Int Surg 2011;**96:**260–265

Ectopic Bone Formation and Extramedullary Hematopoiesis in the Thyroid Gland: Report of a Case and Literature Review

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This purpose of this article is to document ectopic bone formation (EBF) and extramedullary hematopoiesis (EMH) in thyroidectomy specimens. We present a case of multinodular goiter with EMH and EBF, as well as a literature review of studies published in the English language on EMH and/or bone formation in the thyroid gland, accessed through PubMed and Google Scholar databases. Thirteen published cases of EMH and/or EBF in the thyroid gland were evaluated, and a case of multinodular goiter with histopathologically proven EMH and EBF in a 54-year-old woman is herein presented. In the reviewed literature, 12 patients were women, and 1 was a man (age range, 28–82 years; median, 56.46 ± 18 years). EMH was histopathologically detected in 8 patients, EMH and EBF were detected in 4 patients, and only bone formation was detected in 1 patient. Although a solitary nodule was detected in 7 patients, multinodular goiter was detected in 6 patients. Fine needle aspiration cytology was used in the preoperative period to arrive at a diagnosis in 6 of the 13 patients, but it was not possible to obtain proper biopsy material in the remaining patients. Although no previously known hematologic disease was detected in 11 patients, 2 were known to have myelofibrosis in the preoperative period. When EMH is pathologically detected in the thyroid, the question of whether there is an underlying hematologic disease in the patient must be investigated. In addition, it must be kept in mind during fine needle aspiration cytology and frozen section examinations that EMH may be among the differential diagnoses for anaplastic thyroid cancers.

Key words: Thyroid disease – Osseous metaplasia – Ectopic bone formation – Extramedullary hematopoiesis

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Goiter is the most common endocrine disorder requiring surgical management, especially in areas where iodine deficiency is prevalent. In Turkey, it is estimated that ~30% of people suffer from goiter.[1] Although regressive changes, such as hemorrhage, cystic change, infarction, fibrosis, and calcification in thyroid tissue are frequently observed, osseous metaplasia (OM) or ectopic bone formation (EBF) and extramedullary hematopoiesis (EMH) are rarely observed.[2,3]

EMH refers to the presence of hematopoietic elements (myeloid, erythroid, and megakaryocytic elements) in locations other than the bone marrow medullary space. It may be seen in many conditions, including chronic anemias and blood dyscrasias such as leukemia, or it may be an incidental finding. The most common sites of involvement are the liver, spleen, and lymph nodes. Less common sites include the nervous system, adrenal glands, kidneys, perirenal soft tissues, breasts, peritoneal surfaces, and gastrointestinal tract. The thyroid gland is a relatively uncommon location for these hematopoietic deposits.[2–5] At present, 8 cases of isolated EMH in the thyroid gland have been reported.[6–11]

OM or EBF is defined by the presence of heterotopic normal bone tissue in a soft tissue. The incidental finding of bone in histologic specimens, although extremely interesting, appears to have no clinical significance. Heterotopic ossification in the thyroid gland is a particularly rare phenomenon.[12] One case of isolated bone formation in the thyroid gland has been reported.[13] To the best of our knowledge, EMH together with EBF in the thyroid gland, is extremely rare, and there are only 4 case reports available in the English language literature through 2010.[2–4,14] We describe a case of multinodular goiter with pathologically proven EBF and foci of EMH in a 54-year-old female patient.

Materials and Methods

In the present study, we report a new case of EMH with OM in a thyroid nodular lesion. The English language literature in the PubMed and Google Scholar databases were searched from their inceptions to November 2010 using the key words ''extramedullary hematopoiesis and thyroid,'' ''osseous metaplasia and thyroid,'' ''mature bone formation and thyroid,'' ''hematopoietic cells in thyroid,'' and ''bone metaplasia and thyroid.'' Inabilities to access the full text of an article, an absence of adequate information for comparison with other studies, or a lack of sufficient data about the patients were considered exclusion criteria.

Results

Case report

A 54-year-old female patient presented to the surgical outpatient clinic with chief concerns of neck swelling, sore throat, and fatigue. The patient reported that she had previously had fatigue, that her neck swelling had increased in the past 6 months, and that she had visited a physician for the first time in her life. Although grade III to IV multinodular goiter was detected in the neck examination, calcified or very hard nodules were not palpable. Laboratory tests gave the following results: thyroid-stimulating hormone 0.46 μIU/mL (0.27–4.2 μIU/mL), free thyroxine 12.7 pmol/L (12–22 pmol/L), free triiodothyronine 4.48 pmol/L (3.1–6.8 pmol/L), hemoglobin 8.4 g/dL (12.3–15.3 g/dL), hematocrit 26.5% (37.7%–53.7%), mean corpuscular volume 66.9 fL (80–97 fL), mean corpuscular hemoglobin 21.1 pg/cell (28–33 pg/cell), ferritin 7.5 ng/mL (13–150 ng/mL), iron 16 μg/dL (50–170 μg/dL), erythrocyte sedimentation rate 20 mm/h (0–20 mm/h), white blood cell count 8.1 K/UL (4.4–11.3 K/UL), platelets 530 K/UL (142–424 K/UL), alkaline phosphatase 125 IU/L (25–150 IU/L), phosphorus 2.6 mg/dL (2.3–4.7 mg/dL), calcium 8.8 mg/dL (8.4–10.2 mg/dL), and parathormone 25 pg/mL (14–72 pg/mL). The results of her preoperative liver and renal function tests were normal. Chest and neck X-rays revealed no calcification or abnormality. In the thyroid ultrasound, multiple nodular lesions could be seen in both lobes of the thyroid gland, the biggest of which was 2.5 cm. A 2-cm nodule with increased vascularity and intensely calcified foci was observed in the inferior right lobe. In scintigraphy performed with 5 mCi 99mTc at another center, a cold nodule was reported in the inferior right lobe. Despite the failure to detect malignancy on fine needle aspiration cytology (FNAC), total thyroidectomy was performed because ultrasound and scintigraphy findings indicated the presence of malignancy. Histopathologic examination showed nodular hyperplastic thyroid tissue consistent with multinodular goiter. A section from the right lobe demonstrated a small focus of metaplastic bone made of mature bone with plump trabeculae, surrounded by mature fat cells, and exhibiting scattered areas of hematopoietic tissue (Figs. 1–3). On the postoperative abdominal ultrasound, multiple anechoic cystic lesions, the largest

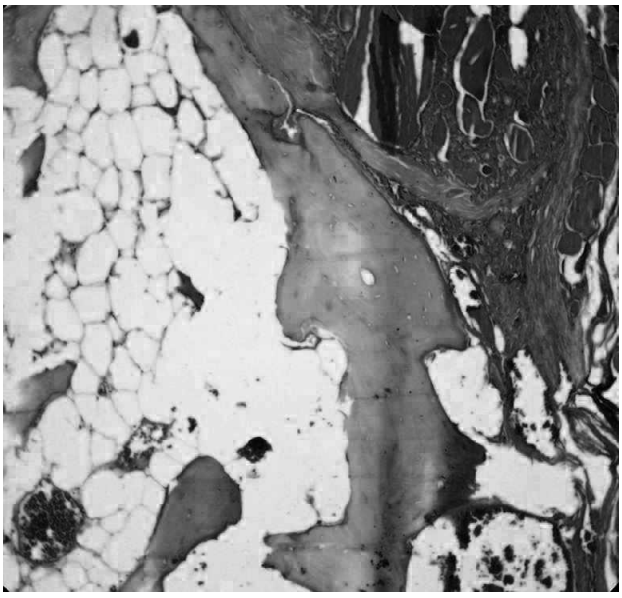

Fig. 1 Microscopic examination showing osseous tissue surrounded by thyroid tissue. H&E (×200).

measuring 28 mm, were detected in both lobes, although the dimensions of the spleen were normal. The blood folate level was 4 ng/mL (3.1–17.50 ng/mL), vitamin B12 level 360 pg/mL, and reticulocyte ratio 66.67% (0.5%–2.5%). Hence, postoperative bone marrow biopsy was planned, but the patient did not agree to this diagnostic procedure. Also, the chromium-tagged red cell scan was not done because this screening test is not used in our hospital.

Results of the literature review

The English-speaking medical literature published through November 2010 in the PubMed and Google Scholar databases was reviewed, and 12 articles concerning 13 patients with EMH and/or EBF in the thyroid gland were explored. Twelve patients were women, and 1 was a man, with ages ranging from 28 to 82 years (mean, 56.46 ± 18.0 years). EMH was detected in 8 of the patients,[6–11,15] both EMH and bone formation were detected in 4,[2–4,14] and only bone formation was detected in 1 patient.[13] Upon investigation of the examinations conducted, 7 of the patients were observed to have solitary nodule goiter, and the remaining 6 were observed to have multinodular goiter. Although a preoperative diagnosis was made with FNAC in 6 of the 13 patients, a biopsy that would yield results could not be obtained due to the hardness of the mass in the majority of the remaining patients. No preoperative hematologic disease was detected in 11 of the cases

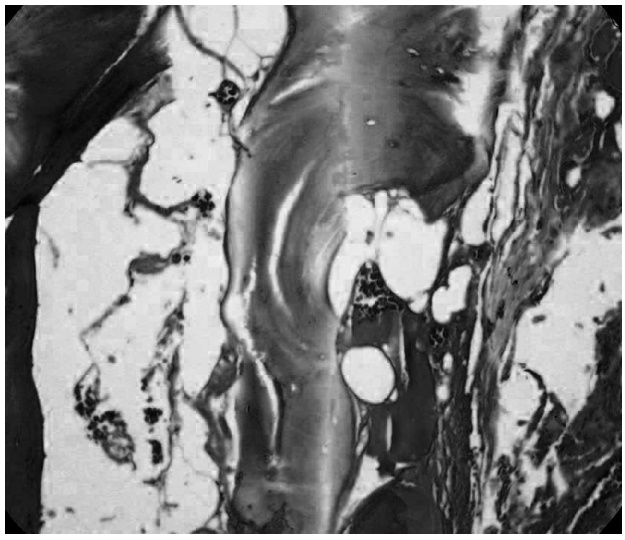

Fig. 2 Microscopic examination showing osseous tissue with a focus on EMH. H&E (×200).

published, the remaining 2 cases were demonstrated to have preoperative hematologic diseases. One of these cases was published by Lazzi *et al*,[9] and the patient was demonstrated to have agnogenic myeloid metaplasia (AMM) 4 years before thyroidectomy. In the other case, published by Schmid *et al*,[10] a bone marrow biopsy was performed because of poor general condition and changes in hematologic parameters; a diagnosis of AMM was made. During the observation, the presence of EMH in the thyroid gland was shown in the autopsy performed after the death of the patient. Leoni *et al*[8] showed that in

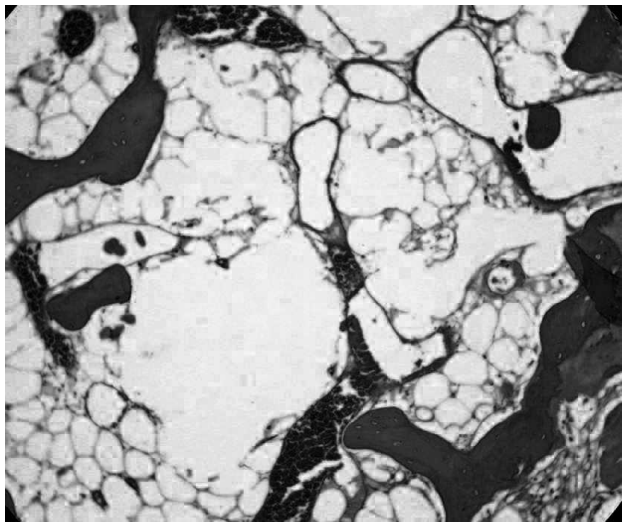

Fig. 3 Microscopic examination showing an area of bone and hematopoiesis in the thyroid gland. H&E (×200).

Table 1 A summary of 13 cases of EMH and/or OM in the thyroid gland reported in the English language literature from 1985 to 2010

Reference (first author)	Year	Age	Sex	TFT	HD	Presentation	Location, size	Radiologic tools	FNAC	Surgical procedure	Histopathologic Summary	
Harsh[4]	2009	50	F	ET	No	SN	L, 2 cm	US	NP	Excision	OM+EMH	Mature bone formation, hematopoietic tissue
Westhoff[2]	2008	34	F	SHT	No	MNG	R, 3 cm	US, Scint.	NP	TT	OM+ EMH	Mature bone formation, hematopoietic tissue
Magalhaes[15]	2007	68	F	ET	No	SN	0.9 cm	US	D	NP	EMH	Bone marrow cells containing all three hematopoietic lines
Pontikides[3]	2003	34	F	ET	No	SN	R, 6.8 cm	US, Scint.	ND	TT	OM+EMH	Mature bone formation, hematopoietic tissue
Ardito[14]	2001	28	F	ET	No	SN	L, 2.4 cm	USG	NP	LL+I	OM+EMH	Mature bone formation, hematopoietic tissue
Fassina[6]	1999	82	M	UN	Yes[a]	MNG	R	US	D[b]	UN	EMH	Scattered giant cells, platelet fragments, nucleated erythroid cells
Leung[7]	1998	49	F	NA	Yes[c]	MNG	1.3 cm	NA	D	NA	EMH	Hashimoto's thyroiditis, bone marrow elements
Leoni[8]	1996	67	F	ET	Yes[d]	MNG	L	US, Scint.	ND	TT	EMH	Hematopoietic cells including all three lines
Lazzi[9]	1996	78	F	UN	Yes[e]	SN	R, 2.5 cm	US, Scint.	D	Resection	EMH	Hematopoietic cells including all three lines
Tzanakakis[13]	1989	47	F	HT	No	MNG	R, 1.5 cm	Scint.	ND	TT	OM	Focal area of fetal adenoma, significant bone tissue
Schmid[10]	1989	82	F	UN	Yes[e]	SN	L, 3 cm	UN	NP	NP	EMH	Autopsy: hematopoietic cells including all three lines
Gay[11]	1985	68	F	ET	No	MNG	UN	US, Scint.	D	NP	EMH	Hematopoietic cells including all three lines
		47	F	ET	No	SN	R, 1 cm	UN	D	NP	EMH	Hematopoietic cells including all three lines
Current case		54	F	ET	Yes	MNG	R, 2.5 cm	US, Scint.	ND	TT	OM+EMH	Mature bone formation and hematopoietic tissue

D, diagnosis; EMH, extramedullary hematopoiesis; ET, euthyroid; FNAC, fine needle aspiration cytology; HD, hematologic disease; HT, hyperthyroidism; LL+I, left lobectomy plus istmectomy; MNG, multinodular goiter; NP, not performed; OM, osseous metaplasia; Scint., scintigraphy; SHT, subclinical hyperthyroidism; SN, solitary nodule; TFT, thyroid function tests; TT, total thyroidectomy; UN, unnoted; USG, ultrasonography.

[a]Agnogenic myeloid metaplasia.

[b]First biopsy: anaplastic carcinoma, second biopsy: EMH.

[c]Chronic iron deficiency anemia.

[d]At time of presentation no evidence of hematologic disease, 3 years later diagnosed as agnogenic myeloid metaplasia.

[e]Myelofibrosis.

patients on whom they had performed total thyroidectomy because of suspected anaplastic carcinoma in the frozen examination, the definitive diagnosis was EMH. In the third-year postoperative bone marrow biopsy performed in the same patient, they reported that the patient had AMM. Fassina *et al*[6] stated that FNAC was performed three times on their patients because of nodular goiter. The first two were performed at another center, and the second was reported as anaplastic carcinoma. They showed that when there was no deterioration in the patient's general condition, a third FNAC was performed with a 21-gauge needle 1 month later in their own center, and its result was EMH. The result of the bone marrow biopsy subsequently performed on this patient was AMM. In conclusion, although no explanation could be provided for the postoperative clinical manifestations in 8 patients diagnosed with EMH and/or bone formation,[2–4,11,13–15] hematologic diseases that could explain the clinical manifestations were detected in the remaining 5 patients.[6–10] Table 1 summarizes information on the references of the study, publication year, age, sex, thyroid function tests, hematologic disease, presentation, location, size, radiologic tools, FNAC, surgical procedure, and histopathologic features of these 13 patients; it also includes information on the current case.

Discussion

Thyroid nodules are usually well circumscribed and often sharply demarcated from adjacent tissues. They vary in size from ~1 mm to several centimeters in diameter. Hemorrhage, fibrosis, infarction, and cystic changes may be evident. Chronic microscopic inflammation, groups of macrophages, hemosiderin, fibrosis, and even calcification can be found. However, mature bone formation and/or EMH in a thyroid nodule is a rare occurrence.[2,3,14]

EMH, also known as myeloid metaplasia, is defined as the production of myeloid, erythroid, and megakaryocytic elements at ectopic sites.[2,3] It has been described in hematologic diseases such as chronic iron deficiency anemia, Hodgkin's disease, thalassemia, sickle cell anemia, pernicious anemia, and spherocytosis. The most common sites of EMH are the liver, spleen, and lymph nodes. However, EMH can occur in almost any organ and in numerous locations.[2,4,15] Involvement of the thyroid gland in mature EMH has rarely been reported.

EBF or OM occurs outside of the skeletal system in fibrodysplasia ossificans. Although various studies have hypothesized that bone morphogenic proteins play an important role in OM in the thyroid gland, the pathogenesis of OM remains unknown. The ossification process is initiated by a local osteogenic factor, which stimulates osteoblasts to differentiate and synthesize ground substance and collagen. Hydroxyapatite crystal formation, which is the final step in bone formation, depends on the presence of adequate concentrations of calcium and phosphate. OM is clinically and prognostically insignificant, and most of the time it is an incidental microscopic finding. This rare finding has been reported in both benign and malignant tumors of various organs, including the thyroid gland. Although OM in the thyroid gland has been described in association with neoplasms, such as teratomas and sarcomas, the presence of OM in benign conditions of the thyroid is extremely rare.[3,9,12]

Acknowledgments

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
Authors Contributions: SA and RY performed surgical procedure; SA, MB and ZA contributed writing the article and review of the literature as well as undertaking a comprehensive literature search; SA and ZA contributed design and manuscript preparation. BA and NS provided the histopathologic information.

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