Case Report

Primary Mucinous Carcinoma of the Thyroid: A Case Report, Literature Review, and Immunohistochemistry Summary

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Abstract

Introduction
Primary mucinous carcinoma of the thyroid is an exceedingly rare malignancy that is histologically similar to mucinous carcinoma of other sites. Accurate diagnosis is a challenging yet crucial component of clinical management for both patients and our understanding of this rare disease.

Case Presentation
We report the case of a 69-year-old male patient with primary mucinous carcinoma of the thyroid. Microscopic examination of a biopsy specimen showed fibrous tissue, which was extensively and irregularly infiltrated by a cytologically malignant epithelial neoplasm showing glandular differentiation with mucin production. Immunohistochemistry demonstrated that tumor cells were positive for TTF1, thyroglobulin, CK7, and PAX8. Co-expression of TTF1 and PAX8 is most commonly seen in thyroid tumors. These findings support our diagnosis of mucinous carcinoma of thyroid origin, which is rare and highly aggressive.

Conclusion
In this report, we present the only documented case of primary mucinous carcinoma of the thyroid reported in the United States in the last decade. The diagnosis of primary mucinous carcinoma of the thyroid can be challenging. Therefore, we discuss and detail the clinicopathologic tumor profile and provide more current, detailed histological criteria to assist in the diagnosis of this rare disease.

Keywords
primary mucinous carcinoma; thyroid; thyroid neoplasms; immunohistochemistry; mucinous neoplasms; adenocarcinoma; mucinous; case reports

Introduction
Primary mucinous carcinoma of the thyroid is an extremely rare tumor that is characteristically defined by histology. The appearance of mucin can suggest locoregional invasion most commonly from the esophagus or trachea and distant metastasis, for example from the lung, gastrointestinal tract, or breast. Moreover, variants of follicular and papillary thyroid carcinoma have been shown to produce mucin.[1] Therefore, up-to-date knowledge and a broad differential are important to make an accurate diagnosis of primary mucinous carcinoma of the thyroid. In this report, we detail a case report of primary mucinous carcinoma of thyroid origin and summarize the published literature regarding the immunohistochemistry (IHC) findings. To the best of our knowledge, this is the only documented case of mucinous thyroid carcinoma reported in the United States (US) in over 10 years. In our report, we also expand the reported immunohistochemical expression profile often associated with this disease.

Case Presentation

A 69-year-old male patient presented for inpatient endoscopy due to his experiencing progressive dysphagia and esophageal stricture for the previous month and a half. The patient also reported a 25-pound weight loss over the previous several months. Due to airway patency concerns, pre-operative assessment included laryngoscopy, which revealed bilateral vocal cord paralysis. These findings were concerning for malignancy, possibly affecting the recurrent laryngeal nerves.

Urgent computerized tomography (CT) of the neck with contrast demonstrated a 6 cm by 10 cm infiltrative mass involving the infraglottic larynx, hypopharynx, trachea, esophagus, and thyroid gland. The thyroid gland was diffusely enlarged and indistinguishable from the mass (**Figure 1**).

A fine needle aspiration of the neck mass was performed, revealing high-grade nuclei suggesting a poorly differentiated malignancy. The differential diagnosis from the initial cytological examination included medullary thyroid carcinoma with potential conversion to anaplastic carcinoma.

The patient was evaluated by otolaryngology, oncology, and radiation oncology during the diagnostic workup. Additional imaging included a CT chest/abdomen/pelvis with contrast, which demonstrated multiple nodules, as large as 0.7 cm, within the lung and subpleural space of the right lower lobe of the lung. The patient was medically stable and discharged with outpatient follow-up for concurrent chemoradiation therapy, including doxorubicin for the treatment of stage III, T4a, N1b, M0 undifferentiated primary thyroid malignancy.

Approximately 1 month later, the patient returned to the emergency department with dyspnea. A contrast-enhanced CT scan of the neck demonstrated progressive cervical disease with circumferential involvement of the trachea. A tracheostomy was performed, and during the procedure, a 2 cm incisional biopsy of the indurated tumor overlying the anterior tracheal wall was also performed and sent for permanent section analysis.

Microscopic examination and IHC analysis of the specimen were performed and demonstrated tumor cells that were positive for cytokeratin 7 (CK7), paired box gene 8 (PAX8), and thyroid transcription factor 1 (TTF1), as shown in **Figure 2**. IHC was negative for cytokeratin 20 (CK20), CDX2, GATA3, and p63. Co-expression of TTF1 and PAX8 is most commonly seen in thyroid tumors, which supports the diagnosis of mucinous carcinoma of the thyroid. Due to the rarity of primary mucinous carcinoma of the thyroid, the case was submitted to a leading academic medical center for an expert second opinion with confirmation. These findings revealed fibrous tissue, which was extensively and irregularly infiltrated by a cytologically malignant epithelial neoplasm, showing glandular differentiation with mucin production. A minor subset of the glandular spaces showed less atypia, which contained colloid-like material. IHC showed focal positivity for PAX8, thyroglobulin (TG), and TTF1 in the small low-grade-appearing glandular structures

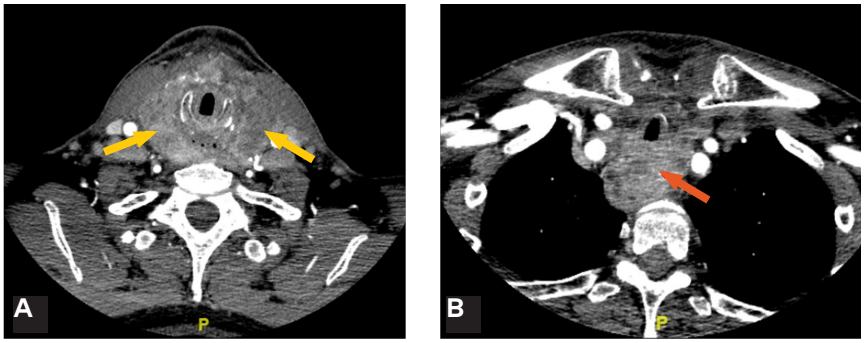

Figure 1. A CT of the neck with contrast showed 2 prominent areas of involvement, the thyroid and esophagus. (A) A large, multi-compartmental neck mass was found at the level of the thyroid (yellow arrows), approximately 6 cm by 10 cm. (B) The involvement of esophageal mucosal space (orange arrow) from the post-cricoid area inferiorly to the carina showed varying degrees of tracheal narrowing.

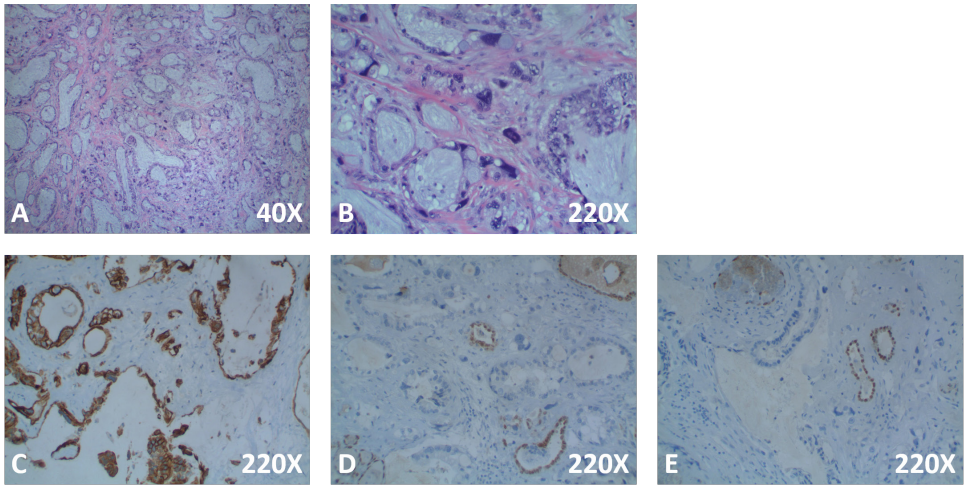

Figure 2. Hematoxylin and eosin stain of a fixed specimen showed: (A) At low power, the tumor was composed of well-to-moderately defined glands with abundant intraluminal mucin. (B) At high power, the cells exhibited abundant intracytoplasmic mucin and marked nuclear pleomorphism, ranging from small bland nuclei to marked nuclear enlargement, hyperchromasia, and pronounced derangement of the nuclear contours. Immunohistochemistry: (C) CK7, (D) PAX8, (E) TTF1. While not expressed diffusely, the more well-differentiated areas exhibited positive nuclear reactions with both TTF1 and PAX8.

with colloid. There were also small foci of convincing positivity in mucinous glandular structures, which showed greater cytologic atypia. Stains for SOX10, SALL4, p63, CD117, CK20, BRAFV600E, and NRAS Q61R were negative. These findings confirmed the diagnosis of primary mucinous carcinoma of thyroid origin.

Discussion

Mucinous carcinoma is a mucin-producing, poorly differentiated carcinoma of primarily thyroid origin. Primary mucinous carcinoma of the thyroid is a rare diagnosis, but the appearance of mucin is similar to mucinous cancers of other locations, such as the lung, breast, or gastrointestinal tract. Therefore, the differential diagnosis should include direct invasion from an esophageal lesion, tracheal lesion, or distant metastatic cancer to the thyroid. Mucin generally will stain positive for periodic acid-Schiff, mucicarmine, and Alcian blue.[1] However, to confirm thyroid origin, IHC for TTF1 and TG should be performed to exclude metastatic disease from other locations.

Mucin identification alone cannot diagnose primary mucinous carcinoma, as some variants of follicular and papillary thyroid carcinoma are known to produce mucin.[1] Histological appearance can differentiate these from primary mucinous thyroid carcinoma, demonstrating the absence of any follicular or papillary structures, nuclear grooves, or hyaline nuclei.[2] Further diagnostic work up can rule out mucin-producing medullary carcinoma with a negative carcinoembryonic antigen (CEA) on IHC. Undifferentiated carcinomas, which occasionally produce mucin, can be ruled out by the absence of high numbers of mitotically active and pleomorphic cells.[3] The characteristic appearance of primary mucinous thyroid carcinoma is trabeculae of epithelial cells with large, prominent nuclei surrounded by abundant extracellular mucus, resembling large mucinous lakes.[4,5]

A literature search was performed in PubMed with the following search terms, “primary mucinous carcinoma” and “thyroid;” and “mucinous carcinoma” and “thyroid.” Additionally, citations from the selected articles and suggested similar articles were reviewed for inclusion. A total of 157 abstracts were screened for inclusion yielding a total of 12 articles. One article was removed because it was written in Mandarin. In total, only 11 cases of primary mucinous carcinoma of the thyroid were identified in the English literature.

Given the rarity of this type of thyroid cancer, it is interesting to note the geographic distribution and timeline of documented cases. In 1976, Diaz-Perez et al documented the first known case in Michigan, US.[6] In 1980, 2 additional cases were identified in New York, US, by De-

ligdisch et al.[7] Over 30 years later also in New York, Yang et al reported a case of mucinous carcinoma.[8] We present the first documented US case of primary mucinous carcinoma in over a decade.

Of the remaining reported cases of primary mucinous thyroid carcinoma, 4 cases were from Asia: 3 from Japan[2,3,9] and 1 from China.[4] Two cases were documented in Africa: 1 in Morocco[10] and 1 from Tunisia.[11] Lastly, 2 cases were reported in Europe: 1 from Italy[12] and 1 from Norway.[5]

Generally, to distinguish mucinous thyroid carcinomas from metastatic mucinous carcinoma, IHC should be positive for TTF1, PAX8, and low molecular-weight cytokeratins.[1] The specific IHC findings for our patient and the previously published reports of primary mucinous carcinoma of the thyroid are summarized in **Table 1**. In all cases, if reported, immunoprofiles were positive for TG (10 cases), TTF1 (8 cases), and PAX8 (3 cases). Additionally, in all cases, immunoprofiles, if reported, were negative for calcitonin (7 cases) and CEA (6 cases). Of note, Mizukami et al 1993, found the CEA monoclonal antibody was negative and pCEAR was positive.[9] Low molecular weight cytokeratin IHC was positive in the present case and 5 cases in the literature: CK7 in D'Antonio et al[12], cytokeratin AE1/AE3 in Matsuo et al[2] and Wang et al[4], cytokeratin MNF116 in D'Antonio et al[12], and lastly cytokeratin CAM5.2 in Kondo et al.[3] However, Bajja et al reported negativity to CK7.[10]

In this case, to help distinguish a primary versus metastatic mucin-producing thyroid lesion, we report for the first time, a specific IHC profile that stains negative for CDX2 (gastrointestinal), GATA3 (breast epithelium), SOX10 (neural

Table 1. Summary of IHC Profile Findings in the Literature and Presented Cases

Case	TG	TTF1	CEA	Calcitonin	Other Positive	Other Negative
Matsuo et al, 2016[2]	+	+	-	-	AE1/AE3	
Kondo et al, 2005[3]	+	+	-	-	CAM5.2, CK19, NSE, p53	34betaE12, Synaptophysin, Chromogranin A, ER, PgR
Wang et al, 2018[4]	+	+	-	-	vimentin, AE1/AE3, PAX8	EMA, CDX2, ER, GATA3, CD68, CD38, CK19, desmin, MyoD1, myogenin
Mnif et al, 2013[11]	+	+	-	-		
D'Antonio et al, 2007[12]	+	+	NR	-	CK MNF116, CK7	CK20
Bajja et al, 2017[10]	+	+	NR	NR		CK7, CK20
Yang et al, 2011[8]	+	+	NR	NR	PAX8	
Mizukami et al, 1993[9]	+	NR	- (mono)	-	CEA (poly), keratin, EMA, vimentin	
Sobrinho-Simões et al, 1986[5]	+	NR	-	-		
Present case	+	+	NR	NR	CK7, PAX8	CK20, CDX2, GATA3, SOX10, SALL4, p63, CD117, BRAFV600E, and NRAS Q61R

Abbreviations: IHC = immunohistochemistry; + = positive; - = negative; NR = not reported; TG = thyroglobulin; TTF1 = thyroid transcription factor 1; CEA = carcinoembryonic antigen; CK19= cytokeratin 19; NSE = neuron-specific enolase; ER = estrogen receptor; PgR = progesterone receptor; PAX8 = paired box gene 8; EMA = epithelial membrane antigen; MyoD1 = myoblast determination protein 1; CK20 = cytokeratin 20; CK7 = cytokeratin 7

crest derivation), SALL4 (germ cell marker), CD117 (gastrointestinal stromal tumors), p63 (myoepithelial marker), BRAFV600E (MAPK signaling pathway), and NRAS Q61R (MAPK and PI3K-AKT).

Conclusion

We present a case of primary mucinous thyroid carcinoma. We describe the predominant pathologic features of this uncommon tumor and provide some novel IHC profile findings that help differentiate primary from metastatic lesions.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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