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Case Report

An interesting case of papillary thyroid carcinoma with heterotrophic ossification

U Bharathi[1,*], Sivaganesh Porko[2], J Priyadharisini[1]

[1]*Dept. of Pathology, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, India*
[2]*Dept. of Pathology, Andaman and Nicobar Islands Institute of Medical Sciences, Port Blair, Andaman and Nicobar, India*

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ABSTRACT

Calcification in thyroid gland is associated with both benign and malignant lesion. However calcification is most frequently seen in malignant lesions. Calcification can give rise to metaplasia and bone containing marrow tissue. Papillary carcinoma with heterotrophic ossification has been associated with high incidence extrathyroidal invasion, multifocality, lymphnode metastsasis and older age group than in those without heterotrophic ossification. It has not been described as a specific entity in WHO classification because of its rarity. Expression of both basic fibroblast growth factor and bone morphogenetic protein was highest in papillary carcinoma with intratumoral heterotrophic ossification. In this case report we described a 71-year-old female patient who sought medical care for swelling in the neck for the past 4 years. The cervical ultrasound showed a 2 well defined nodules measuring 2x2 cms and 4mm in the right lobe with larger lesion showing peripheral rim of calcification and left lobe and isthumus shows well defined lesions measuring 5mm and 4 mm each. The clinical diagnosis was multinodular goitre. Patient subsequently underwent thyroidectomy. On histopathological investigation right lobe showed follicular adenoma and papillary carcinoma thyroid with extensive heterotrophic ossification and calcification within the tumor. The margins were free of neoplasia and there was no extrathyroidal extension. No preineural/ vascular invasion noted. One lymphnode was identified which was free of tumor. pTNM staging was pT1bNxMx.

1. Introduction

There has been a significant increase in thyroid carcinomas in the last 20 years due to early detection with cervical imaging and higher incidence in reporting microcarcinomas.[1] Among thyroid malignancies papillary carcinomas are the most frequent and carries the best prognosis overall. Known risk factor for PTC is radiation exposure. The average time from irradiation to recognition of tumor ranges from 10-30 years.[2] Papillary carcinomas are more common in middle aged adults with male to female ratio of 1:3. The median age of presentation is 50 years. Grossly PTC presents with firm in consistency, poorly defined margins and granular grey white cut sections. Calcifications may be seen frequently. While evaluating thyroid nodules one of the most significant findings in USG/CT is calcifications. They are detected more frequently in PTC than in other thyroid lesions.[3] Degenerative changes are more common in thyroid nodules. Granulomatous reaction, forgein body giant cells, fibrosis and areas of hemorrhage are seen due to rupture of thyroid follicle. All these changes in turn leads to ossification andcalcification. Virchow stated that that osteoblast are derived from fibroblast by metaplasia and termed them as modified fibroblasts.[4] PTC with intratumoral heterotropic ossification is associated with high incidence of extrathyroidal invasion, lymph node metastasis, multifocality, and in older age group. Due to its rarity it

* *Corresponding author*.
E-mail address: bharathi25nov@gmail.com (U. Bharathi).

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has not been described as a specific entity.[5] Bai et al in his study stated that stromal calcification was associated with pT stage and lymph node metastasis.[6] Here we describe a case of papillary carcinoma thyroid with intratumoral heterotrophic calcification which is a rare entity.

2. Presentation of Case

A 71-year-old female patient came to the surgery OPD for swelling in the neck for the past 6 years. She gave history of change in voice, difficulty in swallowing and loss of weight. She is a known diabetic for the past 6 years on medication. She is a known hypertensive for the past 7 years. Examination of neck showed right thyroid nodule which was hard, slightly mobile, non- tender. No cervical lymphadenopathy. The clinical diagnosis was multinodular goitre. In view of loss of weight and change in voice differential diagnosis of papillary carcinoma and follicular carcinoma was considered.

CBC, thyroid, renal, liver function tests, were normal. Thyroglobulin, and thyroid antibodies (thyroid peroxidase, thyroid globulin Antibodies) were also normal. Thyroid Function Test: TSH: 3.1 Um/L (0.3-4.0 mU/L), freeT4: 1.04 (0.7-1.8 ng/dL). The cervical ultrasound showed a 2 well defined nodules measuring 2x2 cms and 4mm in the right lobe with larger lesion showing peripheral rim of calcification and left lobe and isthumus shows well defined lesions measuring 5mm and 4 mm each.

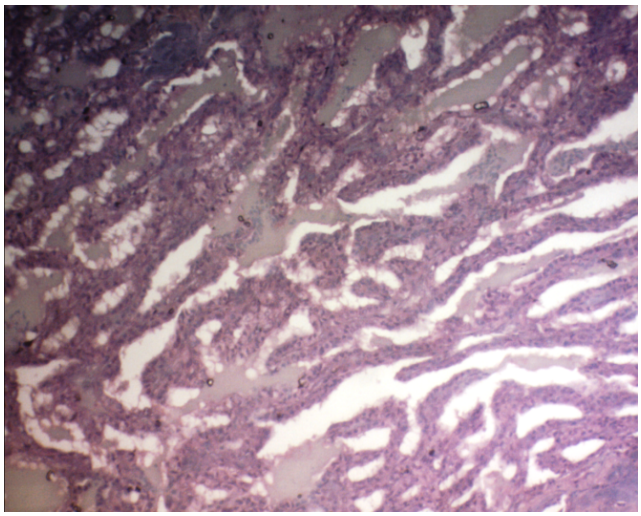

Fig. 1: Papillae with fibrovascular core (H&E stain x100)

2.1. The clinical diagnosis was multinodular goitre

Patient subsequently underwent thyroidectomy. During surgery one suspicious cervical lymph node was identified. At gross examination, the surgical specimen weighed 6g. The right lobe measured 2x2.5x1.5cms. The left lobe measured 1.8x 1.3x 0.8 cms and the isthmus 1.8x1.5x 0.3 cms. The right lobe on sectioning is nodular and on sectioning a grey white nodule was identified measuring 1.7x 1.3 cms situated 0.1 cms from the capsule. The cut surface of which is bony hard and gritty. Also seen is another grey white nodule measuring 0.5x0.3 cms, the cut surface of which is grey white. On sectioning the left lobe another grey white lesion measuring 0.3x0.3cms identified situated 0.1 cms from the capsule. On sectioning the isthmus another grey white lesion measuring 0.4x 0.3 cms situated 0.1 cms from the capsule.

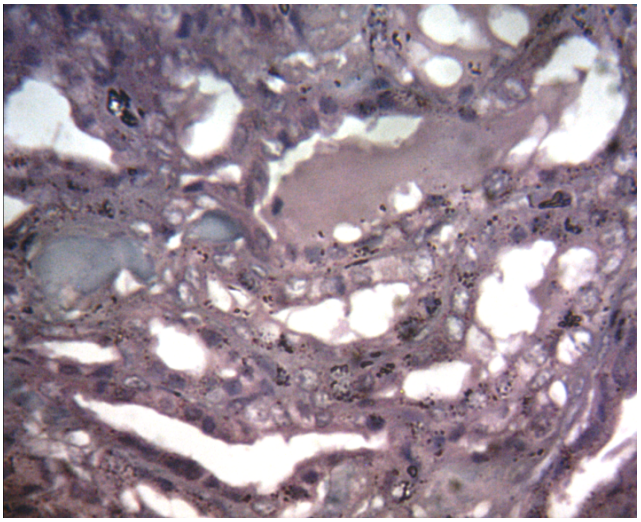

Fig. 2: Nuclear features of papillary carcinoma of thyroid-Optically clear nuclei & nuclear grooves (H&E stain x400)

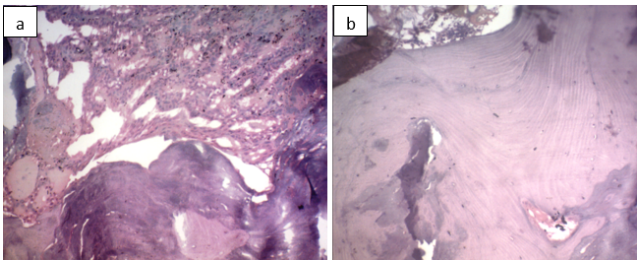

Fig. 3: a,b: Ossification as evidenced by mature bone formation with adjacent tumor (H&E stain x400

On histopathological investigation right lobe showed follicular adenoma and papillary carcinoma thyroid with extensive heterotrophic ossification and calcification (Figures 1, 2 and 3a,b) within the tumor. The margins were free of neoplasia and there was no extrathyroidal extension. No preineural/ vascular invasion noted. One lymphnode was identified which was free of tumor. pTNM staging was pT1bNxMx.

3. Pathological Discussion

Histopathological examination revealed an infiltrating neoplasm arranged in papillary patteren. The epithelial cells exhibit moderate to marked nuclear pleomorphism, optically clear nuclei some of which shows nuclear grooves. Extensive areas of calcification and ossification noted.

Papillary carcinoma thyroid is one of the most common thyroid malignancies. One of the significant findings in CT and ultrasound for evaluating thyroid nodule is calcification.[3] The incidence of calcification is most common in papillary carcinoma compared to other malignant lesions of thyroid. The stroma of papillary carcinoma thyroid consists of fibroblast, inflammatory cells, endothelial cells, calcification and intratumoral heterotopic ossification (IHO). IHO is a rare histological finding in papillary carcinoma. Papillary carcinoma thyroid is commonly associated with nodular fibrosis. This fibrosis is composed of fibroblast, myofibroblasts, collagen fiber, that promote angiogenesis, stimulate proliferation of epithelial cells, and produce extracellular matrix, growth factors, and cytokines.[7] Basic fibroblast growth factor (bFGF) plays a important role as a mitogenic factor as wells a chemotactic factor for proliferation of smooth muscle cells and myofibroblast.[8] Basic fibroblast growth factor acts as a signaling molecules involved in several physiological processes, biological functions, cellular growth, differentiation, tumor invasion and angiogenesis.[9,10] About 20% of papillary carcinoma exhibit heterotrophic ossification which is most commonly associated with a higher incidence of multifocality, extrathyroidal extension, lymph node metastasis and in older age group.[11] In our case, the patient was 71 years old and the tumor was multifocal, but there was neither extrathyroidal extension nor lymph node metastasis. Coarse calcification is most commonly seen in multinodular goitre.[12] But our patient presented with IHO (intratumoral heterotrophic ossification) and coarse calcification in association with papillary carcinoma. Therefore IHO can be seen in both benign and malignant lesions of thyroid.[13,14] The factor which leads to the formation of bone in thyroid nodule remains unclear. Bone morphogenetic protein (BMP) belongs to family of transforming growth factor β (TGF-β) which are capable of inducing bone formation in ectopic muscle tissue when implanted in vivo.[15] Recent research states that BMP also plays an important role in proliferation, apoptosis and differentiation.[16]

It plays important role in synthesizing ground substance and collagen in presence of calcium and phosphate.[17] BMP-1 converts pro-collagen 1,2,3 and 7 into mature forms which results in formation of extracellular matrix. Histologically there was a coexistence of stromal calcification and bone formation. The bone formation was located at the edge of calcification, suggesting that ossification arises from calcified stroma. IHO is more common with longer duration of thyroid disease.[18] In our case duration of disease was 6 year which clearly shows more chances of developing IHO. According to Bataille et al.[19] ectopic bone formation is most commonly seen in older age which is similar to our case. Aurora et al stated that heterotrophic ossification is seen in benign lesions of thyroid as well as in malignant lesions like thyroid hyperplasia, follicular adenoma, papillary thyroid carcinoma and anaplastic carcinoma.[20] Papillary carcinoma with IHO showed high incidence of vascular invasion and their capillaries expressed nestin and vascular endothelial growth factor.

4. Management

The patient's outcome was uneventful. Post operatively, the patient was put on thyroxin replacement dose and was sent to radiotherapy. She has her regular follow up in both the surgery and the endocrine clinics. She is euthyroid and has no more complaint

5. Final Diagnosis

The final diagnosis in our case was papillary thyroid carcinoma with heterotrophic ossification**.**

6. Conclusion

Due to the rare incidence of papillary thyroid carcinoma with intra tumoral heterotrophic ossification it has not been described in as separate entity in WHO classification. Papillary carcinoma with IHO showed frequent lymph node metastasis, multifocality, and extrathyroidal invasion. This suggests that the prognostic outcomes for PTC with IHO are different from those seen in conventional papillary carcinomas. Hence it is important to recognise these features.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

U Bharathi, Associate Professor

Sivaganesh Porko, Associate Professor

J Priyadharisini, Associate Professor

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