

## Commentary on Sclerosing Mucoepidermoid Carcinoma with Eosinophilia of Thyroid Glands

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### Commentary

Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) of the thyroid gland is an extremely rare tumor that predominantly occurs in women with Hashimoto's thyroiditis. Since Chan et al described first series of SMECE in 1991 [1], about 50 cases have been reported in the literature [1-13]. Most of SMECE reports describe the disease in women, and only four cases have been recorded in men so far [2,4,8,11]. The age of patients ranges from 4th decade to 9th decade (mean 55 years) [11,12].

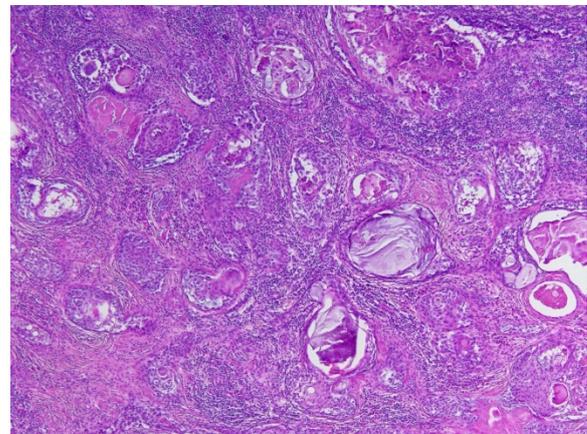
Although rare, similar tumors have been reported in other head and neck organs, including salivary gland, oral cavity and esophagus [14-19].

Histopathologically, SMECE is characterized by nests of epidermoid and mucin-secreting cells in a densely sclerotic stroma with eosinophilic infiltration (Figures 1 and 2). Round to polygonal, medium- to large-sized epithelial tumor cells are usually arranged in nests, anastomosing cords, or short strands. The tumor cells show a mild to moderate nuclear atypism and have hyperchromatic nuclei with coarse chromatin and centrally located distinct nucleoli.

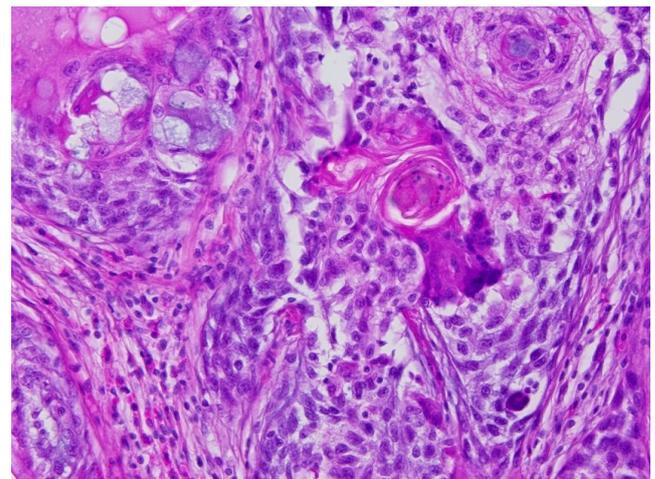
Tumors also display variable degree of glandular differentiation and/or cystic spaces that contained mucinous secretions. Sometimes, single or groups of cells containing intracytoplasmic mucin vacuoles can be observed. Tumor margins are typically ill-defined and infiltrative. In the background of most cases, the residual non-neoplastic thyroid parenchyma shows Hashimoto's and/or lymphocytic thyroiditis (Figure 3).

Although SMECE was originally introduced by a peculiar variant of mucoepidermoid carcinoma (MEC), MECs display several features which are different from SMECEs [2,3,6,12,20]; these are 1) the presence of a ductular component lined by mucus cells admixed with solid sheet of epidermoid elements, 2) lack of eosinophil-rich densely sclerotic stroma, 3) no association with Hashimoto's and/or lymphocytic thyroiditis, 4) usually well-circumscribed tumor margins and 5) positive reaction to TTF-1 immunohistochemistry.

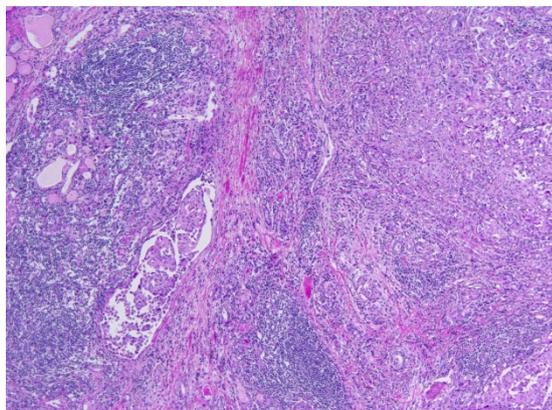
At the molecular level, MECs of the thyroid glands are characterized by a specific translocation  $t(11;19)(q12;p13)$  as MECs of the salivary glands [21-24]. MEC has been studied for the BRAF mutation, and showed no mutation [20]. However, to our knowledge, the molecular study of SMECEs has not been reported yet.



**Figure 1:** Microscopically, SMECE is characterized by nests of neoplastic cells separated by dense fibrotic blands with numerous mixed inflammatory cells. Some of tumor cell nests have cyst.



**Figure 2:** The epidermoid component demonstrates keratin pearl formation and the mucin-secreting cells show intracellular basophilic mucin vacuoles. In addition, considerable amount of eosinophils are present in the background.



**Figure 3:** The tumor has an ill-defined infiltrative border and merges into a background of lymphocytic thyroiditis.

As a list of differential diagnosis of SMECE, several disease entities such as papillary thyroid carcinoma with squamous metaplasia [25,26], metastatic squamous cell carcinoma [27], and nodular sclerotic type of Hodgkin's lymphoma [7] can be considered. However, the morphologic features of SMECE are as distinct as abovementioned description; the proper diagnosis without additional ancillary tests can be made in most of cases, even in metastatic sites. Immunohistochemical staining can be optional and a helpful adjunct to the diagnosis of SMECE.

To date, histogenesis of SMECE is still controversial and two theories have attempted to define its lineage; 1) SMECE originates from pluripotent solid cell nests [8,9], and 2) SMECE originates from squamous metaplastic foci of follicular cells within Hashimoto's thyroiditis [1,2,6]. We believe that SMECEs have a closer relationship with pluripotent solid cell nests that have been characterized as p63 positivity and thyroglobulin or TTF-1 negativity, although some of our cases displayed focal and weak TTF-1 and thyroglobulin positivity.

SMECE shows characteristic combination of two rare microscopic features-tissue eosinophilia and sclerosis. First, tumor-associated tissue eosinophilia (TATE) has been described in many tumors [28,29]. In particularly head and neck area, squamous cell carcinoma and nasopharyngeal carcinoma can be associated with TATE [28,30,31]. Even though eosinophils appear to be associated with a better clinical outcome because of their complex anticancer activity with the release of their cytotoxic proteins, the significance of TATE on prognosis still remains controversial and depends on many factors including the type of cancer [28-32]. Second, there are several theories about pathogenesis of sclerosis in SMECE. Some authors have described that stromal sclerosis results from exaggerated post-inflammatory fibrosis due to extravasated mucin of the tumor [14,17,33]. Recently, there is a new suggestion that IgG4-positive plasma cells have a role in fibrogenesis of sclerosing variant of MECs [34]. However, unfortunately, the exact mechanism of sclerosing process and its clinical significance remain unclear to date.

In SMECE, desmoplasia and/or TATE without serum eosinophilia are so characteristic and constant, even in metastatic site, a diagnosis of SMECE with a possible primary site of the thyroid can be made. When features of MEC are present with abundant eosinophils present,

the possibility of SMECE should be raised, and search for sclerosis and associated Hashimoto's and/or lymphocytic thyroiditis.

An important clinical feature of SMECE highlighted in our previous report [12] was the aggressive behavior exhibited by the majority of our cases. Earlier reports of SMECE characterized this entity as low-grade tumor [1,2,6,20], however, recent evidences including our previous report suggests that they exhibit aggressive behavior with occasional distant metastasis and even death [3,5,9]. We described six cases of thyroid SMECE with an aggressive clinical course in 2015 [12]. Among them, five had positive surgical margins. In addition, regional lymph node metastases were seen in four, and distant metastases in three. These findings are against the low-grade nature of this neoplasm described in the earlier reports, but in agreement with the more recent studies that outline its potentially aggressive biology [3-5,9,11]. Therefore, we recommend a closer follow-up schedule with appropriate additional treatment options such as radioactive iodine treatment and/or chemotherapy in addition to surgical resection.

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