Primary Squamous Cell Carcinoma of the Thyroid: Report of Three Cases

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Abstract. We report three cases of squamous cell carcinoma of the thyroid, which is an unusual malignant tumor that needs to be distinguished from other thyroid pathologies due to its aggressive behaviour. Three men, with an average of 63 years old, presented with progressive enlargement in the neck, hoarse voice or weight loss. Physical and radiological examinations revealed clues where malignancy was suspected and surgical resections were performed. Histopathological examination of the specimens was diagnosed as squamous cell carcinoma. Proper workup excluded the possibility of any primary site of SCC other than the thyroid. All patients died within 5 months. Adjuvant therapy evaluation is still inconclusive. Complete surgical resection still remains the primary choice for cure. We believe that radical resection with clear surgical margins followed by adjuvant chemo-radiation therapy is a curative strategy for achieving any chance of long-term survival.

Key words: Thyroid cancer, Squamous cell carcinoma

PRIMARY squamous cell carcinoma (SCC) of the thyroid is extremely rare, since there is no squamous epithelium in the thyroid tissue, except in some exceptional situations like embryologic remnants [1–4], inflammatory process [5–6] and cancers [5, 7–9]. This type of thyroid malignancy is seen less than 1% of all thyroid cancers and is highly lethal. The first primary SCC case was reported by von Karst in 1858. However, approximately 150 cases have been published until recently in the English literature [8, 10–16]. The tumor behaves aggressively and is clinically identical to an undifferentiated thyroid cancer. Unfortunately, even after surgical resection, there is a high chance of recurrence and local invasion. The present report illustrates three patients with primary SCC out of 426 primary thyroid cancers diagnosed in our institution during the period 1996–2006. The proportion of papillary, follicular, medullary and anaplastic cancer was 70%, 16%, 7% and 3%, respectively. Identified primary SCC accounted for 0.7% of all primary thyroid cancer patients.

Case Reports

Case 1

A 53-year-old male complained of progressive enlargement on the right side of the neck and a hoarse voice of 5 weeks duration. He was diagnosed as nodular goiter 2 years before admission. There was no history of neck radiation or a family history of thyroid cancer. Physical examination revealed a semi-mobile, painless and moderate hard thyroid mass in the right lobe of the thyroid gland, approximately 7 cm in diameter. The mass was non-fixed to the overlying skin and there were no palpable lymph nodes. Doppler ultrasound showed an enlarged thyroid tissue and a solid nodule originating from the right lobe of the gland, 60 mm in size, lobulated in shape and descending to
the retrotracheal region. Increased central vascularity was remarkable. Reactive lymph nodes were observed in the jugular area. Scintigraphy showed a cold nodule that covered the entire right lobe. Computed tomography of the neck and upper thorax demonstrated a thyroid mass, progressing to the retrosternal area and restricting the trachea. Secondary involvement of adjacent structures could not be excluded (Fig. 1). Fiberoptic laryngoscopy revealed paralysis of the right vocal cord. Thyroid hormone profile and calcitonin were in normal range. Anti TG antibody assay was negative, while Anti TPO was positive. There was no significant leukocytosis or hypercalcemia. Clinical malignancy was suspected and a near-total thyroidectomy was carried out. The specimen weighed 64 g and an ill-defined mass, 60 mm in diameter, was noted on the right lobe (Fig. 2). Histological examination of the specimen revealed a SCC. Malignancy of adjacent organs was not identified through radiographic and endoscopic examinations. The patient was commenced on a chemoradiotherapy regimen consisting of doxorubicin, cyclophosphamide and an average dose of 50 Gy radiation therapy. He died 2 months after surgery due to massive upper gastrointestinal bleeding, secondary to portal hypertension.

Case 2

A 71-year-old male applied complaining of hoarse voice and weight loss for 6 months. Physical examination revealed a solid thyroid nodule and multiple cervical lymph nodes. He had no history of neck radiation or a family history of thyroid cancer. Neck ultrasound revealed an enlarged thyroid gland with a solid solitary hypoechoic nodule in the right lobe, 4 × 3 cm in diameter, with calcifying foci. Enlarged cervical pathologic lymph nodes with microcalcific foci were also found on the right side. Thyroid scintigraphy reported a cold nodule in the right lobe. Thyroid hormone profile was unremarkable. Anti TG and Anti TPO antibodies were both negative. There was no leukocytosis or hypercalcemia. The nodule was subjected to FNAB (fine needle aspiration biopsy), which showed poorly differentiated malignant cells but failed to define the type of tumor. During surgery, infiltration of adjacent soft tissue, cervical esophagus and trachea was observed. Palliative debulking with dissection of regional lymph nodes was carried out. Histological evaluation of the specimen revealed SCC. Postoperative investigations ruled out the possibility of other primary sites. The patient refused adjuvant therapy and died within
4 months after surgery of respiratory distress.

Case 3

A 66-year-old male applied complaining of a hoarse voice of 2 weeks duration. On examination, a thyroid mass of 4 × 4 cm in the left lobe was palpated. He had no radiation or family history. Ultrasound imaging showed a hypoechoic solid thyroid nodule in the left lobe, 4.5 × 4 cm in diameter. Scintigraphy showed a cold nodule in the left thyroid lobe. Fiberoptic laryngoscopy revealed paralysis of the left vocal cord. After FNAB, the patient was diagnosed as having poorly differentiated or undifferentiated thyroid cancer, without defining the type of tumor. Thyroid hormone profile was normal. There was no significant leukocytosis or hypercalcemia. Chest radiographic examination showed multiple nodules in both lungs. Further workup did not reveal any other lesion. A palliative thyroidectomy was carried out. During surgery, infiltration of trachea and left recurrent nerve was observed. Histological evaluation of the specimen detected SCC. Postoperative investigations ruled out the possibility of other primary sites. The patient refused adjuvant therapy and developed local recurrence. He died within 5 months.

Histological examination

Histologically, all the cases were comprised entirely of tumor cells with squamous differentiation. Intercellular bridges were observed in all cases, and rare pearl formations were found in one patient (Fig. 3). Infiltrating strand structures and focal areas of necrosis were also detected. The interfaces between the tumor and adjacent thyroid were irregular. The tumors were graded as moderately differentiated in one case and poorly differentiated in two cases. On histological examination of multiple paraffin blocks, there was no evidence of associated papillary carcinoma, follicular carcinoma, anaplastic carcinoma, follicular adenoma or squamous metaplasia in the colloidal nodules. Lymph nodes of Case 2 showed features of SCC metastasis.

Immunohistochemical examination for cytokeratin 19, thyroglobulin, calcitonin, CD5 and MIB-1 was performed in all cases. All of the cases were negative with calcitonin, thyroglobulin and CD5. Concerning cytokeratin expressions, 3 patients were positive for CK19. MIB-1 proliferating index was high in all cases.

Discussion

In a histological review of 600 primary thyroid cancers collected over 20 years, primary SCC accounted for 0.7% [10]. The reported incidence ranges from 0.7% to 3.4% [17, 18]. This unusual tumor of the thyroid usually occurs in the 5th to 7th decades of life [10, 15]. The patients we reported were 53, 71 and 66 years old. There is no sex predilection [19]. However, Lam et al. reported that, like other thyroid carcinomas, SCC of the thyroid was more commonly in women in their study [10]. Meanwhile, our SCC cases were all found in men. Patients usually present with enlarging neck swelling, obstructive symptoms and a hoarse voice. Rarely do patients present with leukocytosis and hypercalcemia [20]. Parathyroid hormone-related peptides produced by SCC are believed to be responsible for hypercalcemia [21]. None of our patients presented with these systemic features, but had classical symptoms. Based on the clinical features, it is nearly impossible to distinguish SCC from anaplastic carcinoma. Meanwhile, transformation of differentiated thyroid cancer into poorly differentiated carcinoma is rare. These rare forms also behave in an aggressive manner similar to anaplastic carcinoma [22].

Detailed examinations must be done to distinguish the origin of thyroid SCC, whether primary or secondary. In the present report, no other primary site of SCC could be identified in organs other than the thyroid. Most SCC patients with local progressed primary dis-
ease have regional lymph node metastasis and invasion to other adjacent structures like the trachea or esophagus. This was apparent in all our patients.

The origin of SCC in the thyroid is uncertain. There are some theories concerning its origin. Some reports suggest that the squamous cells were derived from embryonic remnants such as the thyroglossal duct, thymic epithelium and ultimobranchial body remnants [1–4, 23]. Another theory is that environmental stimulus like thyroiditis or inflammation may be associated with SCC [5, 6]. This theory is based on extensive cell differentiation (metaplasia). SCC may be found together with associated malignant and benign thyroid disease. Squamous metaplasia can be seen in papillary, follicular, medullary and anaplastic thyroid cancers [5, 7–9]. Among benign lesions, Hashimoto’s thyroiditis can show squamous differentiation [24, 25]. This issue, concerning the origin of SCC, has been discussed by Sahoo et al. [12]. They suggested that we should expect a higher occurrence of SCC if the theory based on metaplasia was true. All our patients were pure SCC. In other words, they showed no co-existing thyroid disease, except a colloid goiter. Moreover, no areas of squamous metaplasia were identified.

Histologically, SCC must not be confused with lesions containing regions of squamous cell metaplasia, like papillary and anaplastic cancer [5, 26]. The pathologist should search for cells showing intercellular bridges and forming keratinization [27]. In the present study on histological examination, there was no evidence of associated papillary carcinoma, follicular carcinoma, anaplastic carcinoma or follicular adenoma in the specimens of the three cases. Histologically, the most important differential diagnoses of primary squamous cell carcinoma of thyroid include CASTLE (Carcinoma showing thymus-like differentiation) of the thyroid gland and metastases from squamous cell carcinoma of other sites [10]. CASTLE is a rare neoplasm which exhibits slow growth and a favourable prognosis [28]. These tumors are immunoreactive with CD5 [29]. In the present study, none of the three cases were immunoreactive with CD5 in contrast to CASTLE.

Immunohistochemistry revealed that all SCC were reactive with antibodies for keratin, whereas thyroglobulin was not expressed in any case. Loss of thyroglobulin in cancer cells is expected in SCC [10]. Nevertheless, in 2 cases, reported by Sahoo et al., both showed thyroglobulin staining positivity [12]. Now it is evident that the cell of origin might be from the follicular epithelium. Although anaplastic carcinoma of the thyroid may show cytokeratin positivity, histopathological analysis of the 3 patients’ specimens obviously suggested SCC. Concerning cytokeratin expression profiles, due to an article by Lam et al., CK10/13 was reported to be of utmost importance for differentiating primary thyroid SCC from a secondary SCC [10]. Meanwhile, our 3 cases were positive for CK19, which is expected to be positive in both conditions.

Whether FNAB can be useful in the diagnosis of SCC of the thyroid had been discussed before [30, 31]. Kumar et al. were the first who described FNAB findings of thyroid SCC [30]. In their study, consisting of 2 cases, they emphasized that the presence of dyskeratotic, spindle and tadpole cells and eosinophilic granular keratin material were essential to diagnose SCC. Meanwhile, they could not distinguish a primary tumor from a secondary until an extensive clinical workup was done. In our cases, although cytology showed poorly differentiated or undifferentiated thyroid cancer, the FNAB diagnosis of SCC could not be achieved. Recently, cytology is still not enough to reach histotypes of thyroid cancer other than papillary cancer.

The best treatment for SCC of the thyroid is early diagnosis and aggressive surgery combined with radiation and chemotherapy [17, 19]. But unfortunately, due to its aggressive behavior, complete surgical resection is rarely possible. Surgical treatment of the cases reported in the literature is poor defined. This makes a proportion calculation for the surgical treatment, whether a debulking surgery or a curative procedure has been carried out, impossible. Since airway compromise is generally the cause of death in the majority of patients [16], resection and primary reconstruction of the trachea invaded by carcinoma should be tried in the absence of extensive metastases when technically feasible. This offers prolonged palliation, avoidance of suffocation due to bleeding or obstruction [32].

Compared to sites of SCC in the head and neck region other than the thyroid, SCC of the thyroid has no response to chemotherapy, radiotherapy or a combined adjuvant regimen. Meanwhile, to reduce the risk of locoregional recurrence after surgery of other head and neck cancers (lip, salivary glands, sinuses, oral cavity, pharynx and larynx), adjuvant treatment with radiotherapy and chemotherapy is often recommended. Evidence-based data highly recommends the use of
postoperative chemoradiotherapy for the purpose of achieving better local disease control and survival outcomes [33].

The prognosis is very poor and the tumor is highly lethal. It is difficult to diagnose the carcinoma in the early stage. The largest single series consists of 16 patients from the United Kingdom [19]. These patients had complete surgical excision, with palliative radiotherapy given postoperatively. A median survival time of 6.5 months was reported. All of our 3 patients died within 5 months. Which chemotherapeutic regimen is useful, remains obscure. There were attempts using adriamycin, bleomycin, cisplatin, nitrogen mustard, vincristine, AB-132, doxorubicin and cyclophosphamide providing no survival advantage [7, 34]. The last 2 chemotherapeutics were of no value in our patient. Although there are some encouraging reports [17, 19], it is worth mentioning that adjuvant therapy evaluation is inconclusive due to the small number of cases.

In conclusion, it is important to rule out primary sites of SCC other than the thyroid, since SCC of the thyroid is highly aggressive and has an extremely poor prognosis. Metastatic disease should always be excluded. The only chance for a longer survival is believed to be achieved by curative surgery with clean margins. This goal can only be achieved by early diagnosis of the tumor.

References

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