International Surgery Journal
Prasanth P et al. Int Surg J. 2021 Feb;8(2):757-759
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20210400

Case Report

De-differentiation in thyroid cancer: an increasingly appreciated concept

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Received: 26 October 2020
Accepted: 12 December 2020

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ABSTRACT

Thyroid cancer is the most common endocrine malignancy. In general, they are said to be of good prognosis, still there are a few aggressive variants. Differentiated carcinomas like papillary and follicular comprise of major proportion and have a less aggressive clinical behaviour, even though some of them tend to be otherwise. De-differentiated and undifferentiated cancers are more aggressive. There has been an already existing theory that these de-differentiated cancers arise from differentiated ones by a process of stepwise molecular changes. There are already reported cases of coexistence of multiple histologies. Appreciation of dedifferentiation and identification of the genetic changes may be of help in forming improved treatment strategies, including targeted therapy. This article is to report a rare case we came across, in which three different histologies coexisted and may be pointing towards graded de-differentiation pattern. This is a further support to the stepwise de-differentiation theory.

Keywords: Thyroid cancer, Multiple histology, De-differentiation, Multifocal thyroid cancer

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy.[1] It typically includes differentiated and undifferentiated cancers originating from follicular cells and 'C' cells. Another histologically distinct entity of poorly differentiated cancer has been described in literature, recognized by WHO in 2004. It has a higher predilection for lymph node spread and distant metastasis. Multifocality is common in thyroid cancers and is especially seen in papillary and medullary types. Multiple histologies coexisting in a single case is possible, but rare. The hypothesis of graded tumor progression from good prognostic well differentiated types to bad prognostic types like poorly differentiated and anaplastic types is getting stronger with the support of genetic studies conducted in animal models. This is a case in which three different histologies co-existed- well differentiated papillary carcinoma, follicular variant of papillary carcinoma and poorly differentiated thyroid cancer. Hence being a further support to the existing graded de differentiation hypothesis. The clear understanding of tumor progression pathways is very important in this scenario with a hope of inventing new effective targeted therapies for the more aggressive and challenging variants of thyroid cancers.

CASE REPORT

A 33 years old gentleman with no comorbidity was evaluated for an incidentally detected neck swelling. There was a 1×1 cm, firm, solitary thyroid nodule on the right side. There was no cervical lymphadenopathy. The FNAC report was suggestive of follicular neoplasm. Ultrasound examination of neck showed right lower pole colloid nodule of size 2.1×2.2 cm. There was another irregular hypo echoic lesion with intra lesional micro calcifications and increased internal vascularity in the

right lobe of the thyroid superior to it–follicular variant of papillary carcinoma. Medially the plane with the trachea was lost. In the left lobe of the thyroid, another irregular hypo echoic lesion with increased intralesional vascularity and no capsule-possibly neoplastic. There were suspicious sub-centimeteric right level III nodes (TIRADS 5).

He underwent total thyroidectomy with central compartment neck dissection and right selective neck dissection (II-IV). Intra operatively a 2×2 cm soft nodular swelling in the right lower pole and another 2×1 cm hard nodule in the mid part of the posterior aspect of the thyroid extending to the capsule were identified. There were enlarged nodes at level VI and right level III-IV.

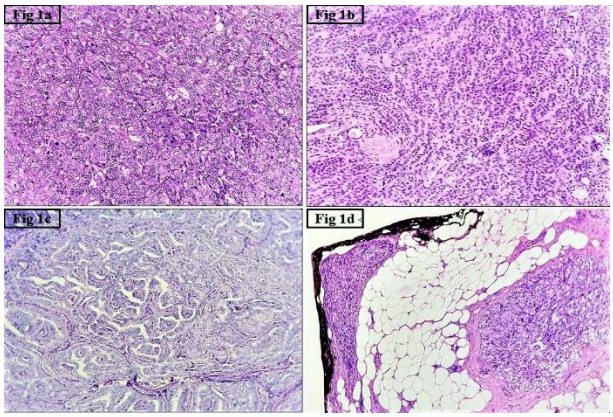

Figure 1: (a) Follicular variant of papillary thyroid carcinoma in the larger nodule of right lobe (H&E, x100), (b) thyroid carcinoma with features between well differentiated and poorly differentiated carcinoma in the smaller nodule of right lobe (H&E, x100), (c) classic variant of papillary thyroid carcinoma in the nodule of left lobe (H&E, x100) and (d) minimal extra thyroid extension noted in the smaller nodule of right lobe and positive inked margin by tumour deposits (H&E, x100).

Here in Figure 1 neoplastic follicular epithelial cells arranged predominantly in microfollicular pattern filled with colloid displaying orphan annie eye nuclei and nuclear grooves. The neoplastic cells were arranged in solid pattern up to 50% composed of poorly differentiated cells displaying hyperchromatic nuclei, brisk atypical mitosis (4-5/10 hpf) and scant cytoplasm. The immune histochemical findings showed p53 and E-Cadherin positivity in tumour cells of the smaller nodule arranged in solid pattern with low proliferation demonstrated in the tumour cells having solid pattern (Ki 67:4-6%) The negative expression for CEA and calcitonin ruled out the differential diagnosis of medullary thyroid carcinoma. displaying typical papillary architecture with true fibro vascular core lined by neoplastic follicular epithelial cells displaying orphan annie eye nuclei, nuclear grooves and occasional intranuclear pseudoinclusion. Capsular invasion/vascular invasion and extra thyroid extension not identified.

The final histopathology report was multifocal thyroid cancer (3 foci) with different histological features. The nodule in the left lobe was papillary carcinoma with no high risk features (1.5×0.7×0.5 cm) (Figure 1c). Nodule in the right lower pole was a follicular variant of papillary carcinoma (3.5×3×3 cm) (Figure 1a). The right upper pole nodule was consistent with thyroid carcinoma with features intermediate between well differentiated and poorly differentiated carcinoma (1.7×1.4×1.4 cm) (Figure 1b). Capsular involvement was seen, no lympho-vascular emboli (LVE), minimal extra thyroidal extension (ETE) (Figure 1d). Three out of 5 nodes in level VI showed metastasis without any extra nodal extension (ENE). The right II-IV nodes were free of metastatic disease.

Three weeks post-operatively, the TSH stimulated serum Thyroglobulin was 37.75 ng/ml, Anti thyroglobulin antibody was 0.6 IU/ml with a TSH level of 48.56I U/ml. PET CT scan was done in view of the poorly differentiated component, which was negative for any local or distant disease deposits. Radioactive iodine (RI) scan was done which showed small areas of disease activity suspicious of involved nodes. 4440 MBeq RIA was done and a follow up scan after one week showed no residual disease activity.

DISCUSSION

Thyroid cancer is the most common type of endocrine malignancy and its incidence has steadily increased over the last three decades.[1] The vast majority of primary malignancies are carcinomas derived from the follicular cells. Such tumors were thought of as differentiated (papillary, follicular and Hürthle cell) and undifferentiated (anaplastic). However, an intermediate class of 'poorly differentiated carcinoma' is also recognized, which is likely to represent a state of dedifferentiated, between classic differentiated and undifferentiated diseases. The para follicular C cells can undergo malignant transformation into medullary carcinoma, and thyroid lymphoma is another primary thyroid malignancy. In addition, the thyroid can be involved by direct spread from surrounding structures (larynx and esophagus) or metastases.

Poorly differentiated thyroid carcinoma (PDTC) is a rare but an independent histological type of thyroid cancer. It was considered as a variant of well differentiated thyroid carcinoma (WDTC) till 2004 when it was first recognized by the World Health Organization (WHO) as a distinct pathologic entity. It is a heterogeneous group of tumors. The clinical and histological features are not suitable for WDTC or anaplastic carcinoma (AC). And in the literature it is defined as "a follicular-cell neoplasm that shows limited evidence of structural follicular cell differentiation and occupy both morphologically and behaviorally an intermediate position between differentiated (follicular and papillary carcinomas) and undifferentiated (anaplastic) carcinoma".[2] Histologically, its diagnosis is based on loss of differentiation (non-

follicular-non papillary growth pattern), and a few high grade features such as invasive growth - high mitotic index and necrosis. The histological characteristics are, predominant solid, insular, or trabecular growth patterns which can coexist with follicular, papillary or anaplastic components of thyroid cancer.[3]

The co-existence of WDTC with PDTC component in the same tumor may be seen as per the current concept of tumor progression (differentiated to undifferentiated). Still, for diagnosis of PDTC, the majority of cells must exhibit poorly differentiated features. 75% is the generally accepted cut off, even though no final consensus is there.[4,5] However, it is important to detect the presence of PDTC components in the conventional WDTC because the PDTC component has prognostic significance.[4]

In the literature, a few cases of multiple histologies occurring in the same case are reported. Medullary carcinoma coexisting with papillary is described. For example, the association of papillary carcinoma occurring in the setting of lymphocytic thyroiditis is well known. Coexistence of spindle cell carcinoma with differentiated thyroid cancers have also been reported.[6]

There have been reports of squamous cell carcinoma and PDTC arising in the back ground of differentiated thyroid cancers. Higher grade tumors are theorized to be arising from dedifferentiation in differentiated thyroid malignancies.[7] Sylvia et al in their review concluded that aggressive behavior can be associated with de differentiated as well as well differentiated subtypes. And this can be predicted based on a host of morphological and molecular features.[8] Alyaksandr et al in an animal model on the pathway of dedifferentiation in thyroid cancers has concluded that expression of STRN-ALK with the simultaneous loss of p53 function in murine thyroid cells initiates a pathway of step wise dedifferentiation from well differentiated PTC to aggressive variants, PDTC and anaplastic thyroid cancer (ATC). They have also suggested the existence of two distinct entities of PDTC inviting further research in PDTC.[9]

Here, in this case of a 33-year old male patient who had multifocal disease with three different foci of disease, with one area of papillary carcinoma one of follicular variant of papillary carcinoma and another one with a carcinoma with features intermediate between well and poorly differentiated carcinoma is a rare one and can be taken as a clinical example supporting the concept of graded dedifferentiation in thyroid cancers.

CONCLUSION

The concept of step wise dedifferentiation in WDTC and conversion to poorly differentiated variant in thyroid may be justified with this findings of co-occurrence of graded histologic pattern as noted in this case. Further studies are required for validation of this hypothesis. Higher predilection for nodal metastasis described in setting of poorly differentiated carcinoma was justified with the observation in this case. The clear understanding of tumor progression pathways is very important in this scenario with a hope of inventing new effective targeted therapies for the more aggressive and clinically challenging variants of thyroid cancers.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Prasanth P, Thavarool SB, Balasubramanyam S, Philip KJ. De-differentiation in thyroid cancer: an increasingly appreciated concept. Int Surg J 2021;8:757-9.