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Mucoepidermoid Carcinoma of the Thyroid with Concomitant Papillary Carcinoma: Comparison of Findings on Fine-Needle Aspiration Biopsy and Histology

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Abstract We report two cases of mucoepidermoid carcinoma (MEC) of the thyroid gland coexisting with, and possibly arising in, papillary thyroid carcinoma (PTC). In the first case, CT-guided fine-needle aspiration (FNA) was performed on a paratracheal mass representing extrathyroidal invasion of a right thyroid lobe tumor. The aspirate showed papillary fronds and cells in honeycombed arrangements with fine chromatin, enlarged nuclei, nuclear grooves, and intranuclear inclusions in a background of mucus and blood; a diagnosis of PTC was rendered initially. However, examination of histologic sections of the mass showed nests of malignant squamous cells with interspersed mucous cells and extracellular mucin, concordant with MEC, as well as PTC. A retrospective review of the FNA specimen identified MEC. In the second case, ultrasound-guided FNA was performed on a right thyroid lobe nodule. The aspirate contained two populations of epithelial cells: larger cells showing foci of both squamous and glandular differentiation that were interpreted as MEC and smaller follicular cells with nuclear changes characteristic of PTC; both were addressed in the diagnostic report. Primary MEC of the thyroid is a rare neoplasm typically exhibiting indolent clinical behavior, although our first case demonstrated extensive local invasion. It is thought to arise from squamous metaplasia associated with PTC, Hashimoto thyroiditis, or other inflammatory or neoplastic processes. In thyroid FNAs, the presence of neoplastic mucous cells and extracellular mucin plus malignant squamous cells is diagnostic of MEC. As MEC is thought to arise in PTC, the finding of the latter in these aspiration specimens is not unexpected.

Keywords Mucoepidermoid carcinoma · Papillary thyroid carcinoma · Fine-needle aspiration

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Introduction

Mucoepidermoid carcinoma (MEC) is a tumor most commonly associated with the salivary glands; however, cases have been reported in such organs as the breast, trachea, esophagus, and pancreas [1–4]. Primary MEC of the thyroid gland is exceedingly rare, as only about 30 to 40 cases have been described [3, 5–8]. Usually, MEC is a relatively indolent neoplasm [4, 5, 7], the clinical behavior of which resembles that of papillary thyroid carcinoma (PTC) in the sense that it presents as a cold nodule, predominantly in women [9], and tends to metastasize only to regional lymph nodes [1, 2, 6]. MEC is traditionally classified into two categories that are thought to correlate with clinical outcome: low grade and high grade [1, 2]. Diagnosis of MEC by fine-needle aspiration (FNA) of the thyroid has been described in only very infrequent case reports [1, 7]; one case of MEC was diagnosed as PTC on FNA [8], as occurred in our case. Other thyroid tumors diagnosed by FNA have been found to exhibit either features of both MEC and PTC [10, 11] or consist of separate areas of MEC and PTC within the thyroid [3]. We report two examples of MEC and PTC in thyroid aspiration specimens.

Case Report

Case 1

An 81-year-old male presented to his primary care physician with an 8-month history of hoarseness and was found to have right vocal cord paralysis. He was subsequently admitted for an unrelated complaint and underwent thoracic CT examination, which showed thickening of the right lateral wall of the trachea below the level of the vocal cords with soft tissue extension into the tracheal lumen, concerning for a neoplasm; a thyroid ultrasound revealed two noncalcified thyroid nodules, the larger of which extended into the trachea. Repeat CT with contrast showed an ill-defined, heterogeneous neck mass, 39 mm in diameter, involving the inferior portion of the right thyroid lobe, posterolateral wall of the trachea, subglottis, and esophagus, as well as, a separate 11-mm hypodense nodule in the right thyroid lobe. Physical examination did not identify a discrete thyroid mass or significant adenopathy in the neck; however, flexible laryngoscopy revealed an erythematous submucosal mass in the anterior right subglottis, with a second raised lesion immediately inferior to it, plus right vocal cord paresis. The patient subsequently underwent direct laryngoscopy with biopsy of the paratracheal mass, in addition to CT-guided FNA of both the paratracheal mass and the smaller thyroid nodule. Histology of the tracheal biopsy was suspicious for superficially invasive squamous cell carcinoma (SCC); the cytologic findings for the paratracheal mass were reported as PTC, and the findings for the smaller nodule as suspicious for malignancy.

He underwent an open biopsy of the paratracheal mass and tracheostomy. Histology revealed MEC in one specimen, PTC in another, and nests of benign squamous cells, with no evidence of malignancy, in a third. The postoperative course was complicated by suspected urinary tract infection and shortness of breath; thoracic CT showed mucous plugging of several bronchi in the left lower lobe, patchy opacities in the left lower lung, and atelectasis and pleural effusions bilaterally, concerning for aspiration pneumonia. A multidisciplinary conference determined that the risks of tumor debulking outweighed the benefits in his case and recommended palliative radiation therapy instead, which the patient declined.

FNA of the right thyroid lobe nodule revealed a hypocellular specimen containing few follicular cells with enlarged nuclei and small but prominent nucleoli, in a background of scattered foamy macrophages and inspissated colloid (Fig. 1); this was deemed suspicious for carcinoma. FNA of the paratracheal mass was positive for malignancy and consisted of a cellular specimen with malignant cells arranged in papillary fronds and honeycomb-like sheets in a background of mucinous material and blood (Fig. 2a, b); no normal thyroid follicles were present. The cells had enlarged nuclei with fine dusty chromatin, longitudinal grooves, and occasional pseudoinclusions (Fig. 2c), fully compatible with PTC. On retrospective review, both malignant squamous and mucin-producing glandular cells (Fig. 2d, e), compatible with MEC, were apparent along with the PTC.

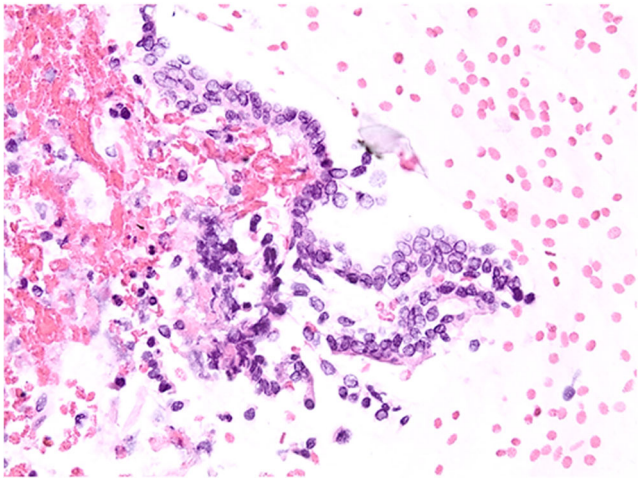

Fig. 1 *Case 1* cell block from FNA of the right thyroid lobe mass showing follicular cells with enlarged nuclei, suspicious for PTC (H&E, 400×)

Histologic sections of a biopsy specimen from the right lobe nodule revealed classical type PTC (Fig. 3a). A biopsy of a different region from the same nodule revealed nests of abnormal squamous cells and much rarer mucin-producing glandular cells resembling signet ring cells (Fig. 3b, c), plus extracellular mucin, infiltrating through dense fibrous stroma and benign thyroid tissue; these histologic features were concordant with MEC coexisting with PTC. No anaplasia, necrosis, cystic component, or perineural invasion were present, and mitoses were rare (fewer than 4 per 10 high-power fields).

Case 2

A 63-year-old female presented with a solitary palpable nodule in the right thyroid lobe. She underwent FNA of the lesion, which was diagnosed as MEC in conjunction with PTC. Two months later, the patient underwent total thyroidectomy, at which time no evidence of lymph node metastasis was found. She remained disease-free 3 years following surgery.

FNA of the right thyroid lobe revealed two distinct populations of epithelial cells. The larger cells, which

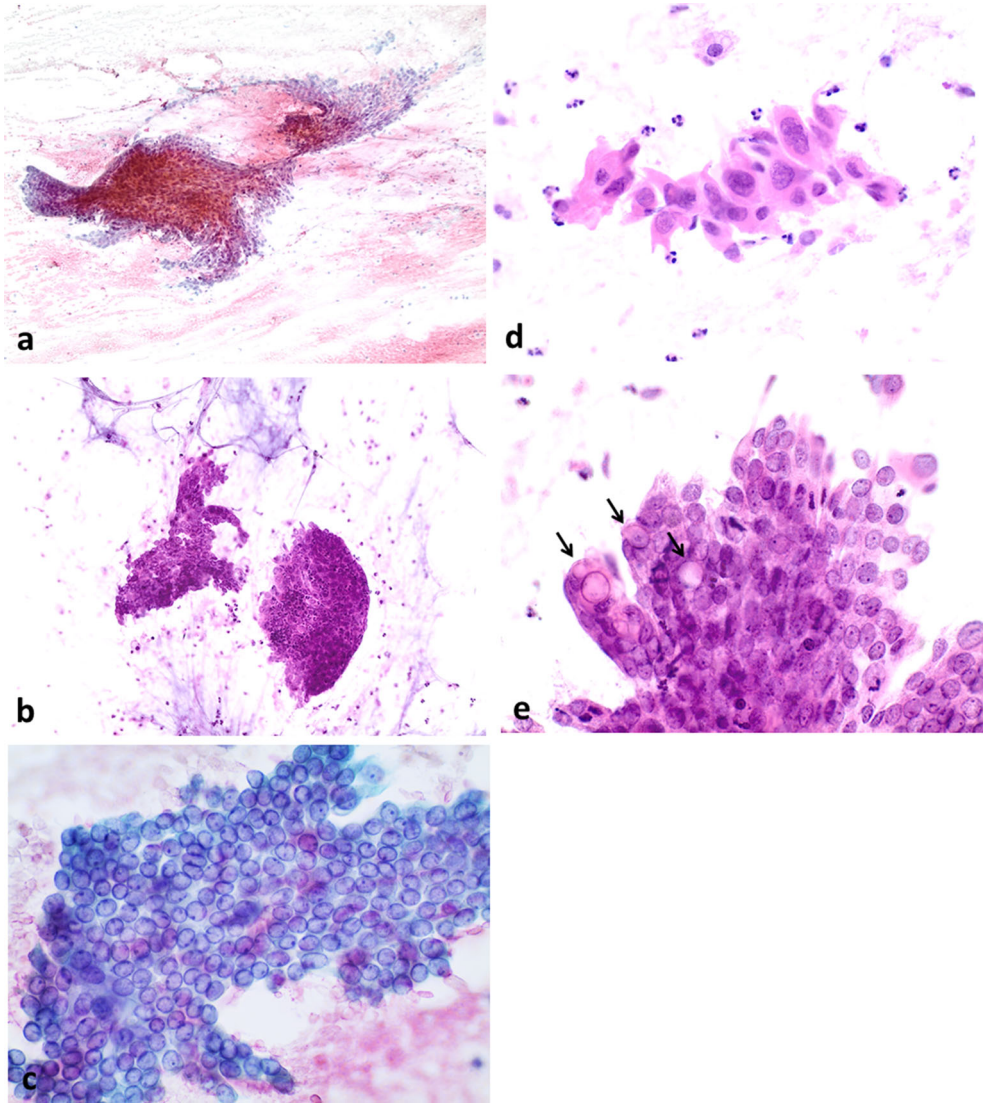

Fig. 2 *Case 1* FNA smear of the paratracheal mass demonstrating malignant cells with papillary architecture (Papanicolau, 100×) in a background of blood (**a**) and mucin (H&E, 200×) (**b**). The majority of tumor cells had enlarged nuclei with fine chromatin, small nucleoli, and occasional grooves, characteristic of PTC (Papanicolau, 600×) (**c**); however, on retrospective review, malignant cells were also identified that showed squamous (**d**) and mucinous differentiation (*arrows*), compatible with MEC (H&E, 600×) (**e**)

were sparser, contained areas of squamous differentiation complete with keratinization and intercellular bridges (Fig. 4a), as well as smaller foci of glandular differentiation with cytoplasmic mucus production (Fig. 4b). The smaller cells, which were more numerous, were follicular epithelial cells that showed the nuclear features associated with PTC (Fig. 4c). Based on these features, the interpretation was given that the tumor was composed of MEC in conjunction with PTC.

Histologic sections of the thyroidectomy specimen showed areas of classical type PTC (Fig. 5a) interspersed with nests of atypical squamous cells surrounded by a lymphocytic infiltrate, with areas of keratinization including keratin pearl formation (Fig. 5b) and foci of mucinous differentiation (Fig. 5c, d). The tumor was described as MEC arising in association with PTC.

Discussion

The histogenesis of primary MEC of the thyroid, a gland to which neither squamous nor mucous cells are native [2, 6, 10], has been extensively debated. Rhatigan et al. proposed in 1977 that MEC was derived from ectopic salivary glands, but this idea never gained traction, since benign salivary gland tissue has not been described in the thyroid [2, 6]. Many authors now postulate that the cells of origin are actually thyroid follicular cells, observing that MEC cells express mRNA of both TTF-1 and Pax-8 [3, 12], plus immunohistochemical staining for thyroglobulin [8]—all hallmarks of follicular cells. MEC is closely associated with such lesions as Hashimoto thyroiditis and PTC [7, 13], which may demonstrate squamous metaplasia [1, 2, 6, 10, 13]; this has led some

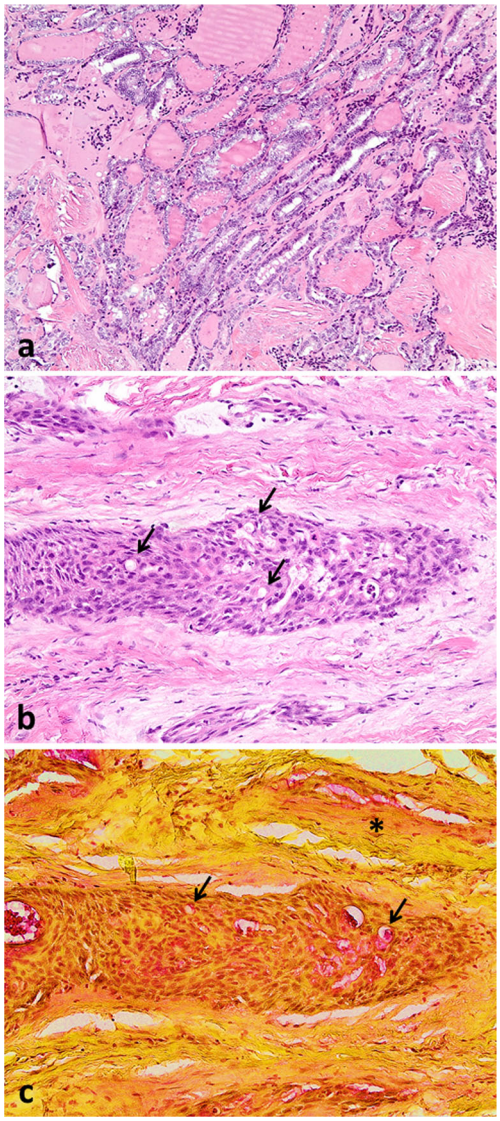

Fig. 3 *Case 1* histologic sections from the right thyroid lobe mass illustrating classical type PTC (**a**) and infiltrative nests of abnormal squamous cells interspersed with mucous cells resembling signet ring cells (*arrows*) (H&E, 200×) (**b**); mucicarmine stain demonstrated mucin in both intracytoplasmic (*arrows*) and extracellular (*asterisk*) compartments (200×) (**c**)

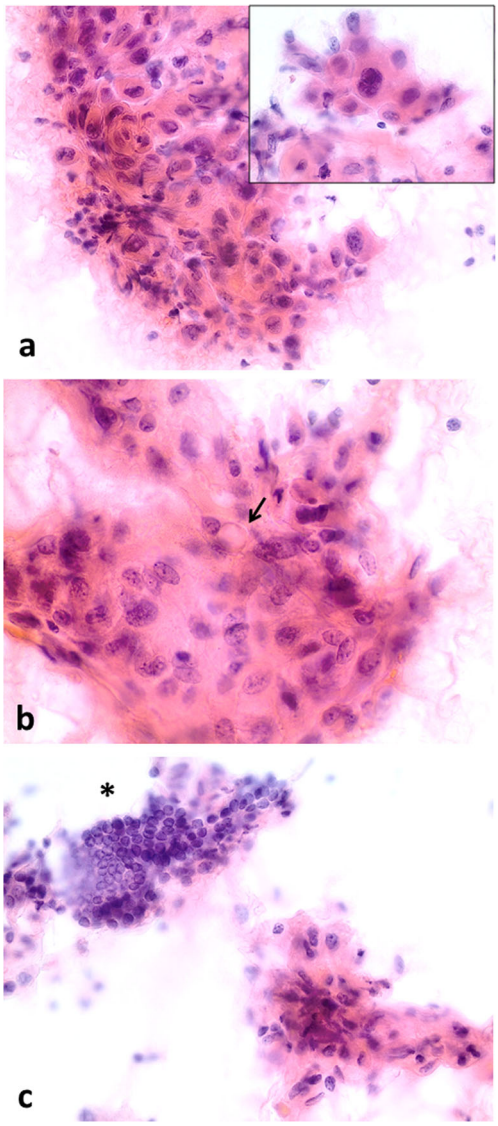

Fig. 4 *Case 2* FNA smear of the right thyroid lobe mass revealing two populations of malignant cells comprising the MEC component. The larger cells showed foci of squamous differentiation demonstrating keratinization and intercellular bridges (*inset*) (H&E, 400×) (**a**), as well as foci of glandular differentiation demonstrating intracytoplasmic mucin (*arrow*) (H&E, 600×) (**b**); the smaller cells were thyroid follicular cells with enlarged nuclei and fine chromatin (*asterisk*), compatible with concomitant PTC (H&E, 400×) (**c**)

authors to suggest that the parent cells of MEC are follicular cells that have undergone squamous metaplasia. These may arise in the context of lymphocytic thyroiditis [5] and/or (more likely) PTC that has undergone simultaneous squamous and mucinous metaplasia [6, 8, 9]. The prevalence of lymphocytic thyroiditis in the uninvolved thyroid of patients with MEC [5, 7], as well as case reports of PTC with areas of mucoepidermoid differentiation [9, 10] or giving rise to MEC [6, 9, 11, 13], lends credibility to both hypotheses, but especially the latter one in which PTC is postulated as the precursor lesion. According to this model, metaplastic squamous cells, irrespective of the cause of the metaplasia, are the common progenitor to both MEC and SCC of the thyroid [5, 6].

Accurate diagnosis of MEC by thyroid FNA requires identification of three malignant components: clusters of squamoid cells, which have distinct cytoplasmic borders and possible cytoplasmic keratinization and/or intercellular bridges; intermediate cells, which have higher nuclear-to-cytoplasmic ratios and more

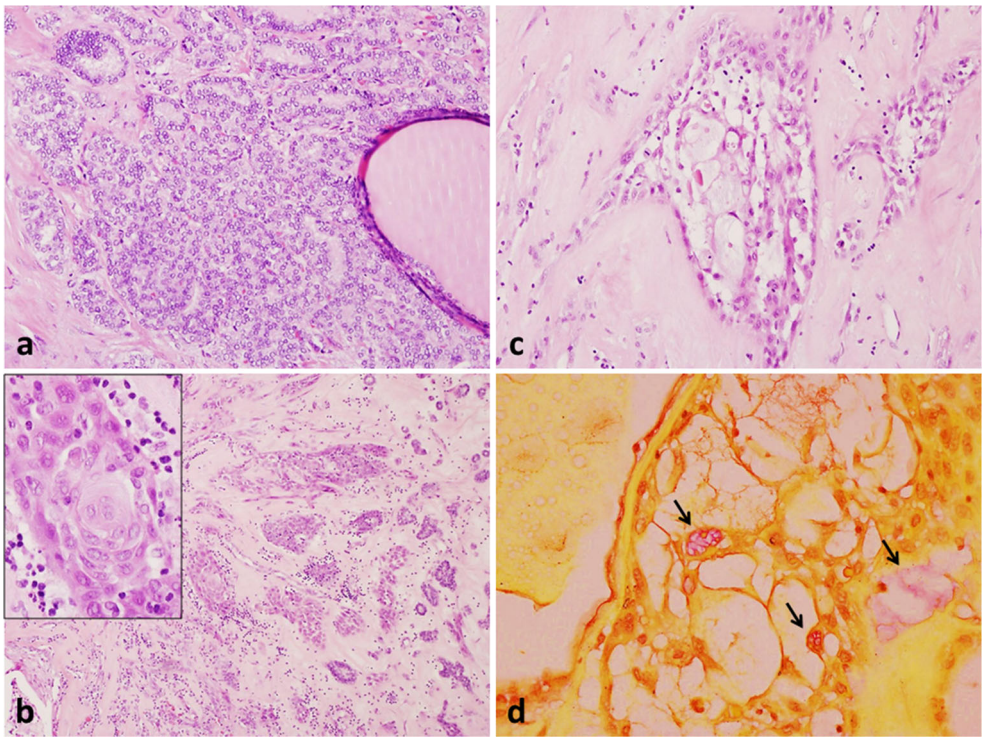

Fig. 5 *Case 2* Histologic sections from the right thyroid lobe mass illustrating classical type PTC (**a**) and atypical squamous nests surrounded by a lymphocytic infiltrate (H&E, 100×); keratin pearl formation was evident (*inset*) (H&E, 400×) (**b**). Other areas of the tumor contained mucous cells and extracellular mucin within cystic spaces (H&E, 100×) (**c**) that was demonstrated with mucicarmine (*arrows*) (400×) (**d**)

prominent nucleoli; and mucous cells [1], which may include signet ring cells. The morphologic and architectural features may vary, especially if residual PTC is present. In the salivary glands, MEC may be divided into low-grade and high-grade neoplasms: Low-grade MEC contains a larger cystic component with predominance of glandular epithelium, whereas high-grade MEC contains a larger solid component dominated by squamous tumor cells and has a more pleomorphic appearance [14]. However, so few MECs have been described in the thyroid that the value of grading is probably lacking validity. In the differential diagnosis of MEC, as determined by thyroid FNA, are PTC, SCC, medullary carcinoma, and metastasis. PTC is characterized by enlarged, hyperchromatic nuclei with very fine chromatin, membrane folds or grooves, and intranuclear pseudoinclusions, all of which are absent in pure MEC. SCC lacks glandular differentiation and may show more anaplasia than that in the typical MEC. Medullary carcinoma manifests a morphologic spectrum, but common findings include isolated tumor cells, often with a plasmacytoid appearance, intracytoplasmic red granules that react immunohistochemically with synaptophysin and chromogranin, a paucity of mucin, and the possible presence of amyloid—none of which are expected in MEC [1]. The most likely metastases with this morphology would originate in the salivary glands or lungs. Clinical history, of course, is crucial.

Histologically, thyroid MEC is characterized by a well-circumscribed but unencapsulated tumor composed predominantly of nests of squamous or epidermoid cells, with interspersed mucous cells [5]. The latter may be columnar cells, goblet cells, or signet ring cells. Keratin pearls and intercellular bridges are common features of the epidermoid component, and glandular or cystic structures containing mucin may also be present [4, 5]. Mucous cells can be confirmed using mucicarmine or periodic acid-Schiff with diastase (PASD), both of which stain intracytoplasmic and luminal mucin. The surrounding stroma may be sclerotic and often contains a lymphoplasmacytic infiltrate; indeed, concomitant lymphocytic thyroiditis is quite common. However, in a potential relative of MEC, sclerosing MEC with eosinophilia, the sclerosis tends to be denser, and the inflammatory infiltrate composed predominantly of eosinophils; the association with Hashimoto thyroiditis is much stronger as well [4, 5]. As befits the close association between MEC and PTC, such features as papillary architecture and psammoma bodies may be present in MEC [2, 6]; likewise, mucin production and squamous metaplasia have been observed in PTC [2].

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Conflict of Interest None.

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