Squamous cell carcinoma of thyroid: a unique type of thyroid cancer in World Health Organization (WHO) classification of endocrine tumours with distinctive features from anaplastic thyroid carcinoma

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ABSTRACT

The aim is to review the features of 117 primary squamous cell carcinomas of thyroid which meet the histological criteria of World Health Organization classification of endocrine tumours. The carcinomas occur in 83 women and 34 men (female to male ratio is 2.4 to 1) and with median age at presentation of 64. Half of these squamous cell carcinomas of thyroid were moderately differentiated. PAX-8 protein is a sensitive marker for confirming the thyroid origin of the carcinoma. The carcinoma is also positive for p63, p40 cytokeratins 5/6, 7,19 and negative for cytokeratins 20 and 10/13. P53 overexpression is common. The most important differential diagnosis is direct infiltration or metastatic involvement by squamous cell carcinoma from other organs. Limited mutation analysis revealed *BRAF* mutation in some squamous cell carcinomas of the thyroid. The genetic profile appears to be different from anaplastic thyroid carcinomas. Primary squamous cell carcinoma of thyroid had lymph node involvement in 59% and distant metastases in 26%. The median survival of the patients was 8 months. Curative surgery offers the best survival for the patients with the carcinoma. To conclude, primary squamous cell carcinoma of the thyroid gland has distinctive clinical, pathological and molecular profiles. It is important to recognize this unique variant of thyroid carcinoma for possible curative surgical resection and to do more genomic works on the entity to uncover the molecular pathogenesis.

Keywords: squamous carcinoma; thyroid; anaplastic carcinoma; WHO, BRAF

1. Introduction

Squamous cell carcinoma is a rare tumour of the thyroid gland. In the second edition of World Health Organization (WHO) Histological typing of thyroid tumours published in 1988, squamous cell carcinoma of the thyroid gland was briefly listed in "Other carcinomas" in the category of malignant epithelial tumours (Hedinger *et al*. 1993). The entity first becomes a separate entity of thyroid tumour in third edition of the WHO classification of tumours published in 2004 (Lam & Sakamoto 2004). In the current (4th edition) of WHO classification of endocrine tumours published in 2017, squamous cell carcinoma remains as a separate entity of thyroid carcinoma (Carcangiu *et al.* 2017). However, there is no great difference in the content of the chapters on this entity between the two editions of WHO book despite 13 years in between. It is worth noting that there is a proposed developmental relationship between anaplastic carcinoma and squamous cell carcinoma (Lam *et al*. 2017). Studies in the recent years have revealed more details on the clinicopathological, genomic and therapeutic characteristics of anaplastic thyroid carcinoma (Molinaro *et al*. 2017). On the other hand, there is a gap of knowledge on the features of primary squamous cell carcinoma of thyroid. This review aims to address this gap of knowledge by analysing the features of squamous cell carcinoma of thyroid and their relationships with other tumours of the thyroid gland.

2. Method

Primary squamous cell carcinoma of thyroid gland is extremely rare. It is not surprising that different authors give different values of the total number of cases reported in the literature because of the variation in criteria adopted for analysis. In population-based studies, there are lack of detail of the individual patients, the number of cases appear to be over-estimated (Au *et*

al. 2017, Yang *et al*. 2019, Limberg *et al*. 2020). The largest of these studies was from the American College of Surgeons National Cancer Database in which 314 cases of primary squamous cell carcinoma of thyroid gland were reported between 2004 to 2015 (Limberg *et al*. 2020).

The current review is based on in depth analysis of the cases reported in the English literature. All the thyroid carcinoma having features of squamous differentiation and been reported as squamous cell carcinoma of thyroid in PubMed database were analysed. Cases without adequate individual data were excluded. In addition, the authorship and institutions were checked to exclude cases that were reported more than once in the literature.

Overall, 253 cases have been termed squamous cell carcinoma of thyroid gland with data on the clinical pathological features of individual patient available for analysis. The data were entered in a database for statistical analysis by the Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, New York, USA). Of these, 18 had no details of thyroid cancer histology, e.g. cases with only fine needle aspiration or core biopsy results without information on the histology of surgical specimens and thus by WHO definition, could not be termed as "squamous cell carcinoma". Of the remaining 235 cases, 118 showed co-exiting carcinomas such as papillary thyroid carcinoma, follicular thyroid carcinoma or anaplastic thyroid carcinoma.

Strict adherence to the WHO definition of primary squamous carcinoma of thyroid was adopted, which is the cancer must be 100% squamous cell carcinoma without the presence of other cancer component. Thus, only 117 cases fit the pathological criteria of the current WHO definition of primary squamous cell carcinoma of thyroid gland and could be entered into in depth review of the features (Roeder 1921, Goldman 1964, Prakash *et al*. 1968, Huang & Assor

1971, Kukreti *et al*. 1972, Bahuleyan 1972, Kampsen *et al*. 1977, Shimaoka & Tsukada 1980, Lee *et al*. 1980, Saito *et al*. 1981, Budd *et al*. 1982, Segal *et al*. 1984, Kapoor *et al*. 1985, Huang & Lin 1986, Riddle & Dincsoy 1987, Elender & Harell 1987, Sarda *et al*. 1988, Misonou *et al*. 1988, Simpson & Carruthers 1988, Korovin *et al*. 1989, Harada *et al*. 1989, Tsuchiya *et al*. 1990, Theander *et al*. 1993, Chaudhary *et al*. 1994, Carter & Milroy 1996, Wan Muhaizan et al. 1998, Kumar *et al*. 1999, Cook *et al*. 1999, Kleer *et al*. 2000, Jones *et al*. 2000, Lam *et al*. 2001a, Agrawal *et al*. 2001, Zhou 2002, Sahoo *et al*. 2002, Zimmer *et al*. 2003, Sanchez-Sosa *et al*. 2006, Ab Hadi *et al*. 2007, Chintamani *et al*. 2007, *Fassan et al*. 2007, Müssig *et al*. 2008, Makay *et al.* 2008, Long *et al.* 2009, Yucel *et al*. 2010, Chen *et al*. 2010, Ashraf *et al*. 2010, Bonetti *et al*. 2010, Batchelor 2011, Ko *et al*. 2012, Chen *et al*. 2012, Rosa & Toronczyk 2012, Shrestha *et al*. 2013, Sapalidis *et al.* 2014, Jang *et al*. 2014, Bolfi *et al*. 2014, Chavan *et al*. 2015, Chu *et al*. 2016, Lichiardopol *et al.* 2016, Wygoda *et al*. 2017, Struller *et al*. 2017, Yasumatsu *et al*. 2018, Koyama *et al*. 2018, Ibrahim *et al*. 2018, Raggio *et al*. 2019, De Cesare *et al*. 2019, Kao *et al*. 2019).

3. Epidemiology

Lam and colleagues revealed the histology of 895 primary thyroid malignant tumours in a single intuition over a 30-year period (Lam *et al*. 2005). They noted that primary squamous cell carcinoma comprised 0.5% and anaplastic thyroid carcinoma accounted for 4.2% of the thyroid cancers. In a population-based study, Limberg and colleagues shown that primary squamous cell carcinoma and anaplastic thyroid carcinoma accounted for 0.3% and 2.6% of primary thyroid malignancies respectively (Limberg *et al*. 2020). In another population-based study, Yang and colleagues reported that primary squamous cell carcinoma of thyroid accounted for 0.12% of

thyroid cancers from 1873 to 2015 in USA (Yang *et al*. 2019). Overall, primary squamous cell carcinoma accounted for no more than 0.5% of primary thyroid cancer. Anaplastic thyroid carcinoma is more than 8 times commoner than primary squamous cell carcinoma. Of interest, Yang and colleagues also reported the annual incidence of primary squamous cell carcinoma of thyroid decreased from 0.4% in 1973 to 0.1% in 2015. The drop in the incidence of the thyroid carcinoma may be related to the earlier diagnosis and treatment of related thyroid disease as well as rise in incidence of papillary thyroid carcinoma.

Geographically, the reported cases in Asia comprised 48% (n=56) of the cases with most of the cases reported in Japanese patients. The other patients were reported approximately equally in America (27%; n=32) (occur mainly in USA) and Europe (25%; n=29) (mainly in United Kingdom).

From the accumulated data in the literature, the 117 primary squamous cell carcinomas occur in 83 women and 34 men. The female to male ratio is 2.4 to 1 with women accounting for 71% of the patients with primary squamous cell carcinoma. The female predominance of the cancer is lower than those in patients with conventional papillary thyroid carcinoma with the ratio of female to male between 3 and 4 to 1 (Lam *et al*. 2005). In a population-based study, Yang and colleague based on the Surveillance, Epidemiology, and End Results Program (SEER) 18-registery database in USA between 1973 and 2015 and noted that the female to male ratio of primary squamous cell carcinoma of thyroid is 1.4 to 1 (Yang *et al*. 2019).

For anaplastic carcinoma, in a large series of 188 patients from Slovenia, the female to male ratio is 2.2 to 1 (Besic *et al*. 2005). Limberg and colleagues analysed the American College of Surgeons National Cancer Database and reported similar gender proportion between anaplastic thyroid carcinoma and primary thyroid squamous cell carcinoma (Limberg *et al*.

2020). Like the findings from the study of Yang and colleagues, lower female to male ratio for both carcinomas were noted and lower when compared to the papillary thyroid carcinoma (Yang *et al*. 2019).

From the pooled data of the 117 primary squamous cell carcinomas of thyroid, the age of patients with primary squamous cell carcinoma ranged from 13 to 89. The carcinoma was most often seen in the seventh decade (Figure 1). The mean age at presentation of these patients was 61 and the median age at presentation was 64. The mean age is lower than those patients with thyroid carcinoma having anaplastic carcinoma and squamous carcinoma component (mean age = 66, p=0.002). There is no gender difference in age distribution for the primary squamous cell carcinoma of the thyroid gland. Seventy-six per cent of the carcinomas occurred in the patients between the sixth and eight decades and more than 60% of the reported cases presented at age 60 or above. The results were like the population-based studies in USA with a mean age at presentation of 68 (Au *et al*. 2017, Limberg *et al*. 2020). Thus, primary squamous cell carcinoma occurs in a much older age group than conventional papillary thyroid carcinoma with mean age of presentation at fifth decade (Lam *et al*. 2005). In addition, patients with primary squamous cell carcinoma were found in patients slightly younger than those with anaplastic thyroid carcinoma (mean age at presentation often at eight decade with median age of 72) (Lo *et al*. 1999, Lam *et al*. 2000, Limberg *et al*. 2020).

4. Clinical Features

Primary squamous cell carcinoma of thyroid resembles anaplastic thyroid carcinoma in clinical presentation. Patients with the carcinoma typically present with rapidly increasing neck mass invading the adjacent structures and with accompanying cervical lymphadenopathy. Obstructive symptoms related to the mass effect of the cancer such as dysphagia, dyspnoea,

hoarseness and neck pain may be present. Also, patients may have a longstanding history of goitre or thyroid diseases. In the literature, 16 of the 117 patients with primary squamous cell carcinoma of thyroid had documented Hashimoto's thyroiditis/lymphocytic thyroiditis. In addition, Yucel and colleagues reported a case of primary squamous cell carcinoma of thyroid 25 years after radioactive iodine treatment of hyperthyroidism (Yucel *et al*. 2010).

Paraneoplastic manifestations have been reported in anaplastic thyroid carcinoma. The manifestations comprise ectopic secretion of human chorionic gonadotrophin (Gu *et al*. 2018), fibroblastic growth factor 23 (giving rise to osteomalacia) (Abate *et al*. 2016), granulocyte colony-stimulating factor (give rise to leucocytosis) (Kang *et al.* 2013), parathyroid hormone-related protein (give rise to hypercalcemia) (Iwai *et al.* 2004) as well as hypertrophic osteoarthropathy likely to be the effect of secretion of platelet derived growth factor or vascular endothelial growth factor (Vico *et al*. 1992) Similar to anaplastic thyroid carcinoma, primary squamous cell carcinoma, paraneoplastic manifestations could occur in patients with primary squamous cell carcinoma of thyroid. Two cases of primary squamous cell carcinoma had rare combination of paraneoplastic features of hypercalcemia and leucocytosis (Saito *et al*. 1981, Riddle & Dincsoy 1987). The features were due to the parathyroid hormone-related protein and granulocyte colony-stimulating factor. Combination of hypercalcemia and leucocytosis in squamous cell carcinoma is rare and have been reported in anaplastic thyroid carcinoma (Yazawa *et al*. 1995) as well as squamous cell carcinomas of lung, penis and tongue (Burzyantseva *et al*. 2009, Doraiswamy *et al*. 2010, Kaneko *et al*. 2016). Thus, hypercalcemia-leucocytosis paraneoplastic syndrome is a features of squamous cell carcinoma and could be a clinical presentation of primary squamous cell carcinoma of thyroid. Overall, paraneoplastic syndromes occur rarely in biological aggressive thyroid carcinomas with follicular cell

differentiation, namely anaplastic thyroid carcinoma and primary squamous cell carcinoma. The spectrum of paraneoplastic syndromes reported is less in primary thyroid squamous cell carcinoma.

5. Pre-operative investigation

Ultrasonic investigation with fine needle aspiration biopsy is the first line investigation for patients with suspected malignant lesion in the thyroid gland. Fine needle aspiration was mentioned in 42 of the 117 patients with primary squamous cell carcinoma. There were eight cases diagnosed as negative for malignancy (including one diagnosed as an abscess) and one case was diagnosed as Hürthle cell neoplasm (Sahoo *et al*. 2002). Thus, fine needle aspiration biopsy was sensitive to detect the malignant nature of the disease in only 79% of cases. In addition, diagnosis of squamous cell carcinoma was made in less than one third of cases (n=11; 26%). In this situation, they were most often diagnosed as either malignant tumour or carcinoma (n=14, 33%). The rest of the cases were diagnosed as anaplastic thyroid carcinoma or papillary thyroid carcinoma. It is worth noting that atypical squamous cell in the fine needle aspiration biopsy of thyroid nodule is not diagnostic of squamous cell carcinoma. The most common diagnosis is squamous metaplasia in the setting of Hashimoto's thyroiditis and degenerative changes. Gage and colleagues have reviewed 15 cases of fine needle aspirates with abundant squamous cells and only one case is confirmed as squamous cell carcinoma (Gage *et al*. 2016).

After the diagnosis of malignant lesion in thyroid, the extent of the disease should be assessed by further radiological means such as computed tomography (CT) scan, magnetic resonance imaging (MRI) scan and up^{18}F-FDG PET/CT (Caballero Gullón *et al*. 2017).

Endoscopic examination of the upper aerodigestive tract should be used to exclude lesion (s) in the upper aerodigestive tract.

5. Macroscopic Features

From the pooled data of 117 cases in the literature, primary squamous cell carcinoma occurs roughly in equal frequencies in right and left side of the thyroid. The tumour involves one or extend to both lobes of the thyroid gland with occasional satellite nodules. Primary thyroid squamous cell carcinoma typically larger than papillary thyroid carcinoma and involves extensively or the entire lobe of the thyroid. The mean diameter of papillary thyroid carcinoma, conventional variant, was small (26 mm) (Lam *et al*. 2005) whereas that of anaplastic thyroid carcinoma was large (80 mm) (Lam *et al*. 2000). It appears that squamous cell carcinoma of thyroid is slight smaller than anaplastic thyroid carcinoma. From the pooled data in the literature, the mean diameter of the squamous cell carcinoma of thyroid was 54 mm and the size of the carcinoma was not dependent on the location of the tumour. Similar findings were noted in population-based studies with mean diameter of 53mm to 68 mm noted respectively in two studies (Yang *et al*. 2019, Limberg *et al*. 2020). Like squamous cell carcinoma elsewhere, squamous cell carcinoma of thyroid often has a firm consistency and greyish-white colour with areas of necrosis and haemorrhages (Figure 2).

6. Microscopic features

Primary squamous cell carcinoma of thyroid often shows extensive infiltration of the peri-thyroidal soft tissue with prominent vascular and peri-neural infiltration. From the data available, 93% of the tumours involve outside the thyroid gland (T3 or T4). Squamous carcinomas were moderately differentiated in 51%, poorly differentiated in 37% and well

differentiated in 12%. Thus, like most of the squamous cell carcinomas from the upper aerodigestive tract which infiltrate the thyroid, squamous cell carcinomas of thyroid gland were often moderately differentiated (Lam *et al*. 1996). Nevertheless, grade 3 (poorly differentiated) carcinoma contributes more than one third of the primary thyroid squamous cell carcinomas (Figure 3). The portion of grade 3 carcinoma in primary squamous cell carcinoma of thyroid is higher than squamous cell carcinoma of upper aerodigestive tract such as in larynx (Lam *et al*. 1996) which may give a hint for the origin of the squamous cell carcinoma in the thyroid gland on histological examination.

7. Histological link with other carcinomas

Squamous cell carcinoma component could be a component of a thyroid carcinoma. In the third edition of WHO classification of tumours of endocrine organs (LiVolsi, *et al*. 2004), papillary thyroid carcinoma with squamous cell carcinoma is a variant of papillary thyroid carcinoma. In the current WHO classification, primary squamous cell carcinoma of thyroid is defined as a carcinoma exclusively of squamous differentiation. Anaplastic carcinoma with squamous differentiation is termed "anaplastic thyroid carcinoma". Papillary thyroid carcinoma could have squamous differentiation. This group of carcinomas is noted to have more poor long-term outcomes (Beninato *et al*. 2018).

Of the 117 thyroid carcinomas with squamous differentiation collected in the English literature in this review, 95% (n=112) had papillary thyroid carcinoma and 5% had follicular thyroid carcinoma (n=5). One case showed squamous differentiation as well as the presence of papillary thyroid carcinoma and follicular thyroid carcinoma. Half (n=56) of these papillary thyroid carcinomas were tall cell variants, which had more aggressive biological behaviour (Lam 2017). In 49 of the papillary thyroid carcinomas having squamous carcinoma component, there

were co-existing anaplastic thyroid carcinoma. By WHO definition, these cases were anaplastic carcinomas with squamous differentiation. Overall, the frequent occurrence of all these carcinomas is a strong evidence for the aetiological link between them. Hence, before diagnosing a primary squamous cell carcinoma of thyroid, it is important to look for the anaplastic thyroid carcinoma and well-differentiated thyroid carcinoma.

8. Immunohistochemical features

From the data of the primary cell carcinoma of thyroid collected in this review, only 4% (1/25) and 17% (3/18) of carcinomas tested are positive for thyroglobulin and TTF-1. Accordingly, primary squamous cell carcinoma of thyroid rarely stains for thyroglobulin or TTF-1 (thyroid transcription factor 1). In thyroid carcinomas other than well-differentiated thyroid carcinomas, PAX-8 (paired box gene 8) protein appears to be a more sensitive marker for confirming the thyroid origin of the carcinoma than TTF-1 or thyroglobulin (Figure 4). In anaplastic thyroid carcinoma, multi-institution study showed that approximately half of the anaplastic thyroid carcinoma were positive for PAX-8 (Lai *et al*. 2020). Due to its rarity, the number of primary squamous cell carcinoma tested for PAX-8 was small. In the literature, only one case was negative for PAX-8 which was performed on autopsy tissue. Other than this, all the primary thyroid squamous cell carcinoma as well as squamous carcinoma component in association with other thyroid carcinomas showed positive to PAX-8 protein. In addition, Suzuki and colleagues shown that 91% (10 of the 11) of thyroid tumours having squamous cell carcinoma component stained positive for PAX-8 (Suzuki *et al*. 2018)

p63 and p40 are sensitive markers for squamous differentiation with p40 more specific than p63 in identifying squamous carcinoma (Bishop *et al* 2012) (Figure 5). All the 10 primary

thyroid squamous cell carcinomas tested in the literature were positive for p63. In addition, p40 was positive in 2 cases tested.

Cytokeratin profiles have been documented in different thyroid carcinomas (Lam *et al*. 2001b). The common pattern of noted in thyroid carcinomas are positive for cytokeratins 7, 18 and 19 (simple epithelial-type/low molecular weight cytokeratins) but negative for cytokeratin 20 (also simple epithelial-type/low molecular weight cytokeratin). Like these carcinomas, primary thyroid squamous cell carcinomas noted in the literature showed positive to cytokeratin 19 (16/16), cytokeratin 7 (13/14) and negative for cytokeratin 20 (0/11) .

Cytokeratin 5/6 and cytokeratin 10/13 are high molecular weight cytokeratins. Cytokeratin 5/6 is a marker of squamous cell carcinomas (Kaufmann *et al*. 2001, Kasem & Lam *et al*. 2020). All the primary thyroid squamous cell carcinomas tested in the literature showed positivity to cytokeratin 5/6 (14/14). On the other hand, cytokeratin 10/13 were negative in the 6 cases tested by Lam *et al.* and Bonetti *et al.* (Lam *et al*. 2001a, Bonetti *et al*. 2010). It is worth noting that cytokeratin 10/13 could be positive in anaplastic thyroid carcinoma (Lam *et al*. 2001b) as well as squamous cell carcinoma from upper aerodigestive tract squamous cell carcinoma, such as oesophageal squamous cell carcinoma (Lam *et al*. 2001a).

P53 overexpression is common in cancers with biological aggressive behaviour (Lam *et al*. 2008, Lam *et al*. 1999). The expression is often absent in well-differentiated thyroid carcinoma (papillary thyroid carcinoma) and poorly differentiated thyroid carcinoma ((Lam *et al*. 2000). On the other hand, Lam and colleagues reported p53 expression in 69% (20/29) of anaplastic thyroid carcinoma (Lam et al. 2000). Similarly, 75% (12/16) of primary thyroid squamous carcinomas collected in the literature showed p53 overexpression. Thus, like

anaplastic thyroid carcinoma, primary thyroid squamous cell carcinoma showed high frequency of p53 overexpression (Figure 6)

9. Differential diagnoses

The most important clinical or pathological differential diagnosis of squamous cell carcinoma of thyroid is the differentiation from the direct infiltration of squamous cell carcinoma of the adjacent aerodigestive tract (oral cavity, tongue, proximal oesophagus, hypopharynx, larynx, nasopharynx and hypopharynx) (Vatsyayan *et al*. 2019, Lam *et al*. 1998). The most common site is from larynx (Nakhjavani *et al*. 1999). In a large series, infiltration of thyroid gland by laryngeal squamous cell carcinoma was present in 16% of cases (Lam & Yuen, 1996). Direct infiltration of the thyroid by adjacent carcinoma is usually discovered at the time of surgery on histological examination. In addition to direct infiltration, squamous cell carcinoma could metastasize to thyroid from organs such as lung or rarely from cervix (Lam & Lo. 1998, Varlı *et al*. 2019).

In contrast to the prominent clinical signs and symptoms of primary thyroid squamous cell carcinoma, the diagnosis of metastatic squamous carcinoma to thyroid gland is more often incidental (Lam & Lo. 1998, Vatsyayan *et al*. 2019). Most metastases to thyroid gland presented either simultaneously (61%) or after detection (42%) of the primaries. Apart from clinical and radiological features, immunohistochemical studies are helpful in the differential diagnosis. Suzuki and colleagues demonstrated that PAX-8 is positive in squamous carcinomas of thyroid gland whereas squamous cell carcinomas from cervix, oesophagus and lung were negative for PAX-8 (Suzuki *et al*. 2018). It is worth noting that PAX-8 is positive for renal epithelial tumours such as renal cell carcinoma and neuroendocrine tumours (El-Maqsoud *et al*. 2016,

Long *et al*. 2010). Thus, if malignant cells were noted on fine needle aspiration, use of PAX-8 could not differentiate metastatic renal cell carcinoma (a common metastatic carcinoma to thyroid) from primary thyroid carcinomas. On the other hand, CD10 antibody may be helpful as renal cell carcinoma is positive and squamous cell carcinoma of thyroid is negative.

Anaplastic carcinoma of thyroid comprises of sarcomatoid, giant cell and epithelial forms (Lam *et al*. 2000). The epithelial form manifests as squamoid or squamous cohesive tumour nests and is the predominate pattern in 18% of anaplastic thyroid carcinoma (Lam *et al*. 2000). Difference from primary squamous cell carcinoma, the epithelial form of anaplastic thyroid carcinoma often has other histological patterns rather than pure squamous carcinoma. The clinical and histological similarities between epithelial form of anaplastic thyroid carcinoma and primary squamous cell carcinoma of thyroid highlight the proposed aetiological link between these two entities.

Intrathyroid thymic carcinoma, carcinoma showing thymus-like element (CASTLE), is a malignant epithelial tumour of the thyroid gland with thymic epithelial differentiation. The carcinoma occurred most often in Asian populations (Kakudo *et al* 2013). The histological features of intrathyroid thymic carcinoma is identical to that of thymic carcinoma in the mediastinum. It is a squamous cell carcinoma with lymphocyte-rich stroma. Occasional single-cell keratinization or stratification of keratinizing tumour cells could be found which could be misinterpreted as squamous cell carcinoma. However, intrathyroid thymic carcinoma is positive for CD5. All the primary thyroid squamous cell carcinomas (n=11) tested in the literature were negative for CD5. In contrast to patients with thyroid squamous cell carcinoma, patients with intrathyroid thymic carcinoma had excellent outcomes after curative resection. In addition, intrathyroid thymic carcinoma often have low Ki-67 index of 10 to 30% whereas primary

squamous carcinoma often has high Ki-67 index (Figure 7). In the current review of literature on primary squamous cell carcinoma of thyroid, approaching 80% (11/14; 79%) had Ki-67 index 30% or above.

Mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia are rare carcinomas of thyroid gland with both epidermoid and mucin differentiation (Le *et al*. 2019, Shah *et al*. 2017). The epidermoid component if predominant could mimic primary squamous cell carcinoma of thyroid. In contrast, in squamous cell carcinoma of thyroid, there is no mucin component. Sclerosing mucoepidermoid carcinoma with eosinophilia also display eosinophilic infiltration and consistently associated with Hashimoto' thyroiditis. Different from primary thyroid squamous cell carcinoma, both mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma carcinomas are low grade malignant tumours though distant metastases could occur in both carcinomas.

Papillary thyroid carcinoma could have focal or extensive squamous differentiation in 20 to 40% of cases (Rosai *et al*. 2017). In addition, there are two variants of papillary thyroid carcinoma have characteristic squamous structures, namely diffuse sclerosing variant and cribriform-morular variant. Diffuse sclerosing variant of papillary thyroid carcinoma (Pillai et al. 2015, Lam & Lo 2006) occurs often in young woman with mean age at presentation at 30. Higher prevalence of the carcinoma was noted in paediatric patients and in patients affected by irradiation. The carcinoma extensively infiltrates the thyroid and has extensive squamous differentiation and fibrosis which could mimic primary squamous cell carcinoma of thyroid. Nevertheless, numerous psammoma bodies in the carcinoma could differentiate the carcinoma from primary squamous cell carcinoma of thyroid. Cribriform-morular variant of papillary thyroid carcinoma occurred almost exclusively in young women (mean age =24) (Lam &

Fridman 2018, Lam & Saremi 2017). These morules together with the absence of psammoma body in this variant of papillary thyroid carcinoma could superficially mimic primary squamous cell carcinoma of thyroid. Nevertheless, the immunohistochemical features of morules are different from squamous differentiation (being positive to bcl-2 and negative or focally positive to high-molecular-weight cytokeratin: cytokeratin 19). In addition to the morules, there is cribriform pattern of tumour cells. Furthermore, nuclear and cytoplasmic staining for beta catenin is a characteristic of cribriform-morular variant of papillary thyroid carcinoma. In contrast with primary squamous cell carcinoma of thyroid, patients with cribriform-morular variant of papillary thyroid carcinoma have relatively indolent behaviour.

10. Molecular biology

Due to the rarity of the disease, there are limited data on molecular biology studies of primary squamous cell carcinoma of thyroid (Table 1). The only gene that have been studied in thyroid carcinomas having squamous carcinoma component was *BRAF* (*v-Raf murine sarcoma viral oncogene homolog B*). *BRAF V600E* mutation is present in many human cancers (Ng *et al*. 2019, Pakneshan *et al*. 2013). It is the main player in papillary thyroid carcinoma and is associated with clinical pathological features and survival of patients with the cancer. The Cancer Genomic Atlas (TCGA) documents that the genomics of papillary thyroid carcinomas are mainly by mutually exclusive driver mutations; either carry the *BRAF V600E*-like signatures or *RAS* (*rat sarcoma viral oncogene homolog*)-like gene signatures (including non-*BRAF V600E BRAF* mutations) {Lam 2017). In primary squamous cell carcinoma of thyroid, only 1 case had mutations in *BRAF* detected by Ko and colleagues (Ko *et al.* 2012). The mutations were in *BRAF V600E* (exon 15) as well as G468A (exon 11). In addition, there were 4 cases of

papillary thyroid carcinoma with co-existing squamous carcinoma component having *BRAF V600E* mutation (Rupani *et al*. 2017, Acosta & Pins 2016, Lee *et al*. 2013, Rausch *et al.* 2010) and one case with *BRAF* mutated protein detected (Dennis *et al*. 2018) in both the papillary and squamous carcinoma component of the carcinomas. The results suggest a strong link between papillary thyroid carcinoma and thyroid squamous cell carcinoma.

Anaplastic thyroid carcinoma is characterized by accumulation of several oncogenic alterations (Molinaro et al. 2017). It is one of the human cancers with the highest mutation loads. Genomic studies have showed that mutations in *BRAF*, *TERT* (*telomerase reverse transcriptase*) promotor, *p53* and *EIF1AX* (eukaryotic translation initiation factor 1A, X-linked) are common in the carcinoma (Molinaro et al. 2017). In the literature, only one short report of primary squamous cell carcinoma studied by whole genome sequencing by Chu and colleagues (Chu *et al*. 2016). The case showed different genetic profiles from anaplastic thyroid carcinoma. It showed no *BRAF* mutation. More genomic studies are needed to confirm the difference between primary squamous cell carcinoma of thyroid and anaplastic thyroid carcinoma.

The genomic profile in primary thyroid squamous cell carcinoma presented by Chu and colleagues showed absence of driver mutations commonly detected in squamous cell carcinoma such as *p53*, *CDKN2A/p16* (cyclin-dependent kinase inhibitor 2A) and *NORCH1* (Chu *et al*. 2016). There was no *K-RAS* mutation mentioned. *K-RAS* mutation was not found in the primary thyroid squamous cell carcinoma presented by Ko and colleagues (Ko *et al*. 2012) as well as a case of papillary thyroid carcinoma with squamous carcinoma component reported by Acosta and Pins (Acosta & Pins 2016).

In primary squamous cell carcinoma of thyroid gland, no *p53* mutation is found by Ko *et al.* (Ko *et al*. 2012) and Kleer *et al.* (Kleer *et al*. 2000). In addition, *p53* genetic changes have been studied in 3 cases of papillary thyroid carcinoma with co-existing squamous carcinoma component (Kleer *et al*. 2000, Rausch *et al.* 2010). Only one of the 3 cases showed loss of heterozygosity (LOH) to *p53* with overexpression of p53 protein (Kleer *et al*. 2000). The low prevalence of *p53* mutation contrasts with the high prevalence of p53 protein overexpression in primary squamous cell carcinoma of thyroid (see section above). It is likely that mechanisms other than *p53* mutation contributes to the overexpression of the protein.

Epidermal growth factor receptor (*EGFR*) alterations are common in human cancers (Tomas *et al*. 2014). *EGFR* mutations or amplifications were not identified in two primary squamous cell carcinomas (Bonetti *et al*. 2010, Chu *et al*. 2016) or in a papillary thyroid carcinoma with co-existing squamous carcinoma component (Acosta & Pins 2016). Nevertheless, Bonetti and colleagues have detected overexpression of EGFR protein and EGFR polysomy in two patients with primary squamous cell carcinoma of thyroid (Bonetti *et al*. 2010). It is unlikely EGFR play a major role in the cancer.

Overall, due to the limitation of molecular studies in primary squamous cell carcinoma, there is molecular evidence to draw conclusions on the molecular profiles of the carcinoma. There should be genomic studies on more primary squamous cell carcinoma and to compare the findings with those of anaplastic thyroid carcinoma as well the squamous cell carcinoma component of thyroid carcinomas.

11. Metastases

From the data in the literature, involvement of neck lymph node was noted in 59% (60 of 102) of the patients with primary squamous cell carcinoma of the thyroid gland. For reference, lymph node metastases were approximately noted in 30% of papillary thyroid carcinoma at the time of surgery (Lam *et al*. 2005). In anaplastic thyroid carcinoma, cervical lymphadenopathy was present in 64% (7 of 11) of cases in a single institution study in 2018 (Deeken-Draisey *et al*. 2018). Also, 56% of the 219 patients with anaplastic thyroid carcinoma noted in Danish databases have lymph node metastases (Hvilsom *et al*. 2018). Thus, primary thyroid squamous cell carcinoma had higher frequency of lymph node metastases than papillary thyroid carcinoma and similar frequency to anaplastic thyroid carcinoma.

Distant metastases were uncommon in papillary thyroid carcinoma. In biological aggressive variant, diffuse sclerosing variant, 5% of cases revealed lymph node metastases (Pillai *et al*. 2015). In the literature, distant metastases were documented in 26% (27 of 106) of patients with primary squamous cell carcinoma of the thyroid gland. Most of the metastatic squamous carcinoma occurred in the lungs (n=24). The other common site of metastases were bones (n=7). Other than these, metastatic squamous cell carcinoma of thyroid had been detected in brain, liver, heart, kidney and diaphragm. The pattern of metastases noted were in concur with those obtained in population-based study by Limberg and colleagues (Limberg *et al*. 2020). Compared to anaplastic thyroid carcinoma in which distant metastases were present in 50% of patients on presentation (Lo *et al*. 1999), the prevalence of distant metastasis was lower in primary thyroid squamous cell carcinoma. The lower prevalence of distant metastases in primary squamous cell carcinoma could be related its local aggressive behaviour causing death of the patients before the occurrence of distant metastases.

12. Prognosis

The prognosis of patients with primary squamous cell carcinoma is dismal. In the 117 patients with squamous cell carcinomas of thyroid noted in the literature, 109 had follow-up data available. Of these, 88 patients died of the disease. The median survival of the patients was 8 months and with the 2-year survival rate of 14%. The results were in concur with those from population-based of Au and colleagues on 199 primary thyroid squamous cell carcinomas which reported a median survival of 9.1 months (Au *et al*. 2017). Lo and colleagues, in a large series of patients with anaplastic thyroid carcinoma, found that the patients had median survival of 1.3 months and the 2-year survival rate of 4% (Lo *et al*. 1999). In population-based studies, the median survival of patients with anaplastic thyroid carcinoma reported was from 3 to 6 months (Chintakuntlawar et el. 2019). Thus, the prognosis of the patients with primary thyroid squamous cell carcinoma is better than those with anaplastic thyroid carcinoma.

Age at diagnosis, tumour grade, tumour size and presence of distant metastases are independent predictors for disease-specific survival of patients with primary thyroid squamous cell carcinoma in population-based studies from USA (Au *et al*. 2017, Yang *et al*. 2019, Limberg *et al*. 2020). From the pooled data in the literature from the primary thyroid squamous cell carcinoma, patients with distant metastases or lymph node metastases at presentation had poorer outcome than those without distant metastases ($p=0.022$ and $p=0.002$ respectively) (Figure 8). On multivariant analysis, patients with primary thyroid squamous cell carcinoma having distant metastases had poorer survival rates ($p=0.01$). Patients with younger age at diagnosis and smaller tumour size also had better prognosis but the difference did not reach statistically significant.

Lymphocytic infiltration including Hashimoto's thyroiditis are commonly associated with thyroid carcinomas and lymphomas (lnár *et al*. 2019, Lam *et al.* 1999). Asik and colleagues analysed the cases reported in the literature and noted that primary thyroid squamous cell carcinoma of thyroid with concurrent lymphocytic thyroiditis had lower pathological stages and frequency of distant metastases (Asik *et al*. 2015). In the current review, patients having primary thyroid squamous cell carcinoma with concurrent lymphocytic thyroiditis had slighter better survival rates than those patients without concurrent lymphocytic thyroiditis. However, the difference did not reach statistical significance (p=0.09). Therefore, it appears that lymphocytic thyroiditis could limit the growth of the primary thyroid squamous cell carcinoma.

Squamous carcinoma component in papillary thyroid carcinoma is associated with demonstrated high rates of locoregional recurrence (60%), pulmonary metastases (30%), and mortality (10%) (Beninato *et al*. 2018). In the current literature review, it is confirmed that squamous carcinoma component confers a poor prognosis in patients with well-differentiated thyroid carcinoma (predominately papillary thyroid carcinoma); with the median survival of the patients being 18 months. Nevertheless, there is a significant difference in the different groups of patients having thyroid carcinoma with squamous carcinoma component (p=0.001) (Figure 9). Patients with primary thyroid squamous cell carcinoma had poorer prognosis than patients with well-differentiated thyroid carcinoma having squamous carcinoma component (median survival, 8 months versus 18 months). In addition, patients having anaplastic thyroid carcinoma having squamous carcinoma component had poorer prognosis than those with pure squamous cell carcinoma of thyroid (median survival, 1 month versus 8 months). Overall, the results indicated that prognosis of squamous cell carcinoma is intermediate between anaplastic thyroid carcinoma

(with squamous carcinoma component) and well-differentiated thyroid carcinoma with squamous carcinoma component.

12. Clinical management

Aggressive treatment approach with multidisciplinary team should be used whenever possible for patients with primary thyroid squamous cell carcinoma. From population-based studies, R1 resection (resection with microscopic residual tumour) is possible in 37.3% (Limberg *et al*. 2020) of the patients with primary thyroid squamous cell carcinoma. Curative resection for patients with squamous cell carcinoma of thyroid is more often possible than patients with anaplastic thyroid carcinomas (Limberg *et al*. 2020).

Primary squamous cell carcinoma of thyroid gland is poorly responsive to radiotherapy and relatively resistant to chemotherapy. The carcinoma does not uptake iodine. Thus, there is no role for radioactive iodine ablation or thyroid suppression. The patients being treated with surgery alone appears to have the best survival rate (Au *et al*. 2017, Yang *et al*. 2019, Cho *et al*. 2014). In addition, patients with complete resection have better survival than those with incomplete resection (Cho *et al*. 2014).

Ultrasound examination of the primary lesion in the neck could detect hypoechoic irregular structure with local invasion suggestive of a malignant lesion before operation and help characterize neck node metastases. After operation, patients with primary squamous cell carcinoma of thyroid should be follow up closely to identify residual carcinoma or recurrence of the carcinoma. Fluorodeoxyglucose (FDG) PET-CT is the most sensitive mean to detect distant metastases.

Target therapies using receptor kinase inhibitors that inhibit multiple angiogenic and oncogenic signalling pathways are the proposed approach for treatment of aggressive recurrent thyroid cancers including anaplastic thyroid carcinoma (Rahman *et al*. 2015; Rahman *et al*. 2014). Lenvatinib is a multiple tyrosine kinase inhibitor in the USA and European Union for this purpose. Yasumatsu and colleagues showed that the drug may show promise to potentially extend survival of patients with primary thyroid squamous cell carcinoma (Yasumatsu *et al*. 2018).

Adjuvant therapeutic approaches (chemotherapy and radiotherapy) have been used with limited benefit for patients with unresectable carcinoma or palliative resection having residual cancer. The new immunotherapy targeting the programmed cell death 1 (PD-1) receptor and its ligand PD-L1 is being used with many metastasizing carcinomas (Ng *et al*. 2018). It stimulates the host response to cancer. In this context, expression of PD-L1 was noted in papillary thyroid carcinoma and anaplastic thyroid carcinoma (Ulisse *et al*. 2019). Immunotherapy has been approved by U.S. Food and Drug Administration (FDA) in many cancers including head and neck squamous cell carcinoma. Although no clinical trials have been on this rare squamous cell carcinoma of thyroid, immunotherapy, alone or in combination with other therapy, could be considered for clinical trial in primary thyroid squamous cell carcinoma with residual or recurrent diseases.

13. Conclusion

Primary squamous cell carcinoma is a very rare carcinoma of the thyroid. It is important to exclude clinically and pathologically other the thyroid lesions with squamous carcinoma component before making the diagnosis. There is a suggested developmental relationship between squamous cell carcinoma and anaplastic thyroid carcinoma from well-differentiated

thyroid carcinoma (predominately papillary thyroid carcinoma). Though anaplastic thyroid carcinoma and squamous cell carcinoma of thyroid share similar aggressive biological behaviour, there is difference between them in aspects like clinical pathological features and patients' prognosis (Table 2). There is need for more genomic studies to identify the pathway of development of anaplastic thyroid carcinoma and primary thyroid squamous cell carcinoma. There are also marked difference in features between primary squamous cell carcinoma of thyroid and thyroid carcinomas with squamous carcinoma component, justifying the classification of squamous cell carcinoma of thyroid as a distinct entity. As curative resection is more often possible in squamous cell carcinoma than anaplastic thyroid carcinoma, it is important to for early detection of primary thyroid squamous cell carcinoma for possible curative surgical resection. In addition, more genomic works done to uncover the molecular pathogenesis and possible new target therapies including immunotherapy as the cancer is relatively resistant to current chemotherapeutic modalities.

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Figure legend

Figure 1. Bar chart showing the distribution of cases of primary squamous cell carcinoma of thyroid gland in different age groups, separated into decades of life.

Figure 2. Macroscopic appearance of squamous cell carcinoma of thyroid showing extensive replacement nearly the whole thyroid gland by firm whitish cancer tissue.

Figure 3. A Microscopic appearance of squamous cell carcinoma of thyroid showing a poorly differentiated (grade 3) squamous cell carcinoma with a few residual normal thyroid glands. B. The other portion of the tumour showing more prominent squamous areas with keratin (arrow) (haematoxylin and eosin)

Figure 4. Squamous cell carcinoma of thyroid showing positive nuclear staining to PAX-8

Figure 5. Squamous cell carcinoma of thyroid showing positive nuclear staining to p40.

Figure 6. Squamous cell carcinoma of thyroid showing positive nuclear staining of p53

Figure 7. Squamous cell carcinoma of thyroid showing high proliferative index with high percentage of Ki-67 stained nuclei in the cancer cells.

Figure 8. Survival analysis of primary squamous cell carcinoma of thyroid showing patients without distant metastasis had better prognosis than those with distant metastasis.

Figure 9. Survival analysis of different groups of thyroid carcinomas with squamous differentiation showing different survival rates. WDTC + SQ: well differentiated thyroid carcinoma with squamous carcinoma component; SQCA: primary thyroid squamous cell carcinoma (100% squamous carcinoma component); ACA+SQ: anaplastic carcinoma with squamous carcinoma component.