Case Report
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A Rare Entity: Papillary Thyroid Carcinoma with Squamous Differentiation Diagnosed in a Middle-aged Man Following Endoscopic Total Thyroidectomy via Axillo-Bilateral Breast Approach

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Abstract

Although squamous metaplasia is a well-known occurrence in papillary thyroid carcinoma (PTC), it is extremely uncommon to diagnose a PTC with squamous differentiation (PTC-SD), especially in a non-elderly patient, thus raising a diagnostic challenge when considering its broad histopathological differential diagnosis. Endoscopic thyroidectomy via axillo-bilateral breast approach (ABBA) has been recently validated as an appropriate surgical alternative to conventional thyroidectomy for treating PTC in the selected patients. Hereby, we report a rare case of PTC-SD diagnosed in a solitary thyroid nodule (STN) in a 30-year-old man with a family history of thyroid cancer who was operated using the endoscopic ABBA. In fact, detection of the squamous cell carcinoma component may not be feasible through fine needle aspiration cytology or frozen section examinations, while permanent paraffin sections and immunohistochemistry (if required) usually allows for its identification. Due to their diverse clinical and biological behaviors, it is important to differentiate PTC-SD from other conditions in which a thyroid specimen contains a squamous epithelium. PTC-SD patients with favorable clinicopathological criteria as young age and localized disease can be fortunate candidates for the minimally invasive thyroidectomy approaches as endoscopic ABBA.

Keywords: Papillary thyroid carcinoma, Squamous, Axillo-bilateral breast approach, Endoscopic thyroidectomy, Differential diagnosis

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Introduction

Although papillary thyroid carcinoma (PTC) is rather known to be associated with focal or extensive squamous metaplasia in 20%-40% of the cases,[1,2] it is extremely uncommon to diagnose a PTC with squamous differentiation (PTC-SD) in a primary thyroid cancer at initial presentation rather than in a lymph node (LN) or distant metastasis or in a late tumor recurrence,[3-6] particularly in a non-elderly patient.

Endoscopic thyroidectomy employs the principle of minimally invasive surgery combined with video. Recently, axillo-bilateral breast approach (ABBA) has been validated as a safe and effective thyroidectomy approach that has advantages in cosmetic results and it does not increase the complication rates or worsen the quality of patient's life.[7,8] Hereby, we report a

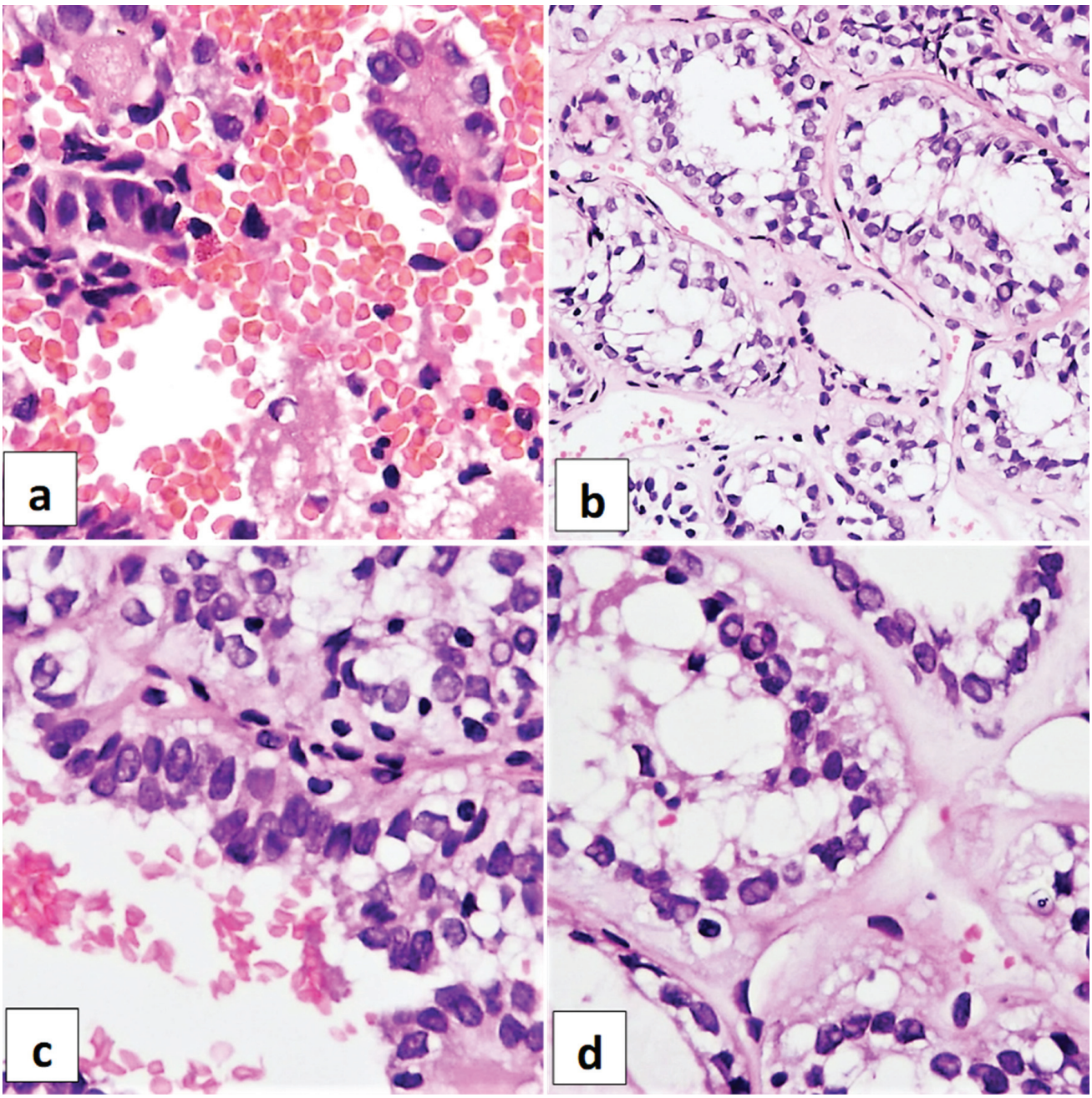

Figure 1. Cytologic examination: Moderately cellular smears with monolayer sheets of thyroid follicular cells, arranged in papillary architectures with fibrovascular cores (a; H&E, ×100), follicular structures or syncytial fragments (b, ×100). The cells have enlarged elongated overlapping nuclei with irregular contours, intranuclear inclusions, nuclear grooves and pale fine chromatin with focal cytoplasmic clearing (c and d; H&E, ×400). No detected psammoma bodies.

rare case of PTC-SD diagnosed in a solitary thyroid nodule (STN) in an initially-presented middle-aged man who was operated via ABBA.

Case Presentation

Clinical presentation

A 30-year-old male patient presented to the Surgical Oncology Clinics of our center complaining of neck swelling. He had irrelevant medical or surgical history. Interestingly, he had a family history of thyroid cancer on his mother's side. No abnormality was detected based on general examination, while local examination of the patient's neck revealed a left-sided neck swelling measuring about 3 by 3.5 cm that was movable by deglutition, indicating a thyroid topography.

Imaging and cytologic examination

Neck ultrasonography revealed homogeneous echo-texture in both thyroid lobes with a mild enlargement of the left lobe that contained a well-defined STN measuring 2.8 × 2.7 × 1.8 cm in its parenchyma. This nodule was solid, iso-echoic with irregular hyperdense areas and increased peripheral and central vascularity. The nodule showed an internal punctuate and a peripheral rim of calcification. No significant cervical lymphadenopathy was detected, both carotid sheaths were intact, parotid and submandibular glands were within normal appearances and the trachea was central in position. The nodule was staged according to the Thyroid Imaging and Reporting Data System (TI-RADS) as TI-RADS 4a (suspicious; 10-80% malignancy). Fine needle aspiration (FNA) from the STN was done. The cytological examination was highly suspicious for PTC and staged as Bethesda V (Figure 1).

Operative procedure and frozen section

The patient was planned for left hemithyroidectomy and intraoperative frozen section examination via left axillo-breast endoscopic approach using three ports. The frozen section of the left thyroid lobe confirmed the diagnosis of the classical type PTC involving a 3-cm left STN. As a result, completion thyroidectomy was accomplished by adding a fourth port in the right breast which modified the approach into ABBA (Figure 2).

Histopathology and immunohistochemistry (IHC)

Permanent histopathological paraffin sections were prepared from the left STN. Microscopically, we detected a capsulated malignant tumoral proliferation arranged into follicles and papillary structures (covered by atypical follicular cells with nuclear overlapping, grooving, inclusions, and washed-out nuclei), which is typical of classic PTC. In admixture, there were sheets of equivocally moderately-differentiated malignant squamous epithelial cells (high nuclear-to-cytoplasmic ratio, irregular nuclear contour, coarse

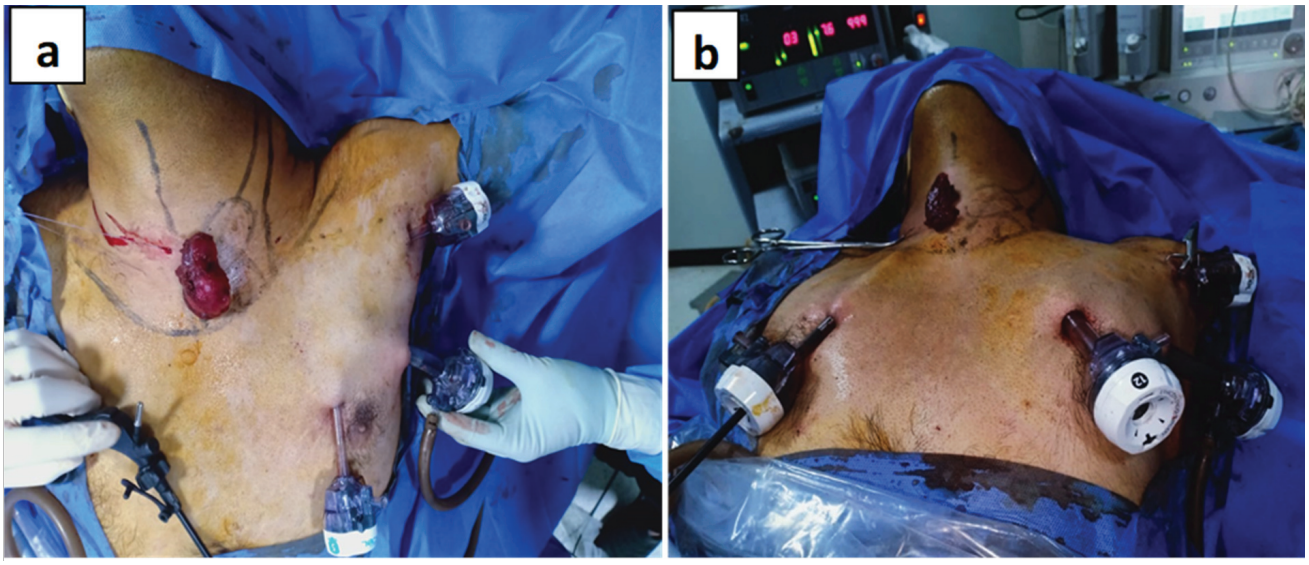

Figure 2. Thyroidectomy via axillo-bilateral breast approach: Intraoperative image of the left lobe (a), intraoperative picture after extraction of the right lobe (b).

or dark chromatin, prominent nucleoli and scattered mitotic figures) showing keratinization and intercellular bridges. Squamous areas constituted more than 10% of the tumor at every examined section. Psammoma bodies, capsular invasion and lympho-vascular emboli were detected but there was no extra-thyroidal extension. The right lobe revealed unremarkable grossly pathological changes and was negative for tumor microscopically. Based on the World Health Organization (WHO) diagnostic criteria and the American Joint Committee (AJCC) staging principles, a final diagnosis of PTC-SD, AJCC Stage I [T2NxMx]) was confirmed. IHC was performed using thyroglobulin and CK5/6 that highlighted the PTC and squamous cell carcinoma (SCCa) components, respectively (Figure 3).

Discussion

Within a thyroid neoplasm, SD is defined as squamous cell carcinoma associated with a well-differentiated thyroid cancer without anaplastic or poorly-differentiated components.[3] Normally, the squamous epithelium does not form a histological component of the thyroid gland. Once existing, it would raise a differential diagnosis including any of the following possibilities: (1) well-differentiated squamous metaplasia in a non-neoplastic (nodular goiter and lymphocytic thyroiditis) or neoplastic thyroid lesion,[1,2] (2) SCCa de-differentiation in a recurrent pre-existing thyroid carcinoma usually in association with anaplastic features,[5,6] (3) primary SCCa of the thyroid,[9,10] (4) metastatic SCCa from another site, (5) carcinoma showing thymus-like differentiation,[1] (6) and finally SD in an otherwise

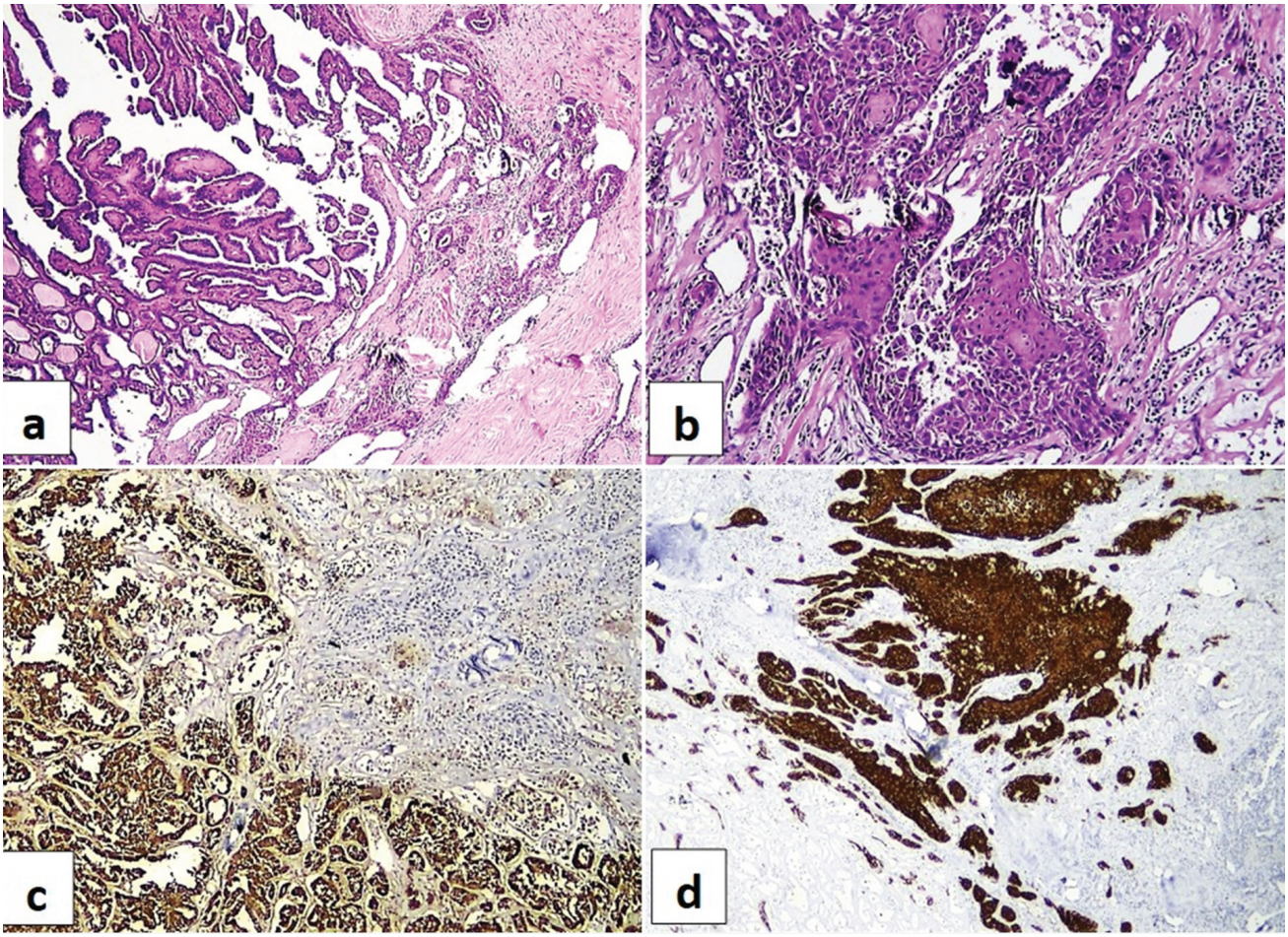

Figure 3. Permanent histopathologic sections and immunohistochemistry (IHC): A papillary thyroid carcinoma admixed with areas of squamous cell carcinoma differentiation (a and b; H&E, ×100 and ×200 respectively). IHC shows cytoplasmic positivity of the papillary areas for thyroglobulin (c) and negativity for CK5/6 (d); in contrast, the squamous component is negative for thyroglobulin (c) and positive for CK5/6 (d) (c and d; diaminobenzidine, ×200).

typical primary PTC at initial presentation,[3] which is the case here. By nature, the squamous cell component carries the features of a moderately- or poorly-differentiated SCCa in the latter five conditions. Importantly, these conditions need to be differentiated from each other due to their diverse clinical and biological behaviors.[6] In our experience, the diagnosis should be based on the following criteria: (1) the precision of the squamous epithelium and whether it is benign or malignant, (2) the knowledge of a pre-existing thyroid neoplasm and its former histologic type, (3) the presence or absence of associated intermixed malignant components as PTC or anaplastic thyroid carcinoma with the squamous component, (4) the existence of SCCa at other sites especially in the head and neck area, and (5) the clinical interpretation of a recurrent or metastatic lesion from a previously diagnosed thyroid carcinoma. Additionally, IHC using squamous and thyroidal differentiation antibodies may provide a diagnostic aid to highlight the biphasic pattern of the SCCs component and the admixed malignant areas of thyroid-follicular origin differentiation.

Etio-pathogenetically, thyroidal squamous epithelium is thought to be derived from thyroglossal duct, thymic or ultimobranchial remnants or can be caused by chronic inflammation or scarring from thyroiditis, and patients with squamous metaplasia even carry the risk of transformation into pure SCCa, SD or de-differentiation in thyroid carcinomas.[2]

Although PTC harbors a good prognosis with a survival rate of more than 90% at 20 years, some factors do change the prognosis, such as age more than 45 at diagnosis, larger tumor size, incomplete excision, staging/metastasis, extrathyroidal extension, certain histopathology variants such as tall cell, columnar and diffuse sclerosing variant, and the presence of local invasion. Reported adverse molecular prognostic factors include TERT promoter mutations and multiple concurrent mutations, but BRAFV600E mutation is controversial.[1] Generally, the unpredictable nature of PTC is commonly seen in very elderly patients who present with rapidly progressive clinical behavior.[6] In this context, PTC-SD is reported to usually affect elderly patients (mean 56 years).[3] Surprisingly, PTC-SD was reported here in a middle-aged man who had a positive family history of thyroid cancer. Unfortunately, neither TERT nor BRAF mutational analyses were performed prior to surgery in this case.

In the largest case series of PTC-SD, Beninato et al.[3] considered this phenomenon as a step in the progression towards the de-differentiation of PTC. From the limited designated cases, PTC-SD has demonstrated aggressive clinicopathological features including ability to spread outside the thyroid capsule, metastasize to LNs or distant organs, and invade local structures rendering poor long-term outcomes. Accordingly, the previous study recommended that PTC-SD cases should be treated according to evidence-based guidelines for high-risk thyroid cancers.

The current case was operated via ABBA. With the increase in the importance of patient satisfaction, different extra-cervical "remote" approaches have evolved to avoid visible scars in the neck for better cosmetic outcomes. The most common remote approaches are the trans-axillary ones.[8] Overall, the perioperative outcomes are similar for all endoscopic compared with open thyroid surgeries in experienced high-volume centers. Moreover, conventional and endoscopic thyroidectomy via ABBA has similar surgical outcomes in PTC patients with no reported differences in the postoperative complications and thyroglobulin levels. Therefore, ABBA may be an appropriate surgical alternative to conventional thyroidectomy for treating PTC in patients who can tolerate the slightly longer operation time.[7] This was applicable in our case as the patient was a 30-year-old male with a generally good health status, irrelevant medical and surgical history, with a single relatively small-sized well-defined tumor nodule, and no detected extrathyroidal extension or involvement of cervical LNs or neck structures in the imaging studies. Moreover, no extrathyroidal extension was detected in the histopathological examination.

With such adequate initial surgery, this patient is expected to benefit from a long disease-free interval that was previously demonstrated in PTC-SD cases with similar favorable clinico-pathological criteria.[3]

Conclusion

PTC-SD is a rarely encountered thyroid cancer entity. Detection of the SCCa component may not be feasible through fine needle aspiration cytology or frozen section examinations, while permanent paraffin sections and IHC (if required) usually allow for such identification. Due to their diverse clinical and biological behaviors, it is important to differentiate PTC-SD from other conditions where a thyroid specimen contains a squamous epithelium. The selected PTC-SD patients with favorable clinicopathological criteria are fortunate potential candidates for the minimally invasive thyroidectomy approaches as endoscopic ABBA.

Ethical Statement

Ethical approval was obtained from the Institutional Research Board (IRB, code: R.2021.04.xx.R1). Patient identification is not possible through the presented data and images.

Informed Consent

Informed consent was obtained from the patient according to the recommendations of the IRB.

Conflict of Interest

None declared.

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