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Primary Squamous Cell Carcinoma of the Thyroid Gland

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Abstract **Case Report**

Primary squamous cell carcinoma of the thyroid gland (ThSCC) is extremely rare. It accounts for less than 1% of thyroid malignancies with an aggressive behavior and poor prognosis. We report a case of an early stage ThSCC revealed through the histopathological findings of a total thyroidectomy for a non-toxic multinodular goiter. A 49 years old women presented with two years history of nodular goiter. Ultrasonography confirmed an enlarged thyroid gland with multiple nodules, one was ranked EU-TIRADS V without enlarged cervical lymph nodes. The patient underwent total thyroidectomy. Per operative exploration found few enlarged central lymph nodes that were harvested. Pathology examination found SCC proliferating in the thyroid gland staged pT3 N0. The patient received an adjuvant radiotherapy. Post treatment course is uneventful after one year follow up. Although there is a large agreement regarding the management of advanced ThSCC stage, the management of early stage disease is still controversial.

Keywords: Thyroid cancer, squamous cell carcinoma, non-follicular thyroid carcinoma.

INTRODUCTION

Primary squamous cell carcinoma of the thyroid gland is extremely rare and accounts for less than 1% of thyroid malignancies [1]. In 2017 *World Health* Organization classification of endocrine tumors, squamous cell carcinoma is considered a distinct entity among thyroid carcinomas [2]. The diagnosis of squamous cell carcinoma of the thyroid gland is based on the fact that the neoplasm should be composed entirely of tumor cells with squamous differentiation without any other cancer component. Other differential diagnosis in the histological examination should be excluded, and another SCC primary site should be ruled out since advanced tumors of adjacent structures and metastasis of a distant carcinoma on the thyroid gland occurs 10 times more frequently [3]. Due to its low incidence, clinical behavior and treatment strategy are not well codified [4]. It has been described as being highly aggressive with poor prognosis since it is most frequently diagnosed at advanced stages [5]. In this article, we report a case of an early stage primary cell thyroid carcinoma, revealed through histopathology findings of routine total thyroidectomy for a non-toxic multinodular goiter. Also, we discuss the different theories involved in its pathogenesis, benefits of early diagnosis and treatment strategies according to available to date literature.

CASE PRESENTATION

A 49 years old women with no significant medical history presented to the outpatient clinic for a nodular goiter that evolves for two years without other complains. Clinical examination disclosed a nodular goiter of moderate volume with no cervical lymph nodes or suspicious lesion of the upper aerodigestive tract. Moreover, vocal folds mobility was preserved.

Thyroid hormones and calcitonin were in normal range. A cervical ultrasonography showed a multinodular goiter with a nodule highly suspected of malignancy in the right lobe of the thyroid gland, measuring 11 mm ranked EU TIRADSV. Also, there was a 37 mm nodule EU TIRADS IV in the left lobe, with no lymphadenopathy. Those findings were highly suggestive of thyroid malignancy, especially follicular thyroid carcinoma.

Routine total thyroidectomy was performed. Per operatory exploration found a few enlarged central lymph nodes that have been harvested. Pathology

examination of the 11mm nodule disclosed a well limited epithelial proliferation with big size vesicles boarded by regular cubic epithelial cells. Focally, in this lesion, there was polygonal cell spans, with big nucleus and heterogenous chromatin without papillary nucleus type (Figures 1 and 2). There was no capsular effraction or vascular emboli. The rest of the thyroid tissue corresponded to a benign multinodular thyroid hyperplasia. Immunohistochemical examination showed an expression of cytokeratin 5/6, P63, P53 and thyroglobulin (Figures 3 & 4). The 4 central lymph nodes harvested were negative. Pathology examination concluded to a pT3 N0 infiltering and moderately differentiated squamous cell carcinoma (SCC) of the thyroid gland.

A body CT scan performed to rule out the possibility of other primary sites squamous cell carcinoma or distant metastasis was clear. Our patient received an adjuvant radiotherapy of 60 Gray. A clinical and cervical ultra sound survey was suggested each 3 months for the first year follow up then each 6 months. She is doing well for now, with no sign of recurrence after 2 and half years.

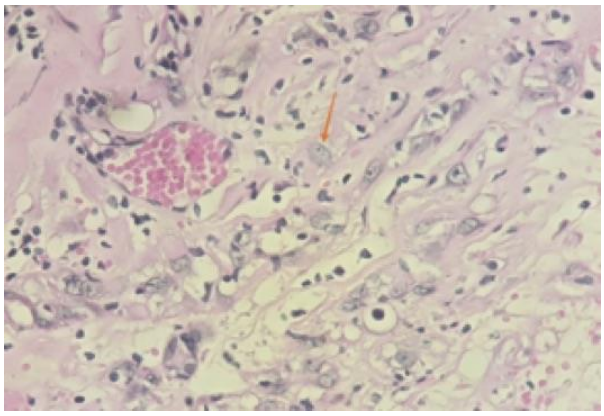

Figure 1: Microscopic view showing cellular and nuclear abnormalities (red arrow) (HESx400)

Figure 2: Immunohistochemical examination showing expression of cytokeratin 5/6

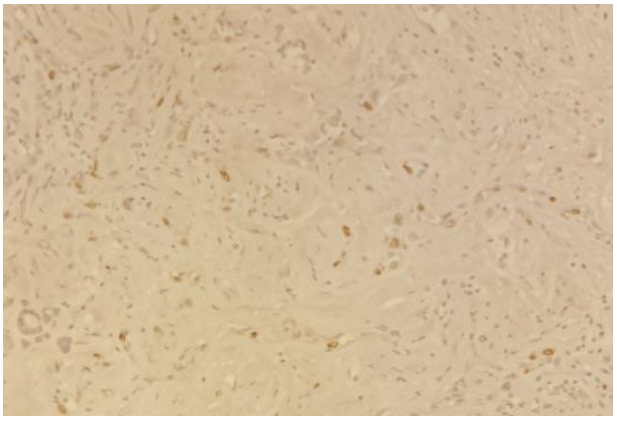

Figure 3: Immunohistochemical examination showing expression of P53

DISCUSSION

Primary squamous cell carcinoma of the thyroid gland (ThSCC) is extremely rare since there are normally no epidermoid cells in the thyroid gland. It represents less than 1% of all thyroid neoplasms with an aggressive clinical course. Therefore, it tends to be revealed at advanced stages [5]. ThSCC is often assumed to follow an analogous disease course of anaplastic thyroid carcinoma with an equally poor prognosis [6]. By definition, squamous cell carcinoma of the thyroid gland should be composed entirely of tumor cells with squamous differentiation without any other cancer cells component [7]. Therefore, ThSCC must be distinguished from areas of squamous metaplasia seen in papillary carcinoma, areas of squamous differentiation existing in many anaplastic tumors and the squamous element forming adeno-squamous cell carcinoma. Most important pathology differential diagnosis are carcinoma showing thymus like elements (CASTLE), anaplastic thyroid carcinoma, mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia [8]. Also, association of tall cell variant of papillary thyroid carcinoma and squamous cell carcinoma of thyroid gland has been described [9]. Moreover, direct extension and metastatic involvement of the thyroid occurs 10 times more frequently than primary thyroid gland SCC [10]. Thus, well conducted physical examination, upper aerodigestive tract endoscopy, body CT scan, or ideally PET CT scan has to be performed to rule out other location of primary SCC [11]. In our patient, the investigations did not show any other localization, and pathology examination confirmed the absence of papillary or anaplastic carcinoma component coexisting with the SCC.

Pathogenesis of SCC in the thyroid gland remains controversial, since there is no squamous epithelium in the thyroid gland. Several theories have been proposed concerning its origin but remain debatable. One of the earliest theories suggested is the embryonic nest, such as the ultimobranchial body, the thymic epithelium, or the thyroglossal tract, but remains

largely unproven. Goldberg and Harvey [3] suggested that squamous cells were derived from embryonic remnants of the thyroglossal duct. According to this theory, ThSCC would be expected to arise in the pyramidal lobe, since the thyroglossal duct ends in its lowest part by forming the pyramidal lobe, but most of ThSCC cases reported arise from lateral lobes. Our case, is more likely to support the "metaplasia theory" suggesting that the squamous metaplasia of the thyroid tissue occurring in certain benign diseases such as nodular goiter, chronic thyroiditis or malignant tumors could degenerate and form SCC [1]. Sahoo *et al*., suggested that we should expect a higher incidence of ThSCC than reported if this theory was true [12]. The largest series found in literature was published in 2020 by Limberg *et al*., including 314 cases from the US national cancer database between 2014 and 2015 [6]. A. K. Lam stated that in the population-based studies, the number of cases appears to be over-estimated. Since there is a shortage of information about individual patients, he retained only 117 cases from the English literature that strictly adhere to the WHO definition of thyroid squamous cell carcinoma [13]. The mean age at presentation was 64 years with a female predominance (female to male ratio 2.4 to 1) [13]. Anterior neck mass was the commonest complain, followed by voice change, dysphagia and dyspnea [13]. The mean diameter was 54 mm and the locoregional invasion was found in 93% with a lymph node involvement in 59% [13]. Also, 26 % of the patients had distant metastasis. The median survival was 8 months, and 2 years survival rate was 14% [13]. Tumors were well differentiated in 12%, moderately differentiated in 51% and poorly differentiated in 37% of the cases [13]. Moreover, high grad carcinoma in primary squamous cell carcinoma of the thyroid gland seems to be proportionally higher than squamous cell carcinoma of the upper aerodigestive tract [13].

Ultrasound Investigation with fine-needle aspiration biopsy is the first investigation proposed for patients with suspected malignant lesion in the thyroid gland. It was helpful to detect the malignant nature of the disease in less than 80% of cases and sensitive to make the diagnosis of squamous cell carcinoma in less than 26% of cases [13]. Therefore, it is the only investigation that could make the diagnosis in the preoperative management, since there are no specific radiological features of thyroid SCC [11].

The immunohistochemical examination is very helpful to retain the SCC diagnosis, and more importantly, to confirm the thyroid origin of the tumor. Thyroglobulin and T-T-F-1 are the most commonly tested in thyroid carcinoma, but they are rarely positive in ThSCC [13]. On the other hand, paired box gene 8 protein (PAX-8) seems to be a more sensitive marker for confirming the thyroid origin of the carcinoma given that more than 91% of thyroid tumors containing squamous cell carcinoma component were positive for PAX-8. [14] Primary squamous cell carcinoma of the thyroid gland showed positive staining for P40 and P63, Cytokeratin 19,7 and 5/6, but was negative for Cytokeratin 20 and 10/13, with an overexpression of p53 commonly found in cancers with biological aggressive behavior. Our patient showed an expression of cytokeratin 5/6, P63, P53 and thyroglobulin.

Due to its low incidence, ThSCC management and treatment strategy is still unclear [4]. This tumor is widely reported to be poorly responsive to chemotherapy and relatively resistant to radiotherapy [11, 15]. Thus, surgery is an essential part of management particularly if complete resection is possible [16]. Cho and al. stated that early detection and extensive surgical resection of the tumor were the only significant prognostic factors in multivariable analysis [9]. The median age survival of patients with R0 resection was 23 months and 4 months for R1 resection, with no clinical difference between the two types of thyroidectomy (Total thyroidectomy/ Hemithyroidectomy). Also, the benefit of adjuvant treatment was not proven [16]. Limberg *et al*., identified independent factors impacting overall survival [6]. Age greater than 55 years old, presence of lymph nodes metastases, distant metastasis at the diagnosis and extra thyroidal extension were associated with worse Overall Survival (OS). Furthermore, successful surgical resection of ThSCC (R0/ R1) was associated with improved median OS (R0: 55.5 months vs. R1: 10.2 months vs. R2: 3.4 months). Additionally, patients who underwent surgical resection with lymphadenectomy had a better median OS, regardless of pathologic lymph nodes status, compared to those who did not have lymphadenectomy. Adjuvant therapy, by external beam radiation, chemotherapy, or combination, combined to R0 or R1 surgery, was not associated with any improved OS [6, 16]. On the other hand, adjuvant therapy was associated with improved OS for the patients who did not qualify for surgery or had an R2 resection [6]. These patients had a median OS of 2.5 months that increased to 3.2 months with adjuvant radiation, to 5.7 months with adjuvant chemotherapy, and to 8.8 months with concomitant chemoradiotherapy [6].

Follow up using PET CT scan is the most sensitive mean to detect cancer recurrences and metastasis [14]. Also, the proposed approach for treatment of aggressive recurrent thyroid cancers are target therapies using kinase inhibitors [17].

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