Case Report
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Extramedullary Hematopoiesis and Osseous Metaplasia in Thyroid Gland in Association with Papillary Thyroid Carcinoma: A Report of two Cases

Sohaila Fatima*♦, MD, Shaymaa Ahmed Sadek, MD, Wajih Ahmed Siddiqui***, MD**

*Department of Pathology, King Khalid University, Abha, KSA
**Department of Laboratory Medicine, Aseer Central Hospital, Abha, KSA
***Hematology-Oncology Department, Aseer Central Hospital, Abha, KSA

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Abstract

Bone marrow is known as the major site of hematopoiesis. It could occur in several other tissues both during fetal development and after birth. Extramedullary hematopoiesis (EH) is known to occur in the organs of reticuloendothelial system, mainly spleen and liver. It is very uncommonly seen and reported in thyroid normally in association with anemias and myeloid metaplasias. Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma and the most common endocrine malignancy. Herein, we reported two cases of PTC with osseous metaplasia and EH without any other underlying hematological disorders. Even though programmed EH is required to supplement the hematopoietic activity in the bone marrow, excessive and disease-associated EH can occur and mediate chronic inflammation. PTC with osseous metaplasia could be regarded as a unique subtype of thyroid carcinoma, which is more aggressive. Further studies are required in this regard so that PTC with osseous metaplasia could be considered as a prognostic marker.

Keywords: Extramedullary hematopoiesis, Thyroid gland, Papillary carcinoma, Osseous metaplasia

Introduction

Extramedullary hematopoiesis (EH) is known to occur in the organs of reticuloendothelial system, mainly spleen and liver.[1] EH is very uncommonly seen and reported in thyroid usually in association with anemias and myeloid metaplasias.[2] Papillary thyroid carcinoma (PTC) is the most prevalent type of thyroid carcinoma and the most common endocrine malignancy. Malignancy of thyroid gland-associated EH has been rarely reported; however, PTC with osseous metaplasia has been suggested as an aggressive subtype of thyroid carcinoma.[3] In the current research, we reported two cases of

♦**Corresponding Author:**
Sohaila Fatima, MD
Department of Pathology, King Khalid University, Abha, KSA
Tel: +966-502184094
Email:sohailafatima@gmail.com

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PTC with osseous metaplasia and EH without any other underlying hematological disorders. Further studies are needed in order to ascertain whether osseous metaplasia and EH in PTC could be a marker of aggressiveness and play a role in prognosis determination.

Case Presentation

Case 1

A 37-year-old woman presented with anterior neck mass and difficulty in swallowing for 3 weeks. Laboratory results: hemoglobin (Hb): 14.0 g/dL (12.0-15.5 g/dL), hematocrit (Hct): 41.6 % (36-46%), mean corpuscular volume (MCV): 90.5 fL (80-100 fL), white blood cell (WBC) count: 10.1×10^3 /uL ($4\text{-}11\times10^3$ /uL), platelet count (Plt): 359×10^3 /uL ($150\text{ - }400\times10^3$ /uL), thyroid stimulating hormone (TSH): 12.32 uIU/mL (0.27-4.2 uIU/mL) g, free thyroxine (FT4): 7.04 Pmol/L (12-22 Pmol/L), free triiodothyronine (FT3): 5.19 Pmol/L (3.39-5.82 Pmol/L). Ultrasound (USG) neck demonstrated bilateral enlargement of thyroid lobes and isthmus with heterogenous echogenicity, tiny calcifications, increased vascularity, and cystic changes. The largest nodule seen in the right lobe measured 18×13×10 mm, and in the left lobe it measured 35×14×11 mm respectively along their anteroposterior (AP), transverse (TS), and craniocaudal (CC) dimensions with no evidence of significantly enlarged cervical lymphadenopathy. Fine needle aspiration (FNA) of the nodule was suggestive of PTC. Total thyroidectomy was

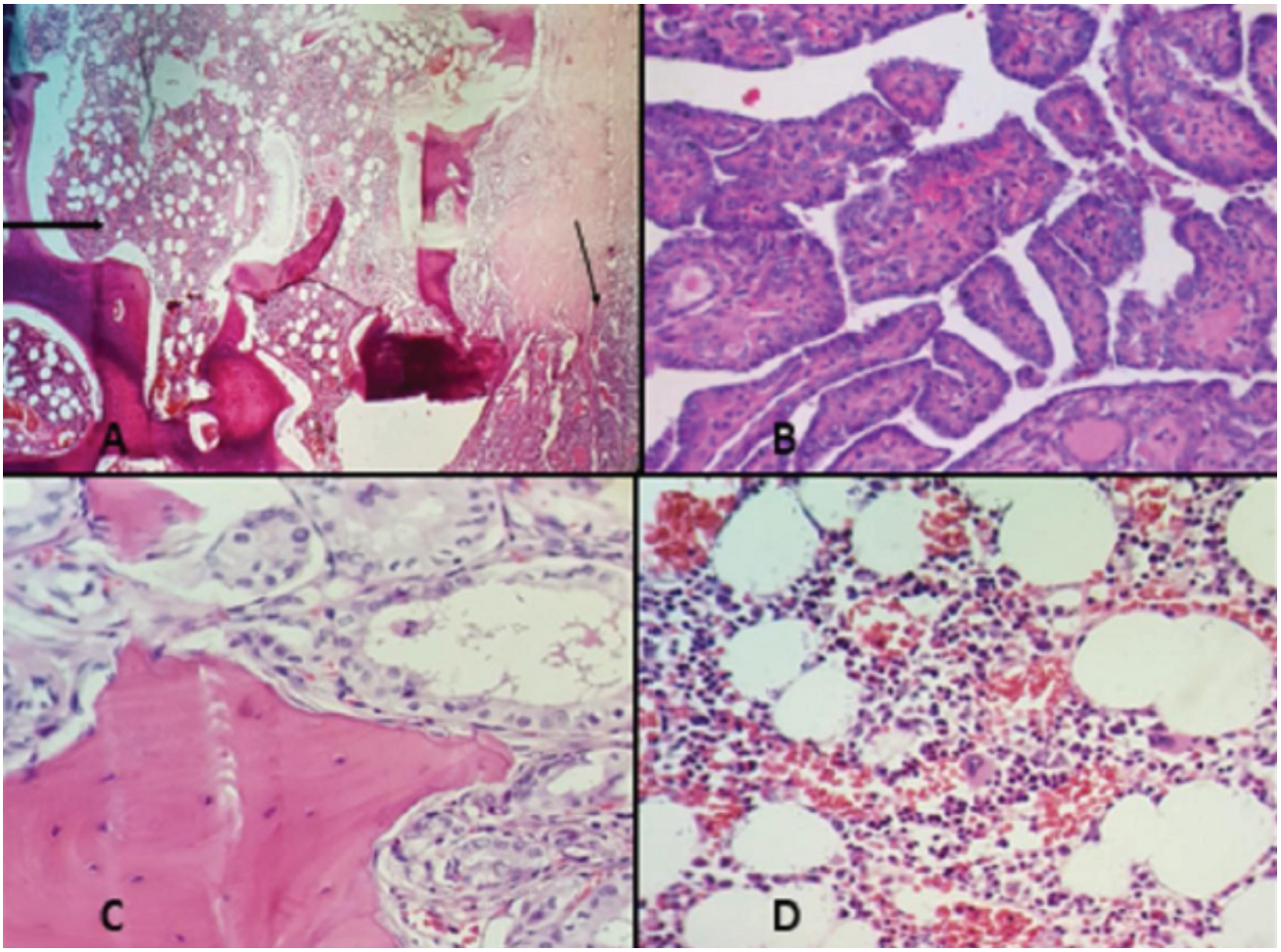

Figure 1. A. Sections from thyroid tissue showing follicles (thin arrow) and osseous metaplasia with hematopoiesis (thick arrow). B. Sections from papillary thyroid carcinoma showing papillary structures lined by pleomorphic cells with pale, overlapping nuclei, nuclear grooves, and scattered intranuclear inclusions. C: Sections from PTC showing follicular structures lined by pleomorphic cells with pale, overlapping nuclei, nuclear grooves, and scattered intranuclear inclusions with osseous metaplasia. D. Section showing hematopoietic elements with megakaryocytes. (Hematoxylin and Eosin: A: 10×, B: 20×, C and D: 40×).

performed, and on sectioning the right lobe, it showed greyish white firm to hard mass of 5×3×1.7 cm. Isthmus showed two nodules of 0.6 cm in the greatest dimension; whereas, the left lobe was hemorrhagic with a greyish white nodule of 0.7 cm in the greatest dimension. Microscopy illustrated multifocal infiltration of thyroid tissue with a mixture of follicular and papillary structures lined by pleomorphic cells with pale, overlapping nuclei, nuclear grooves, and scattered intranuclear inclusions. The tumor was surrounded by marked sclerotic stroma with frequent psammomatous calcifications and focal osseous metaplasia with hematopoietic elements. Lymphovascular invasion was noted and a diagnosis of multifocal PTC was made in a background of multinodular goiter with osseous metaplasia and EH (Figure 1). Written informed consent was taken from the patient.

Case 2

A 55-year-old man presented with progressively increasing neck swelling of one month duration. Laboratory results: Hb: 15.0 g/dL, Hct: 43.8%, MCV: 87.3 fL, WBC count: 4.79×10^3 /uL, Plt count: 213×10^3 /uL, TSH: 2.83 uIU/mL, FT4: 9.9 Pmol/L), FT3: 4.47 Pmol/L. USG neck revealed enlarged right thyroid lobe measuring 13×18×43 mm, left lobe 16×18×40 mm respectively along their AP, TS, and CC dimensions, and isthmus was 4 mm in AP diameter. Multiple variable sized nodules with coarse calcifications were seen along bilateral cervical lymphadenopathy, among which the largest measured 1.2×1.8 cm. FNA of the nodule was suspicious of PTC. We carried out a total thyroidectomy and gross examination revealed that the right lobe measured 4×2.5×2 cm, and the

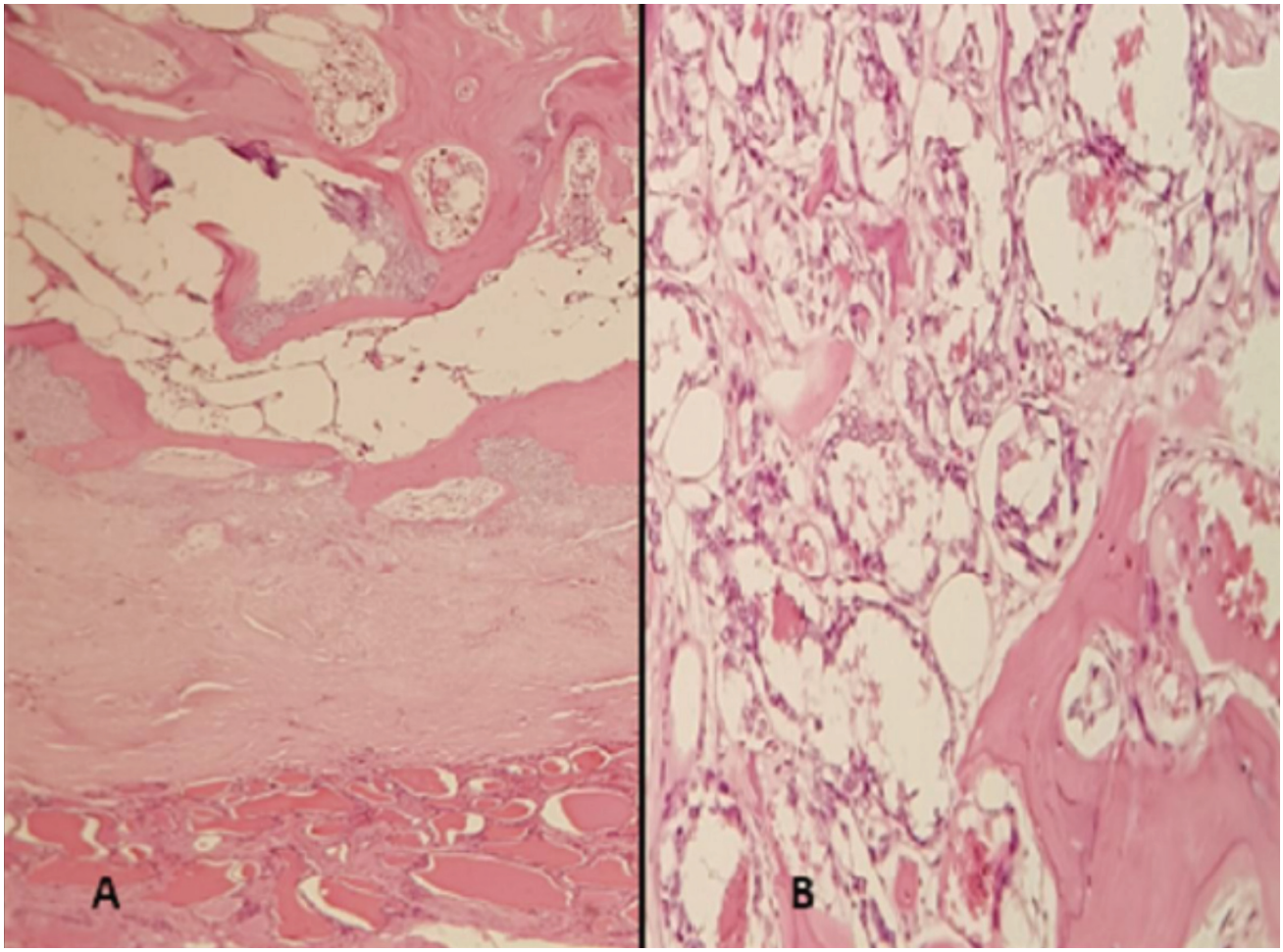

Figure 2. A. Sections from thyroid tissue showing thyroid follicles, fibrosis, and osseous metaplasia with hematopoiesis. B. Sections showing follicular structures lined by pleomorphic cells with pale nuclei and scattered intranuclear inclusions with osseous metaplasia . (Hematoxylin and Eosin: A: 20×, B: 40×).

left lobe measured 2×2×1.5 cm. On sectioning, the right lobe showed greyish white firm to hard mass of 3×2.2×1.2 cm; whereas, the left lobe showed a 2.5×1.5×1 cm mass. Microscopy demonstrated multifocal infiltration by tumor cells, lymphovascular invasion with osseous metaplasia, and EH. With a diagnosis of multifocal PTC, conventional type was made (Figure 2). Written informed consent was taken from the patient.

Discussion

The major site of hematopoiesis is believed to be the bone marrow. It could occur in several other tissues both during fetal development and after birth. EH might occur as long as there are appropriate supporting cells, accommodation of hematopoietic progenitors, and local production of soluble and cell-bound hematopoietic factors that maintain and induce differentiation of the stem and progenitor cells.[1] EH may be reestablished in liver and spleen in certain disorders, such as myelofibrosis or in chronic severe hemolytic and megaloblastic anemias either from reactivation of dormant stem cells or homing of stem cells from the bone marrow to these organs.[2] EH has been very rarely reported in thyroid gland, predominantly in association with hematological disorders.[3,4,5] In two series, the incidence of EH on thyroid FNAs was found to be 0.005% and 0.006%, respectively, with no evidence of malignancy.[6,7] In our cases, EH was observed in carcinoma, similar to a case reported by Xavier-Júnior et al.[8] In hematological stresses, this may occur as a mechanical process once the marrow expands beyond its confines as a result of increased cellularity, as in severe anemia. In myelofibrosis and myeloid metaplasia, this could be attributed to inadequate cell to cell interaction with the stroma, or injury to the endothelial cells of the bone marrow sinuses. The activation of cytokines or other factors required for hemopoiesis might occur in the spleen in pathological conditions, in which structural changes may produce a microenvironment more amenable to cell growth, or the cells themselves may alter their character and develop a predilection to grow outside the marrow.[2] Myelopoiesis occurs in the spleen and liver to produce phagocytic cells and antigen-presenting cells as a normal response to infection and inflammation. Programmed EH is required to supplement the hematopoietic activity in the bone marrow, excessive and disease-associated EH can occur and mediate chronic inflammation.[1] In our cases, it could also be due to the associated tumoral inflammation.

PTC has several variants according to the latest classification[9] of World Health Organisation. Nevertheless, PTC with osseous metaplasia has not been described as a specific subtype due to its rarity.[8] In a study conducted on PTC, tumors with osseous metaplasia showed frequent lymph node metastasis, multifocality, and extrathyroidal invasion suggesting different prognostic outcomes from those seen in other conventional papillary carcinomas.[10] Both our cases also showed multifocality and lymphovascular invasion. The basic fibroblast growth factor produced by carcinoma cells is considered to stimulate myofibroblast proliferation, which results in nodular fibrosis, and old nodular fibrosis, which indicates ossification induced by bone morphogenetic protein-2 from carcinoma cells. Such carcinoma cells tend to produce vascular endothelial growth factor which leads to neovascularization and lymphatic invasion. PTC with osseous metaplasia could be regarded as a unique subtype of thyroid carcinoma with aggressive behavior.[8]

In conclusion, EH is very rarely seen in thyroid, specifically in association with hematological stresses. In our cases, it was observed in association with PTC without any associated anemias or hematological malignancy involving the bone marrow. PTC with osseous metaplasia and EH could be a more aggressive subtype and may play a pivotal role in prognostication. Future researches are required to determine whether osseous metaplasia and EH could be considered as histological variant of PTC, and to study its management and prognostic implications.

Informed Consent

Written informed consent was taken from both patients.

Conflict of Interest

None declared.

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