, follicular adenoma, papillary thyroid carcinoma, and anaplastic thyroid carcinoma have been reported with histopathologic findings of osseous metaplasia (OM), bone marrow metaplasia (BMM), ectopic bone formation (EBF), ossification, and extramedullary hematopoiesis (EMH) [2–11]. These cases are exceedingly rare. To date no report of a follicular adenoma with OM and mature EBF in the absence of EMH has been made in the English language. In line with SCARE criteria, we present a case of osseous metaplasia and mature bone formation in a follicular adenoma of the thyroid [20].

2. Case history

A 63-year-old woman was investigated after an incidental finding of a thyroid nodule on MRI done for cervical spondylitis. The nodule was not palpable on physical exam nor did she have compressive symptoms or abnormal values of TSH or free T4. She underwent thyroid ultrasound demonstrating a normal left lobe and a circumscribed hypoechoic nodule with internal echoes measuring 2.2 × 2.2 × 2.3 cm overlying the lower pole of the right lobe. Due to the significant calcification of the nodule, fine needle aspiration of the nodule was unsuccessful. The patient was referred to our academic surgical oncology clinic.

Her vitals were within normal physiological limits for her age. She was a daily smoker with more than 35 pack years. She did not have any previous radiation exposure to her head or neck. Her past medical history is significant for bilateral infiltrating ductal carcinoma of her breasts requiring chemotherapy, bilateral mastectomy, and reconstruction. The patient also had family history of lung can-

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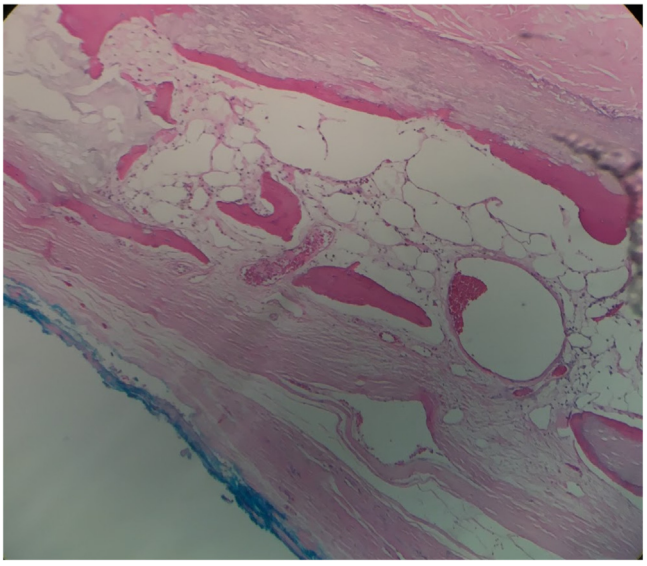

Fig. 1. area of lamellar bone and fatty infiltrate located adjacent to the calcified thyroid capsule. No evidence of megakaryocytes or other marrow elements.

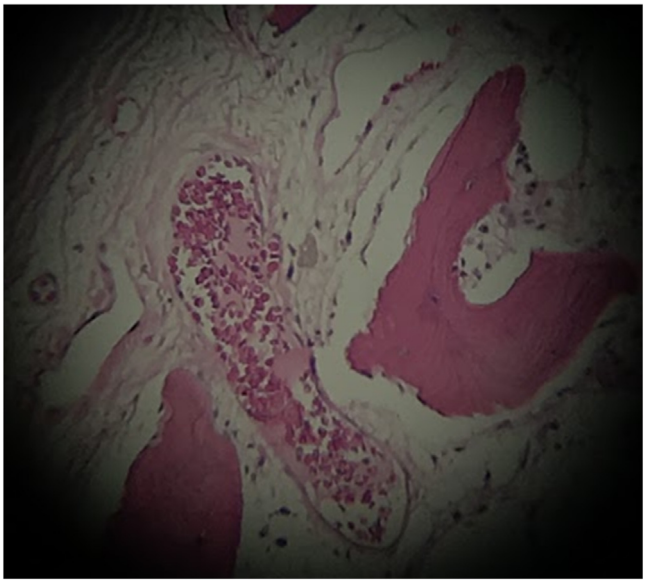

Fig. 2. Mature bone showing characteristic lamellar structure and lacunae.

cer and benign brain tumor, and denied family history of breast, ovarian, colon, or prostate cancer.

After failing the attempt to biopsy, the patient underwent right thyroid lobectomy under general anesthesia. The right thyroid lobe measured 14.5 g, 6.0 × 3.0 s 2.0 cm. The cut surface was tan-brown variegated revealing red-brown spongy parenchyma and a 2.8 × 2.5 × 1.6 cm nodule in the lower pole. The nodule itself was encapsulated by a thick, fibrotic, calcified capsule. Microscopic examination revealed the nodule to be a follicular adenoma. One area was found to contain OM with mature EBF and without vascular invasion (Figs. 1 and 2). The surrounding tissue was unremarkable, and no malignancy was found.

3. Discussion

This is the case first report of a follicular adenoma with OM and EBF in the absence of EMH. In this case, this adenoma was an incidental finding and the patient had no symptoms or accompanying laboratory abnormalities. Her benign presentation underscores the importance of awareness of the more common changes a thyroid nodule can undergo, such as hemorrhagic, cystic, and fibrotic changes, as well as the rarer changes of calcification with eventual ossification. A study of incidental thyroid nodules found that 20% of those identified on imaging required further workup, and only 2.3% of those requiring further evaluation were diagnosed with malignancy [12]. However, the strongest correlation of malignancy was presence of calcification, as was seen in this case during attempt to biopsy. The clinical significance of further workup upon identification of calcification is again substantiated by this case.

Ectopic bone formation and osseous metaplasia in a thyroid nodule has an extensive differential diagnosis, from thyroid related pathologies to parathyroid causes, congenital syndromes, and hamartomas. A common theory amongst these is the role of basic fibroblast growth factor (bFGF) and bone morphogenetic protein-2 (BMP-2), signaling factors involved in cellular proliferation and growth [11]. The pathophysiology of this is not quite understood, however a proposed explanation is increased BMP-2 (bone morphogenetic proteins) in calcified thyroid gland. BMP is a group of proteins that are found in demineralized bone and are associated with ectopic bone formation. These proteins initiate bone formation by inducing local ossification and synthesizing ground substance and collagen.

In this patient with an incidental finding of a thyroid nodule during an MRI done for cervical spondylitis, a malignant cause such as papillary thyroid cancer or congenital hamartomas is less likely given her clinical presentation. Nodular hyperplasia, follicular adenoma, and parathyroid related causes are reasonable alternatives due to the less aggressive nature of the disease. This case not only exemplifies a unique presentation, but also displays overlapping findings on histopathology addressing possible causes in both benign and malignant disease processes.

OM, EBF, EMH, and BMM have been reported in benign conditions such as nodular hyperplasia and follicular adenoma. Nodular hyperplasia has the most reported cases of findings of these pathologic processes [2–8]. The reported cases had varied combinations of these pathologic findings (see Table 1), with most suggesting the aid of bone morphogenic proteins (BMPs) in OM and EBF. These proteins play a vital role in bone formation, primarily in initiation of ossification. Follicular adenoma, as in this case, is another benign condition where OM and mature EBF can be found [9,10]. However, the case reports that identified this finding had concurrent EMH, which was absent in this case.

Cases of thyroid malignancy presenting with findings of ossification have also been published, but have not shown EBF [11]. Papillary thyroid carcinoma is the thyroid malignancy most commonly associated with ossification [12]. Mature bone formation is of higher suspicion in diagnoses of papillary thyroid carcinoma compared to other malignant or benign pathologies in the thyroid gland.

Hyperparathyroidism has been a cause of heterotopic ossification (HO) in many patients, especially those with CKD and spinal cord injury. Heterotopic ossification is defined as lamellar bone formation in soft tissues. In the study of HO in spinal cord injury, 12 of the 96 subjects developed HO.12 Nine of these 12 had secondary hyperparathyroidism, with levels ranging from 72 to 169 pg/mL. A proposed mechanism is that parathyroid hormone (PTH) enhances BMP activity in premature osteoblasts which can lead to HO [12,13]. A clinical review of literature done in 2013 states that twenty percent of spinal cord injuries exhibit HO afterwards. However, this HO usually affects the hip and knee joint [14].

Many congenital syndromes can show ossification of heterotopic structures. Fibrodysplasia ossificans progressiva is a rare congenital disorder that can cause heterotopic bone formation. Inflammation of soft tissues in injury throughout life can cause

TABLE 1
Differential Diagnosis of OM and EBM in a Thyroid Nodule.

Disease	Benign vs. Malignant	Histologic Finding	First Author	Year
Nodular hyperplasia (nodular or multi- nodular goiter)	Benign	BMM, fetal adenoma	Tzanakakis [2]	1989
		OM, EBF, EMH	Pontikides [3]	2003
		EBF, EMH	Westof [4]	2008
		EBF, EMH	Akbulut [5]	2011
		OM, EBF	Basbug [6]	2012
		2 cases OM, EBF, EMH, 1 case calcification and ossification	Chun [7]	2013
		BMM	Sayar [8]	2015
Follicular adenoma	Benign	EBF, EMH	Ardito [9]	2009
		OM, EBF, EMH	Harsh [10]	2009
Papillary carcinoma	Malignant	IHO	Takeda [12]	2013
Parathyroid	Malignant	Mesenchymal proliferation	Verdelli [19]	2015

BMM = bone marrow metaplasia; OM = osseous metaplasia; EBF = ectopic bone formation; EMH = extramedullary hematopoiesis; IHO = intratumoral heterotopic ossification; CM = chondroid metaplasia.

swelling that progresses to ossification and heterotopic bone formation [15]. These patients usually do not present until the second decade of life, and the bone formation can be debilitating. GNAS activation disorders can also lead to pseudo-hypoparathyroidism that can cause ectopic ossification, seen in conditions like Albright's hereditary osteodystrophy [16].

PTEN Hamartoma syndrome (PHTS) includes a spectrum of disorders that arise from mutation in the PTEN tumor suppressor gene.16 This can cause a wide variety of tumors, including thyroid adenoma, hamartoma, and an intramuscular lesion with unique properties [17]. One study looked at thirty-four patients with known or suspected PHTS who underwent histopathological study of these unencapsulated, often nodular, masses. 50% of these masses had lymphoid follicles present. In about 20% of the lesions, there was a focus of ossification [18].

4. Conclusion

Although osseous metaplasia and bone formation may be seen in a broad spectrum of diseases involving the thyroid gland especially in malignant neoplasms of the thyroid gland, they are not quite as common in benign thyroid diseases, such as follicular adenoma. Awareness of thyroid nodules undergoing hemorrhagic, cystic, and fibrotic changes, as well as calcification and ossification is paramount in proper diagnosis and treatment of these pathologies. Particularly, patient's history, associated risk factors including the size and the texture of the nodule and clinical presentation are the most important factors to consider in clinical differentiation of malignant and benign diagnoses. Even though this is an interesting case from histopathology perspective, one still should consider it suspicious for malignancy until proven otherwise.

Conflicts of interest

None.

Funding

None.

Ethical approval

No ethical approval needed for the case study presented and submitted.

Consent

Our patient consented for publication of the case.

Author contribution

Nadia Aurora MS3: Data collection, Data analysis, writing the paper.

Insia Hashmi MS3: Data collection and data analysis, writing the paper.

Subhasis Misra MD: Data analysis.

Nail Aydin MD: Study concept, design, data analysis and interpretation, review of the paper.

Registration of research studies

This case report does not require to be enrolled in a registry.

Guarantor

Nail Aydin MD FACS.

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