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Ectopic bone formation in thyroid gland: report of sixteen cases and comprehensive literature review

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Abstract. – OBJECTIVE: This study aimed to analyze the outcomes of patients with ectopic bone formation (EBF) diagnosed in thyroidectomy specimen.

PATIENTS AND METHODS: We retrospectively analyzed the data of 16 patients who underwent thyroidectomy between February 2009 and June 2018 and whose pathology examination diagnosed EBF.

RESULTS: Fourteen patients underwent bilateral total thyroidectomy (BTT), one patient required BTT with central lymph node dissection, and one patient was subjected to BTT with functional lymph node dissection. On histopathological examination, left lobe EBF was diagnosed in four patients; left lobe EBF with bilateral papillary thyroid carcinoma (PTC) in two; left lobe EBF with left lobe PTC in one; left lobe EBF with left follicular adenoma in one; left lobe EBF with right lobe papillary thyroid microcarcinoma in one; bilateral EBF in one; right lobe EBF with extramedullary hematopoiesis in one; right lobe EBF in three; right lobe EBF with right lobe medullary thyroid carcinoma in one, and right lobe EBF with bilateral lymphocytic thyroiditis in one. One of the five patients who underwent bone marrow biopsy was diagnosed with myeloproliferative dysplasia, and another with polycythemia vera. Three patients were treated medically for anemia because no other pathological findings could be observed.

CONCLUSIONS: There is a lack of literature data about the clinical significance of EBF in the thyroid gland in cases with no concomitant hematological diseases. People who have been diagnosed with EBF in the thyroid gland should be checked for hematological diseases.

Key Words:
Thyroid, Multinodular goiter, Ectopic bone formation, Osseous metaplasia.

Introduction

Nodules are benign or malignant tumors that have various development patterns in the thyroid gland, and multinodular goiter is the most prevalent thyroid disease. The most common diagnosis of these nodules in FNAC include colloid nodule, follicular adenoma, papillary carcinoma, benign cysts, hemorrhage, fibrosis, and cystic change may also be present. However, ectopic bone formation (EBF) and/or extramedullary hematopoiesis (EMH) in a thyroid nodule is rarely reported[1,2].

EMH refers to the production of trilineage bone marrow elements at sites outside of the bone marrow[1]. While EMH is typically found in organs of the reticuloendothelial system, which are involved in fetal hematopoiesis (liver, spleen, and lymph nodes), and this process has been described for every organ. EBF, also known as osseous metaplasia (OM), is defined by the presence of heterotopic normal bone tissue in soft tissue[1]. Although the discovery of bone in histologic specimens is intriguing, it appears to have little therapeutic importance[1]. Despite the fact that some studies[1] have proposed that bone morphogenic proteins play a significant role in ectopic bone development in the thyroid gland, the specific pathophysiology of EBF remains unclear.

In this study, we report 16 patients whose thyroid pathology examinations detected EBF. The pathological and clinical features associated with this finding are described in detail. In addition, a review of the English literature until the beginning of November 2021 was performed and the available reports reviewed[1-29]. The cohort of this study was also compared with other cases of thyroid EBF reported in the English literature.

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Patients and Methods

The primary aim of this study was to analyze the results of patients who underwent thyroidectomy for any reason in our center and whose histopathologically ectopic bone formation (EBF) was detected in the thyroidectomy specimen. To achieve this objective, the demographic and clinicopathological data of patients who underwent thyroidectomy due to any indication at Diyarbakir State Hospital and Diyarbakir Education and Research Hospital between February 2009 and June 2018 were retrospectively evaluated (Table I). In addition, the pathology reports of patients who underwent thyroidectomy at another center and were referred to our hospital's pathology department for consultation were also retrospectively evaluated. Sixteen patients who were found to have EBF (OM) and/or EMH in the histopathological examination of their thyroid gland met the study inclusion criteria. The patients' data, including their age, sex, thyroid function tests, presence of hematologic disorder, clinical presentation, nodule location (ultrasonographic largest nodule diameter), radiologic diagnosis, pathological location of EBF and/or EMH in the thyroid gland, surgical approach, and histopathologic findings were analyzed. The pathology preparations of all patients were examined by a single pathologist experienced in thyroid pathology. Then, the preparations were consulted with an experienced pathology professor, and the diagnoses were confirmed. In seven patients, the preparations were stained with myeloperoxidase (MPO) to check if they contained blood elements. One of the patients who took part in this study had already been reported as a case study[1]. This retrospective study involving human participants was under the ethical standards of the institutional and national Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients gave written and verbal consent before the surgical procedure was performed. Ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2022/3805). STROBE (Strengthening the reporting of observational studies in epidemiology) guideline was utilized to assess the likelihood of bias and overall quality for this study[30].

Histopathological Evaluation

All thyroidectomy specimens were delivered to the pathology laboratory preserved in formaldehyde solution. Thyroidectomy materials were weighed, right lobe, left lobe and isthmus size were measured, and the outer faces were stained with Chinese ink. Then serial sections were made at 5 mm intervals. Macroscopically, the features of the cross-sectional faces, the presence of nodular formation, the diameter of the nodules, the distance to the capsule, and other details were noted. Decalcification solution (Biodec R-Bio-Optica®) was used for hard areas. After decalcification, sampling was performed from the tissues. After the tissue processing, 4-micron-thick sections were made, and the sections were stained with Hematoxylin-Eosin. Microscopically, there was a multinodular appearance separated by fibrous bands. Thyrocytes were generally non-atypical, monotonous, and cubic. Sclerosis and calcification were accompanied by mature bone formation (MBF). In one of the thyroid materials with mature bone formation, bone marrow tissue with hematopoietic elements was observed accompanied by mature fat cells, several megakaryoblasts, and myeloid series precursors. Two of the MBF-containing thyroid materials were accompanied by follicular adenoma with thick fibrous encapsulation of follicular, solid, and trabecular patterns composed by cuboid-low columnar thyrocytes. In one of the thyroids, a papillary carcinoma focus was observed, adjacent to the follicular adenoma, with nuclear enlargement, paleness, and nuclear crowding. This area showed positive staining with HBME1 and CK19. Two of the thyroidectomy materials had areas with similar morphological appearance, and since these areas were immunohistochemically stained positive for HBME1 and CK19, a diagnosis of papillary carcinoma was made. In one of the cases, osteoid metaplasia was accompanied by hematopoiesis. Immunohistochemically, myeloperoxidase staining was applied to the thyroidectomy case in which hematopoiesis was observed and positive staining was detected. In one of the thyroid specimens, nodular follicular disease was associated with lymphocytic thyroiditis. In another thyroid specimen, 4 mm from the MBF, a tumoral area composed by round, plasmacytoid and polygonal cells was surrounded by a focal thin fibrous capsule. Tumor also included micro calcification foci, as well as areas containing homogenous eosinophilic acellular amyloid-like material. In an immunohistochemical study, the tumor cells were stained positive with CEA and Chromogranin but did not show staining with thyroglobulin and were diagnosed as medullary carcinoma (Figures 1-10).

Table I. Clinical and histopathological features of 16 patients with mature bone formation in thyroidectomy specimens.

ID	Age	Sex	TFT	Hematologic Disorder	Presentation	Radiologic Diagnosis	Nodule Location (Largest size)	Surgical Approach	Histopathologic Findings
TE	60	F	SHT	Anemia	Dyspnea	MNG (Substernal)	Bilateral (35 mm)	BTT	Left EBF+ Left PTC (5 mm)
NU	48	F	SHT	Anemia	Neck swelling	MNG	Bilateral (19 mm)	BTT	Left EBF
KC	47	F	ET	Anemia	Neck swelling	MNG	Bilateral (35 mm)	BTT	Left EBF+Left Follicular Adenoma
BC	61	F	ET	No	Neck swelling	MNG	Bilateral (17 mm)	BTT	Left EBF
ZO	64	F	ET	No	Neck swelling	MNG	Bilateral (44 mm)	BTT	Left EBF
AY	42	F	ET	No	Neck swelling	MNG	Bilateral (NS)	BTT	Left EBF
SG	46	F	ET	No	Dyspnea	MNG (Substernal)	Bilateral (left 15 mm)	BTT	Bilateral EBF
KE	54	F	ET	Myeloprolif.	Neck swelling	MNG	Bilateral (20 mm)	BTT	Right EBF+EMH[a]
SA	66	M	SHT	Polycythemia	Dyspnea	MNG (Substernal)	Bilateral (34 mm)	BTT	Right EBF
AB	50	F	ET	No	Neck swelling	MNG	Bilateral (13 mm)	BTT+CLND	Right EBF+MTC (13*10 mm)
BNC	43	F	ET	No	Neck swelling	MNG	Bilateral (34 mm)	BTT	Right EBF+Lymphocytic thyroiditis
PA	65	F	ET	No	Neck swelling	MNG	Bilateral (44 mm)	BTT	Right EBF
CT	58	F	ET	No	Neck swelling	MNG	Bilateral (55 mm)	BTT	Right EBF
HK	59	M	HT	No	Dyspnea	MNG	Bilateral (50 mm)	BTT	Left EBF+ PTC(right lobe: 65 mm, left lobe: 7 mm)
HT	51	F	ET	No	Neck swelling	MNG	Bilateral (23 mm)	BTT	Left EBF+ PTMC (right lobe: 6 mm)
TN	62	M	ET	No	Neck swelling	MNG (presumed diagnosis malignancy)	Bilateral (34 mm)	BTT+FLND	Left EBF+PTC (right lobe: 10 mm, left lobe: 19 mm)

SHT: Subclinical hyperthyroidism; HT: Hyperthyroidism; EU: Euthyroidism; MNG: Multiodular goiter; BTT: Bilateral total thyroidectomy; NA: Non-available; MTC: Medullar thyroid carcinoma, PTC: Papillary thyroid carcinoma; PTMC: papillary thyroid microcarcinoma; EBF: ectopic bone formation; CLND: Central neck dissection; FLND: Functional neck dissection; [a]: bone marrow biopsy was performed for differential diagnosis and myeloproliferative disease were detected with immunohistochemical stain.

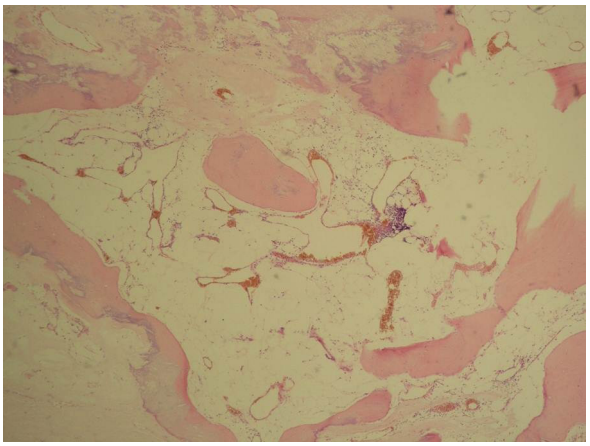

Figure 1. Mature bone formation and bone marrow in thyroid gland (HE x40).

Literature Review

The second aim of this study was to review the articles published in the medical literature on EBF and/or extramedullary hematopoiesis EMH in the thyroid gland. A medical literature search was conducted on PubMed, Medline, Google Scholar, and Google databases. Keywords used include "goiter", "thyroid gland", "mature bone formation", "extramedullary hematopoiesis", and "osseous metaplasia". There were no language restrictions for the literature research, and all papers published until the beginning of November 2021 were reviewed. As a result, articles without an accessible full-text version, those that did not provide adequate information in their abstracts, and those that did not involve as comprehensive information as that provided in other studies were excluded. As some enrolled articles were published in the form of a literature review, their tables were also used. The following information was collected: publication year, age, sex, clinical presentation, thyroid function tests, presence of hematologic disorder, pathologic location (location of the thyroid nodule that contains the EMH and/or MBF), nodule count, radiologic tools (ultrasonography, scintigraphy, etc.), fine needle aspiration cytology (FNAC), surgical approach (lobectomy, subtotal thyroidectomy, total thyroidectomy, etc.), histopathologic findings, and definitive diagnosis.

Results

In the present study, 16 patients aged 42-66 years (median age: 56 years; IQR: 14 years) were retrospectively analyzed. Thirteen patients were female, and three were male. While 12 patients were euthyroid in the preoperative period, three patients had subclinical hyperthyroidism, and one had hyperthyroidism. In preoperative tests, serum calcium levels were normal in all patients. Three patients were incidentally found to have anemia in preoperative tests. Further tests revealed that two patients were diagnosed with myeloproliferative disease and polycythemia vera. Twelve patients presented with swelling in the neck and four patients with dyspnea as the presenting symptom. Preoperative radiological examinations revealed MNG in all patients, with the thyroid gland growing inferiorly to extend into the substernal space. As a result of the surgical intervention, 14 patients underwent bilateral total thyroidectomy (BTT),

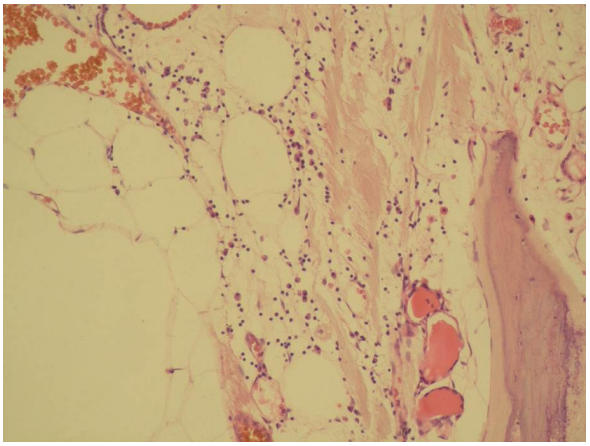

Figure 2. Extramedullary hematopoiesis and mature bone formation at thyroid tissue. There is mature bone formation and thyroid follicles at right site (HE x200).

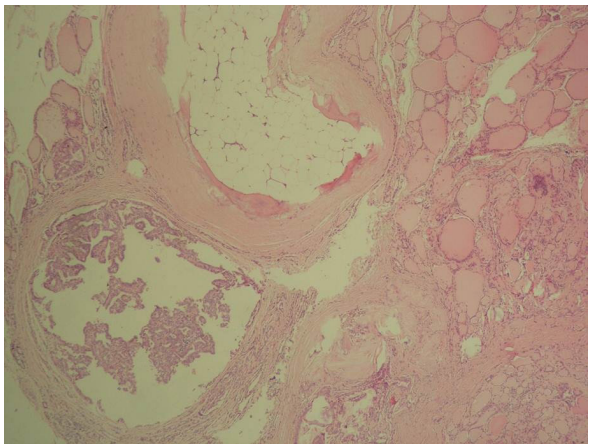

Figure 3. Extramedullary hematopoiesis and papillary carcinoma are together in the thyroid gland (HE x40).

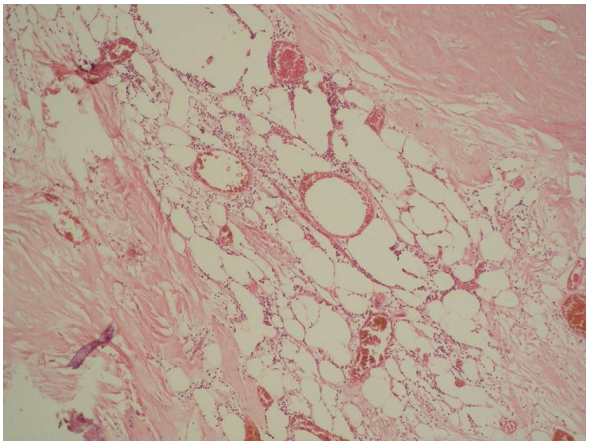

Figure 4. Hematopoietic cells are present. Sinuses and capillaries are prominent. A section from the center of thyroid gland (HE x100).

one patient with central lymph node dissection, and one patient with functional lymph node dissection. Histopathological examination revealed left lobe EBF in four patients, left lobe EBF with bilateral papillary thyroid carcinoma in two patients, left lobe EBF with left follicular adenoma in one patient, left lobe EBF with right lobe papillary thyroid microcarcinoma in one patient, bilateral EBF in one patient, right lobe EBF with extramedullary hematopoiesis in one patient, right lobe EBF in three patients, right lobe EBF with right lobe medullary thyroid carcinoma in one patient, and right lobe EBF with bilateral lymphocytic thyroiditis in one patient. All patients consulted with the hematology department during the postoperative period; one of the patients who underwent bone marrow biopsy was diagnosed with myeloproliferative disease, and another with polycythemia vera. These two patients were placed in a regular follow-up protocol by the hematology department. Since no other pathological findings were observed in the patients' further examinations, they were treated for anemia solely with medical therapy. All patients were administered postoperative thyroid hormone therapy. Five patients diagnosed with thyroid cancer were also put under follow-up by the nuclear medicine department. Thyroglobulin (Tg) was used for monitoring patients with papillary thyroid cancer, and calcitonin (Ctn) and carcinoembryonic antigen (CEA) were used to monitor patients with medullary thyroid cancer. The patients were followed for a median of 3,181 days (IQR: 1,048 days; mean: 2,914±919 days). Two of sixteen patients died from causes unrelated to their primary disease. All patients diagnosed with a tumor accompanying EBF are still alive without recurrence.

Discussion

EMH, also known as myeloid metaplasia, is defined as the production of myeloid, erythroid, and megakaryocytic elements at ectopic sites[11]. Some also define it as the process of blood cell formation in sites other than those that are normally active[24]. EMH has been described in hematologic diseases as in patients with severe chronic diseases of hemopoietic tissue such as chronic granulo-

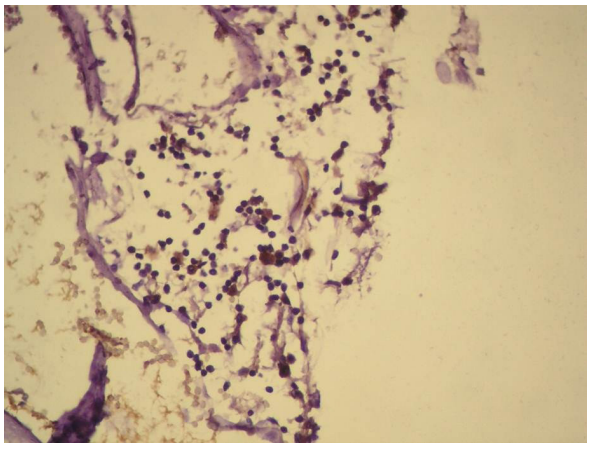

Figure 5. Myeloperoxidase reactivity in some hematopoietic cells. Myeloperoxidase (x400).

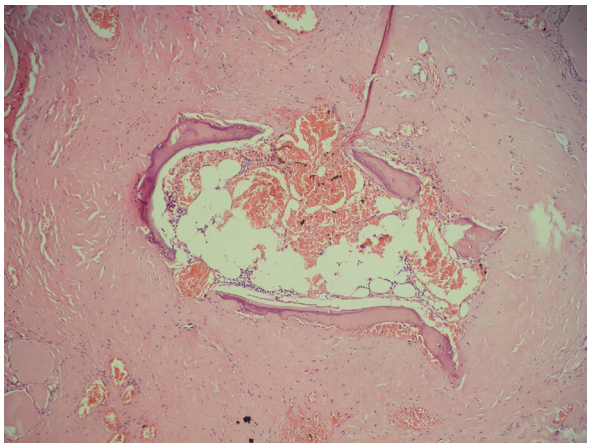

Figure 6. There is osteoid metaplasia; mature bony trabeculae and fatty marrow in thyroid tissue (HE x40).

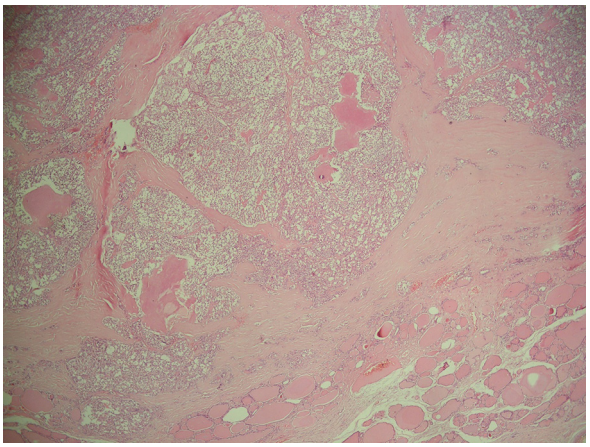

Figure 7. Low power view of medullary carcinoma showing nests of cells surrounded by dense pink stroma containing amyloid (HE x40).

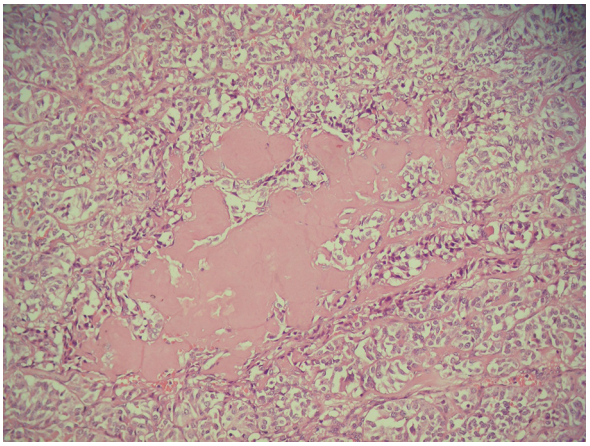

Figure 8. Higher power view of medullary carcinoma showing round uniform cells with a punctate chromatin pattern and mild variation in nuclear size (HE x200).

cytic leukemia, Hodgkin's disease, primary polycythemia, thalassemia, and in cases where there is increased demand for blood cells after severe and continuing hemorrhage or hemolysis in newborns or young children[21].

It has been suggested that EMH can be present at virtually any site in the body[13]. EMH has been described in every body organ other than the bone marrow. The most common sites involved by EMH in adults are organs of the mononuclear phagocytic (reticuloendothelial) system that were involved in hematopoiesis during fetal life (liver, spleen, and the lymph nodes etc.)[13]. However, non-hepatosplenic EMH is a rare lesion, often associated with myeloid metaplasia, and preferentially affects the thoracic spine region[31]. It is worth mentioning that the spleen is not one of the common organs involved in mass forming EMH. It has been suggested that the splenic environment produces diffuse or multifocal microscopic EMH rather than a discrete mass[32].

Thyroid nodules are common, and the reported frequencies detected by ultrasound correlate with the prevalence reported at surgery and autopsy, with ranges between 50% and 65%[33]. The thyroid gland is a very rare location for the presence of hematopoietic elements. A wide range of degenerative changes can accompany thyroid nodular hyperplasia. Among changes frequently observed, dystrophic calcification is well-appreciated. However, osseous metaplasia with mature bone formation, is extremely rare, especially in patients without any hematologic abnormality. In this study, out of 3,100 thyroidectomy spec-

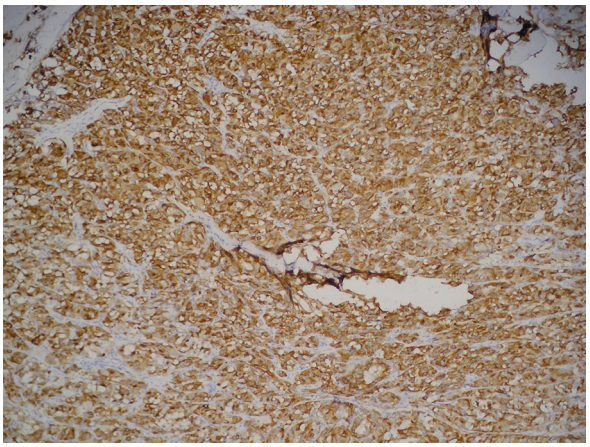

Figure 9. Calcitonin immunostaining in medullary carcinoma shows strong reactivity in neoplastic cells (x100).

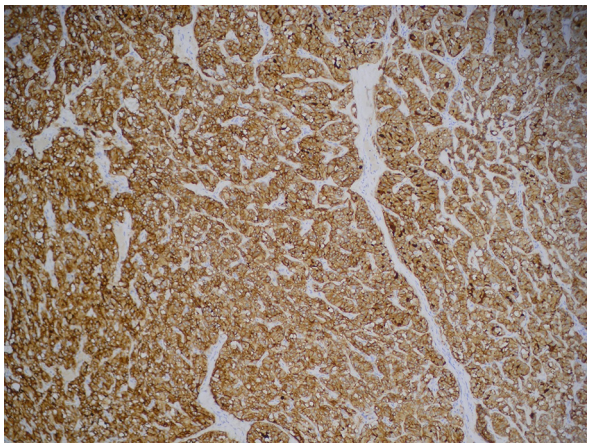

Figure 10. Immunostaining for CEA is positive in tumor cells (x100).

Table II. A summary of 47 cases of EMH and/or EBF (=OM) in the thyroid gland reported in the English language literature from 1985 to 2021.

References	Year	Country	Age	Sex	TFT	Hematologic Disorder	Clinical Presentation	Nodule Location	Size (mm)
Chajnowska and Karpińska[9]	2020	Poland	46	M	UN	No	SN	Left	22
Hejazi et al[16]	2019	Saudi Arabia	41	F	ET	No	MNG	Left	20
Al Khader et al[3]	2019	Jordan	44	F	ET	No	MNG	Bilateral	12
Kishore et al[18]	2019	India	45	F	SHT	Chronic myeloid leukemia	SN	Right	46
Jan et al[17]	2018	Taiwan	58	F	UN	No	SN	Right	9
Jan et al[17]	2018	Taiwan	71	F	ET	No	MNG	Right	41.5
Jan et al[17]	2018	Taiwan	59	F	ET	No	MNG	Left	9.2
Jan et al[17]	2018	Taiwan	76	F	ET	No	MNG	Left	17.5
Mizutori-Sasai et al[23]	2017	Japan	73	F	ET	No	MNG	Bilateral	NA
Mizutori-Sasai et al[23]	2017	Japan	58	M	ET	No	NS	NS	17.3
Aurora et al[5]	2017	USA	63	F	ET	No	SN	Right	28
Gupta et al[13]	2016	India	71	M	ET	No	SN	Right	10
Been et al[8]	2016	USA	77	F	ET	No	MNG	Isthmus	30
Been et al[8]	2016	USA	32	F	ET	No	NS	Isthmus	8
Been et al[8]	2016	USA	61	F	ET	No	NS	Right	20
Been et al[8]	2016	USA	66	F	UN	No	NS	Left	16
Been et al[8]	2016	USA	70	M	UN	No	MNG	Right	20
Been et al[8]	2016	USA	71	F	UN	No	NS	Left	16
Been et al[8]	2016	USA	59	F	ET	No	NS	Left	13
Been et al[8]	2016	USA	52	F	ET	No	SN	Left	16
Been et al[8]	2016	USA	76	F	UN	No	SN	Left	19
Handra-Luca et al[14]	2015	France	51	F	HT	No	Toxic goiter	NS	2.5
Handra-Luca et al[14]	2015	France	33	F	ET	No	MNG	Bilateral	10
Handra-Luca et al[14]	2015	France	63	F	ET	No	MNG	Bilateral	10
Handra-Luca et al[14]	2015	France	83	F	HT	No	Trachea deviation	Left	10
Handra-Luca et al[14]	2015	France	71	F	ET	No	Compressive cyst	NS	8
Sayar et al[25]	2014	Turkey	57	F	ET	No	MNG	Left	21
Zeck et al[29]	2014	USA	78	M	ET	No	MNG	Right	19
Chun et al[10]	2013	S. Korea	41	F	ET	No	MNG	Right	10
Chun et al[10]	2013	S. Korea	49	F	ET	No	MNG	Bilateral	40
Chun et al[10]	2013	S. Korea	72	F	ET	No	MNG	Bilateral	NS

M: Male; F: Female; TFT: Thyroid function tests; UN: unnoted; ET: euthyroidism; SHT: Subclinical hyperthyroidism; HT: hyperthyroidism; SN: Solitary nodule; MNG: Multinodular goiter; NA: non-available; AMM: Agnogenic Myeloid Metaplasia.

Table continued

Table II. ***(Continued).*** A summary of 47 cases of EMH and/or EBF (=OM) in the thyroid gland reported in the English language literature from 1985 to 2021.

References	Year	Country	Age	Sex	TFT	Hematologic Disorder	Clinical Presentation	Nodule Location	Size (mm)
Arpaci et al[2]	2012	Turkey	73	M	ET	No	MNG	Bilateral	90
Basbug et al[6]	2012	Turkey	65	F	ET	No	MNG	Bilateral	44
Akbulut et al[1]	2011	Turkey	54	F	ET	Yes	MNG	Right	25
Harsh et al[15]	2009	India	50	F	ET	No	SN	Left	20
Westhoff et al[28]	2008	Germany	34	F	SHT	No	MNG	Right	30
Magalhaes et al[22]	2007	Brazil	68	F	ET	No	SN	NS	9
Pontikides et al[24]	2003	Greece	34	F	ET	No	SN	Right	68
Ardito et a[14]	2001	USA	28	F	ET	NS	SN	Left	30
Fassina et al[11]	1999	Italy	82	M	UN	AMM	MNG	Right	NA
Leung et al[21]	1998	Canada	49	F	NA	Iron deficiency anemia	MNG	Right	13
Leoni et al[20]	1996	Italy	67	F	ET	AMM	MNG	Bilateral	NS
Lazzi et al[19]	1996	Italy	78	F	UN	Myelofibrosis	SN	Right	25
Tzanakakis et al[27]	1989	Greece	47	F	HT	No	MNG	Right	15
Schmid et al[26]	1989	Austria	82	F	NS	AMM	SN	Left	30
Gay et al[12]	1985	USA	68	F	ET	No	MNG	Bilateral	NS
Gay et al[12]	1985	USA	47	F	ET	No	SN	Right	10

M: Male; F: Female; TFT: Thyroid function tests; UN: unnoted; ET: euthyroidism; SHT: Subclinical hyperthyroidism; HT: hyperthyroidism; SN: Solitary nodule; MNG: Multinodular goiter; NA: non-available; AMM: Agnogenic Myeloid Metaplasia.

imens' reviewed, 16 patients were found to have ectopic bone formation (0.5%). In a study by Jan et al[17], out of 63,361 specimens of thyroid FNAs taken between 2000 and 2016, four specimens contained hematopoietic elements. Another large case series reported that nine samples (0.005%) contained trilineage bone marrow elements out of 172,939 thyroid FNAs that were examined. Nodule calcifications were present in seven patients. None of the patients in this study had a history of a blood disorder, nor was there any evidence of thyroid malignancy[8].

A summary of cases of EMH and/or EBF in the thyroid gland has been reported in the English language literature from 1985 to 2021 (see Table II). There were 47 reported cases, the majority of patients were females (40 females *vs.* 7 males), with a median age of 61 years. With regard to coexisting hematological disorders, only 3 patients were reported to have angiogenic myeloid metaplasia, one patient with chronic myeloid leukemia, and one patient with anemia, while most patient reported to have no associated hematological disorders. 26 of these patients had multinodular goiter, 19 patients had solitary nodules and one of them was reported to be present with a compressive cyst. Most patients (n=32) had extramedullary hematopoiesis on histological examination. EBF was reported in 19 patients. Calcification reported in 28 patients, 6 patients had no calcification, and 13 patients the presence of calcification was not specified.

EMF or OM in a thyroid nodule differential diagnosis is diverse, including thyroid-related pathologies, parathyroid disease, congenital syndromes, and hamartomas. If not recognized, trilineage hematopoiesis can be mistaken for malignancy. The cytologic differential diagnosis of trilineage hematopoiesis includes lymphoma, myeloid sarcoma and anaplastic carcinoma[29]. The presence of numerous giant cells, the cytologic presentation might be mistaken for anaplastic thyroid carcinoma particularly in intra-operative frozen sections and fine-needle aspiration biopsy[11,28]. 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, EBF, ossification, and EMH. In this study, out of 3,100 thyroidectomy specimens reviewed, a total of 16 patients found to have ectopic bone formation. All of these patients were over 40 years in age and had multinodular goiter, and on further assessment one patient was diagnosed with myeloproliferative disease and another one with polycythemia vera. On histological examination, four of these patients had papillary thyroid carcinoma, one of them had follicular adenoma and one had medullar thyroid carcinoma. However, no significant association between thyroid EBF and thyroid tumors could be identified.

In the present study, the STROBE guidelines were explored for reporting the results of the cases examined[30]. Thence, case reports that meet reporting guidelines can assist in providing proper intervention to the correct patient at the proper time.

Conclusions

EBF and EMH are two of the rare conditions diagnosed in the thyroid gland. According to current data, there is no evidence-based recommendation about the clinical significance of EBF in the thyroid gland. Based on our view, we recommend that all patients with histopathological findings of EBF or EMH in thyroid biopsy or thyroidectomy specimens should be evaluated with further analysis such as bone marrow biopsy and genetic tests for possible underlying hematological problems.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NS, SA, AS, RY, and YY. The first draft of the manuscript was written by NS, SA, and CC, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Informed Consent

Informed consent was obtained from all individual participants for the surgical procedures.

Ethics Approval

The study was approved by the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2022/3805).

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References

1) Akbulut S, Yavuz R, Akansu B, Sogutcu N, Arikanoglu Z, Basbug M. Ectopic bone formation and extramedullary hematopoiesis in the thyroid gland: report of a case and literature review. Int Surg 2011; 96: 260-265.
2) Arpaci RB, Serinzos E, Kara T, Porgali C, Dag A. [Multinodular goiter with osseous metaplasia showing extramedullary hematopoiesis]. Turkiye Klinikleri J Endocrin 2012; 7: 32-34.
3) Al Khader A, Nsour E, Alneweiri A, Al-Saghbini M. Mature bony metaplasia in multinodular goiter: A case report. Int J Surg Case Rep 2019; 60: 1-3.
4) Ardito G, Fadda G, Revelli L, Modugno P, Lucci C, Ardito F, Pontecorvi A, LiVolsi VA. Follicular adenoma of the thyroid gland with extensive bone metaplasia. J Exp Clin Cancer Res 2001; 20: 443-445.
5) Aurora N, Hashmi I, Misra S, Aydin N. A rare presentation: A case report of osseous metaplasia and mature bone formation in a follicular adenoma of the thyroid. Int J Surg Case Rep 2017; 37: 83-86.
6) Basbug M, Yavuz R, Dablan M, Akansu B. Extensive osseous metaplasia with mature bone formation of thyroid gland. J Endocrinol Metab 2012; 2: 99-101.
7) Been L, Ogden L, Traweek ST. Fine Needle Aspiration Diagnosis of Extramedullary Hematopoiesis in the Thyroid: A Report of 7 Cases. J Am Soc Cytopathol 2015; 6: S80.
8) Been LC, Ogden L, Traweek ST. Extramedullary hematopoiesis involving the thyroid: Fine-needle aspiration features and literature review. J Am Soc Cytopathol 2016; 5: 133-138.
9) Chajnowska B, Karpińska K. Osseous metaplasia of thyroid cancer. Endokrynol Pol 2020; 71: 279-280.
10) Chun JS, Hong R, Kim JA. Osseous metaplasia with mature bone formation of the thyroid gland: Three case reports. Oncol Lett 2013; 6: 977-979.
11) Fassina A, Fedeli U, Borsato S. Extramedullary hematopoiesis of the thyroid gland diagnosed by FNA cytology. A case report. Acta Cytol 1999; 43: 1181-1183.
12) Gay JD, Bjornsson J, Goellner JR. Hematopoietic cells in thyroid fine-needle aspirates for cytologic study: report of two cases. Mayo Clin Proc 1985; 60: 123-124.
13) Gupta D, Kotwal S, Suri J. Extramedullary hematopoiesis in thyroid gland: A rare case report. Indian J Pathol Oncol 2016; 3: 354-357.
14) Handra-Luca A, Dumuis-Gimenez ML, Bendib M, Anagnostis P. Thyroid Sporadic Goiter with Adult Heterotopic Bone Formation. Case Rep Endocrinol 2015; 2015: 806864.
15) Harsh M, Dimri P, Nagarkar NM. Osseous metaplasia and mature bone formation with extramedullary hematopoiesis in follicular adenoma of thyroid gland. Indian J Pathol Microbiol 2009; 52: 377-378.
16) Hejazi SY, Zaidi NH, Ahmad Ghanem A, Aljawhari A. Osseous metaplasia in thyroid nodule: A case report and review of literature. Int J Case Rep 2019; 3: 97.
17) Jan IS, Weng MH, Wang CY, Chang TC, Shih SR. Extramedullary hematopoiesis involving the thyroid: A rare cytologic finding in otherwise healthy patients and review of literature. J Formos Med Assoc 2018; 117: 1108-1114.
18) Kishore M, Kaushal M, Marwah S, Sharma M, Sharma N, Mittal V. Cytodiagnosis of extramedullary hematopoiesis in thyroid gland unravelling an asymptomatic hematological malignancy. Diagn Cytopathol 2019; 47: 320-324.
19) Lazzi S, Als C, Mazzucchelli L, Kraft R, Kappeler A, Laissue J. Extensive extramedullary hematopoiesis in a thyroid nodule. Mod Pathol 1996; 9: 1062-1065.
20) Leoni F, Fabbri R, Pascarella A, Marrani C, Nozzoli C, Ciolli S, Marchetti G, Rossi Ferrini P. Extramedullary haematopoiesis in thyroid multinodular goitre preceding clinical evidence of agnogenic myeloid metaplasia. Histopathology 1996; 28: 559-561.
21) Leung N, Yazdi HM, Walsh SM, Lewandowski B, Markman SJ, Ooi TC. Extramedullary Hematopoiesis in a Thyroid Nodule. The Endocrinologist 1998; 8: 369-372.

22) Magalhaes LC, Oliveira DN, Nogueira TN, Rocha Filho FD. Hematopoietic cells in thyroid fine needle aspirates. Acta Cytol 2007; 51: 251-252.

23) Mizutori-Sasai Y, Maeda T, Suzuki A, Hirokawa M. An anomalous abundance of megakaryocytes in thyroid fine needle aspirates: two immunocytochemically confirmed cases. Cytopathology 2017; 28: 341-342.

24) Pontikides N, Botsios D, Kariki E, Vassiliadis K, Krassas GE. Extramedullary hemopoiesis in a thyroid nodule with extensive bone metaplasia and mature bone formation. Thyroid 2003; 13: 877-880.

25) Sayar I, Isik A, Akbas EM, Eken H, Demirtas L. Bone marrow metaplasia in multinodular goiter with primary hyperparathyroidism. Am J Med Sci 2014; 348: 530-531.

26) Schmid C, Beham A, Seewann HL. Extramedullary haematopoiesis in the thyroid gland. Histopathology 1989; 15: 423-425.

27) Tzanakakis GN, Scopa CD, Vezeridis MP, Vagenakis A. Ectopic bone in multinodular goiter. R I Med J 1989; 72: 171-172.

28) Westhoff CC, Karakas E, Dietz C, Barth PJ. Intrathyroidal hematopoiesis: a rare histological finding in an otherwise healthy patient and review of the literature. Langenbecks Arch Surg 2008; 393: 745-749.

29) Zeck JCB, A. Case of the month; 2014. Available at: http://papsociety.com/cotm14/cotmfeb14.html.

30) Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014; 12: 1500-1524.

31) Koch CA, Li CY, Mesa RA, Tefferi A. Nonhepatosplenic extramedullary hematopoiesis: associated diseases, pathology, clinical course, and treatment. Mayo Clin Proc 2003; 78: 1223-1233.

32) Policarpio-Nicolas ML, Bregman SG, Ihsan M, Atkins KA. Mass-forming extramedullary hematopoiesis diagnosed by fine-needle aspiration cytology. Diagn Cytopathol 2006; 34: 807-811.

33) Popoveniuc G, Jonklaas J. Thyroid nodules. Med Clin North Am 2012; 96: 329-349.