# Primary mucoepidermoid carcinoma of the thyroid gland - misdiagnosed as metastatic adenocarcinoma to the thyroid

**Ngo Thi Minh Hanh[1]*, Nguyen Thi Lan Huong[2], and Nguyen Thi Ngoc Anh[1]**

*[1]108 Military Central Hospital,*
*[2]Military Institute of Medical Radiology and Oncology*

**Summary**

Thyroid primary mucoepidermoid carcinoma is a malignant tumor classified as a salivary gland-type carcinoma of the thyroid. This type of tumor is extremely rare, with only a dozen cases reported to date, and has a high incidence in females. Due to its rarity, misdiagnosis can occur in clinical practice. We report a case of a female patient who presented with a thyroid nodule and vague clinical symptoms. Histologically, the tumor was characterized by intermediate and epidermoid (squamous) tumor cells with mucin-forming cystic and solid components. Despite immunohistochemical staining showing tumor cells positive for TTF1, Napsin A, Thyroglobulin, PAX8, CK19, p63, and negative for CK20, the initial conclusion still required differential diagnosis from metastatic adenocarcinoma to the thyroid. After cancer screening and consultation, the patient was confirmed to have a primary mucoepidermoid carcinoma of the thyroid. This case report and literature review provide additional information about the disease, definitive diagnosis, and treatment to improve the diagnostic capabilities and management of this patient group.

*Keywords:* Mucoepidermoid carcinoma, immunohistochemistry, follicular epithelial cell origin, thyroid gland.

## I. BACKGROUND

Mucoepidermoid carcinoma is a malignant tumor that combines epithelial cells and mucous cells, classified in the salivary gland cancer group[1].

The cancer has low-grade histological characteristics and slow progression (indolent biological behavior). Primary mucoepidermoid carcinoma of the thyroid is rare, with only some cases or serial reports. Although the pathogenesis is believed to be from solid cell nests, ectopic salivary glands, and metaplastic follicular epithelium, diagnosis is still difficult in practice, and misdiagnosis is considered metastatic carcinoma. We report a rare case, analyze histopathological images and differential diagnosis to determine the diagnosis, and update the diagnosis and treatment to improve the ability of pathological diagnosis.

## II. CASE PRESENTATION

A 36-year-old female patient, working as an industrial embroidery machine operator, sought medical attention due to two-week fatigue. Basic blood tests and general ultrasound were performed, revealing a thyroid nodule. Fine needle aspiration cytology results suggested papillary thyroid carcinoma and surgery was recommended. The patient had no history of prior illness or radiation exposure. No family members had a history of thyroid disease.

The complete blood count was within normal limits: RBC 4.56 (4.3-5.8) $10^3$/µl, HGB 12.6 (12.50-

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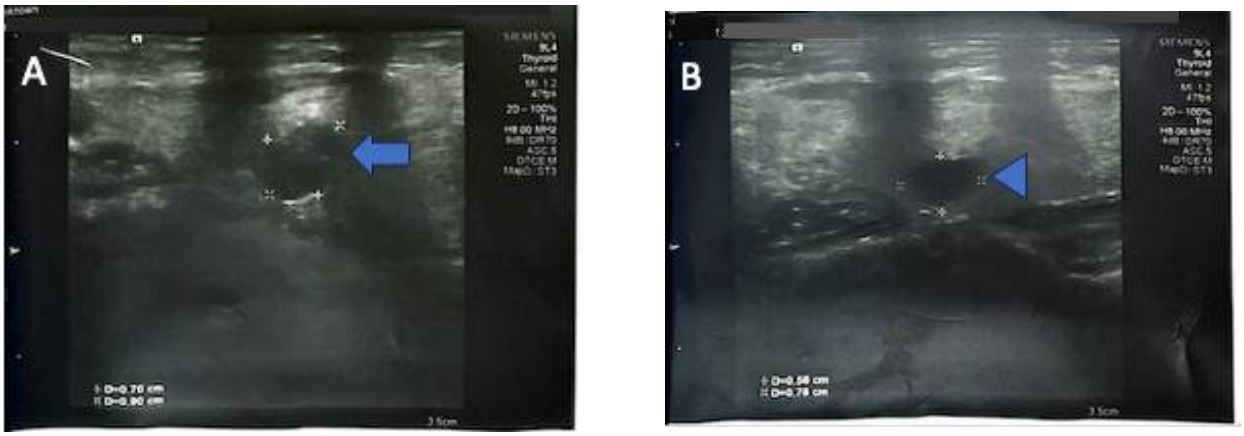
***Correspondence to**: ngominhhanh108@gmail.com - 108 Military Central Hospital*

16.30) g/dL, HCT 38.3 (35-50) %, MCV 83.8 (79-96) fL, MCH 27.6 (25-34) pg, MCHC 32.9 (30.50-37.30) g/dL (WBC 6.28 (4-12)T/l, NEU 4.07 (2.0-7.8) $10^3$/µl, LYM 1.68 (0.8-5.1) $10^3$/µl, EO 0.16 (0.2-1)$10^3$/µl, PLT 254 (140-400) $10^3$/µl.

Blood biochemistry: Glucose 6.08 (3.9-6.4) mmol/l, ure 6.16 (1.7-8.3) mmol/l, creatinin 97.33 (44-106), AST (GOT) 28.28 (< 40) u/l, ALT (GPT) (23.27) (< 40) u/l.

Thyroid function test: T3 1.87 (1.3-3.1) pmol/L, FT4 12.51 (13-23) pmol/L, TSH 0.517 (0.27-4.2) mcrolU/ml.

Ultrasound: The thyroid gland was normal in size and had heterogeneous echogenicity. The left lobe had several hypoechoic nodules, the largest measuring 5.8 x 7.6mm, with clear boundaries and smooth edges (TIRADS 3). The right lobe had a mixed nodule measuring 7 x 9mm, with clear boundaries, irregular edges, and internal calcification (TIRADS 4). Neck muscles and tendons appeared normal bilaterally; no abnormalities were detected around the thyroid; no enlarged cervical lymph nodes were observed. *Ultrasound conclusion*: Nodule in the right lobe TIRADS 4, left lobe thyroid cyst TIRADS 2.




A. Image of the hypoechoic nodule in the right lobe (TRADS 4) (arrow); B. Image of the cyst in the left lobe (TRADS 2) (head arrow)

**Figure 1.** Ultrasound images of the two lobes of the thyroid gland

*Abdominal ultrasound* revealed no significant findings.

Chest X-ray: normal.

Cytological results: The slides of fine needle aspiration from the right lobe showed epithelial cells with round nuclei of varying sizes, coarse chromatin, and irregular nuclear membranes, occasionally arranged in glandular or papillary structures or with nuclear overlapping, without polarity.

*Conclusion:* Papillary thyroid carcinoma (Bethesda VI)

Pre-operative diagnosis: Right thyroid lobe carcinoma cT1NxMx/ bilateral thyroid nodules.

The patient underwent surgery: A 4cm incision was made along the lower neck crease. Examination of the thyroid revealed several nodules of varying sizes in the left lobe, benign; the right lobe had a nodule measuring 0.5 x 0.7cm, firm, adjacent to the thyroid capsule, invading the capsule and strap muscles, not invading the trachea or nerves, ivory-white in color, with malignant characteristics. Examination of central neck lymph nodes showed multiple nodes measuring 0.2 - 0.5cm, soft, not invading surrounding fat or tissue, with unclear lymph node characteristics. Total thyroidectomy and central neck dissection were performed, preserving the parathyroid glands and recurrent laryngeal nerves.

Post-operative pathological results:

Gross examination: Right lobe and isthmus of normal size, right lobe with an 8mm opaque white nodule; left lobe without nodules. A few small pieces

of soft fibro-fatty tissue, suspected to contain lymph nodes.

Microscopic examination: Sections of the right thyroid lobe nodule showed a tumor without clear boundaries with the thyroid tissue, accompanied by infiltration of mononuclear inflammatory cells in clusters. The tumor structure consisted of epithelioid and intermediate cells with round or oval nuclei of varying sizes and clear cell boundaries. The cells were arranged in clusters and large cords interspersed with glandular cysts, with scattered mucus-producing cells. The tumor stroma showed fibrous proliferation with inflammatory cell infiltration. Some clusters of tumor cells invaded and disrupted the thyroid capsule. No vascular or perineural invasion was observed.

Sections of the left thyroid lobe showed areas of dilated colloid follicles with benign lining epithelium.

Some small lymph node tissues showed intact lymphoid follicle structure, with no evidence of metastatic carcinoma.

*Histopathological conclusion:* Thyroid carcinoma with capsular invasion - Immunohistochemistry required.

The patient's slides and paraffin blocks were transferred to a specialized center for immunohistochemical staining. Tumor cells were diffusely positive for PAX8 and Napsin A, focally positive for TTF1, P63, and Thyroglobulin, strongly and diffusely positive for CK19, and negative for CK20 (Figure 3).

*The pathological diagnosis after immunohistochemistry* is metastatic adenocarcinoma of the thyroid. Clinical correlation, imaging studies, and other tests are needed to identify the primary tumor's origin.

The patient underwent cancer screening tests:

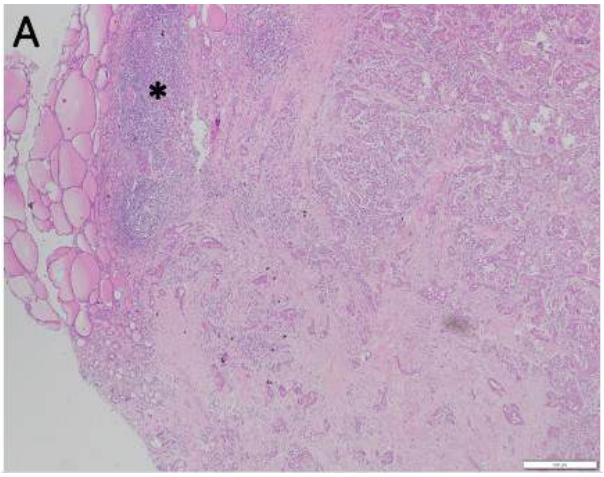
Abdominal ultrasound: No abnormalities detected in the liver, biliary tract, pancreas, spleen, kidneys, ureters, bladder, or uterus.

Gastrointestinal endoscopy: No abnormalities detected in the esophagus, stomach, or colorectum.

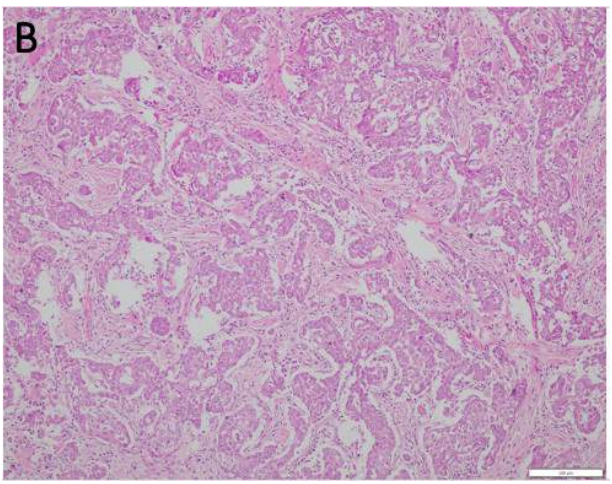
Brain - chest - abdominal CT: No abnormalities detected.

ENT endoscopy: Bilateral intermediate bronchial cord paralysis

After a consultation with expert pathologists, the final pathological diagnosis was: Primary mucoepidermoid carcinoma of the right thyroid lobe, without lymph node metastasis.

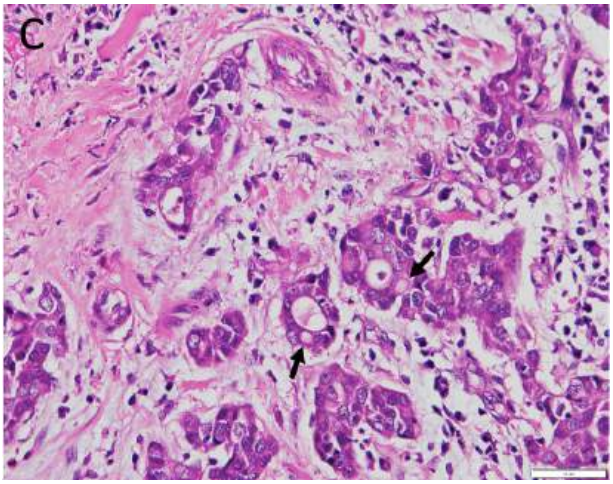



A. Tumor with no clear boundary with normal thyroid tissue accompanied by clusters of chronic inflammatory lymphocytes (asterisk *) (HE x 40);

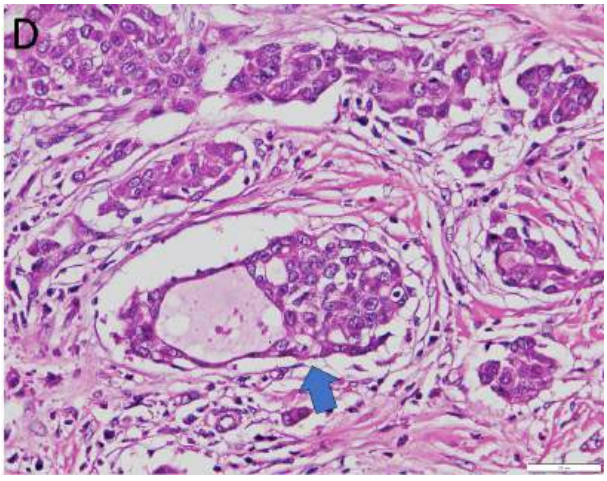



B. Image of clusters of intermediate and epidermal tumor cells arranged in cords, in clusters interspersed with cystic areas with fibrous tissue infiltrated with inflammatory cells (HE x 100);

**Figure 2.** HE histopathology images of primary mucoepidermoid carcinoma of the thyroid gland

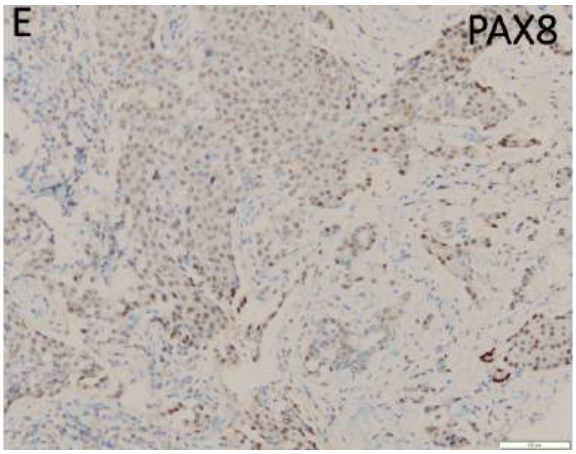



C. Tumor cells arranged in cystic form with mucus in the cytoplasm (small arrow) (HE x 200);

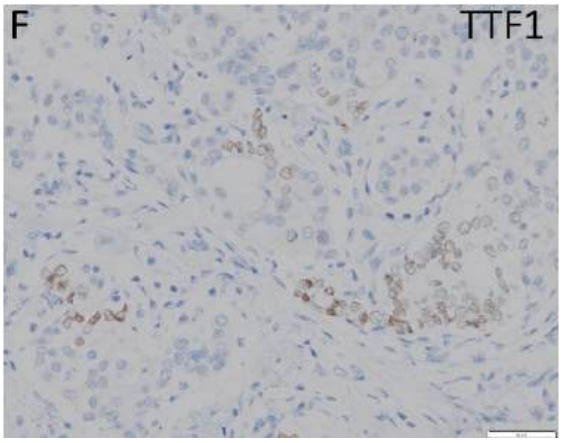



D. Tumor cells arranged in dense clusters adjacent to cystic structures (large arrow) (HE x 400)

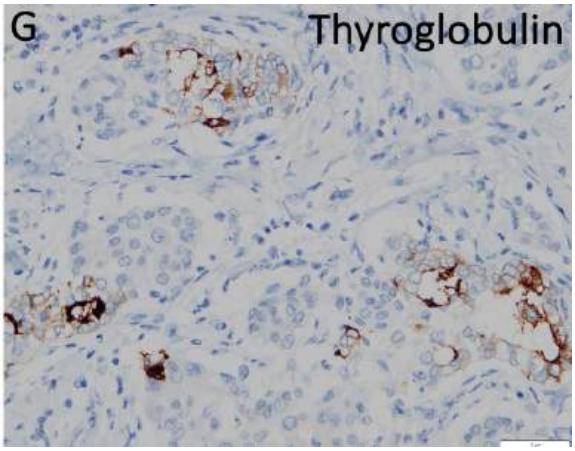
**Figure 2.** HE histopathology images of primary mucoepidermoid carcinoma of the thyroid gland *(Next)*



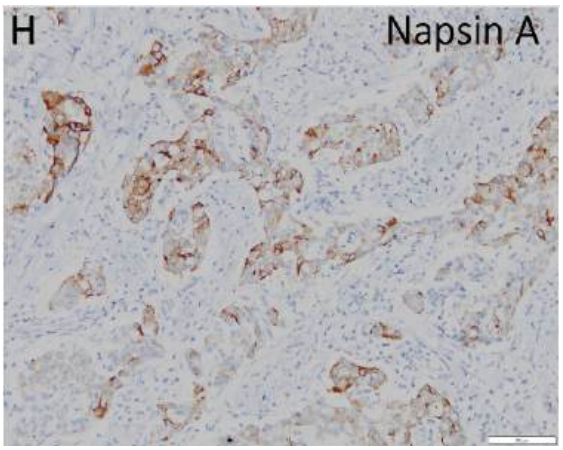

E. Tumor cells were diffusely positive for PAX8 (x 100);




F. Tumor cells were focally and weakly positive for TTF1

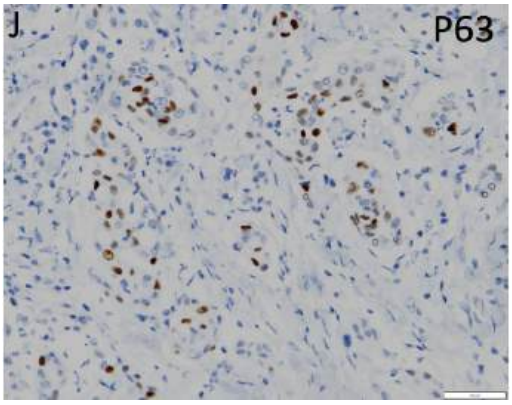



G. Tumor cells were strongly and focally positive for Thyroglobulin;

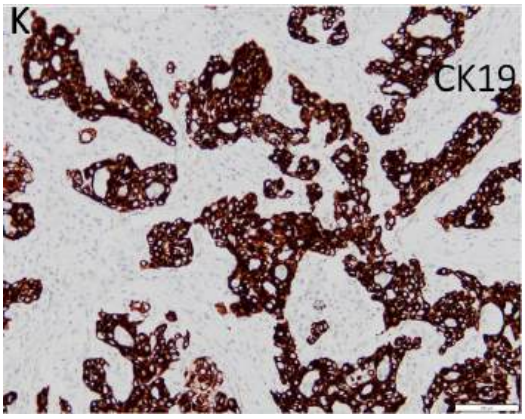



H. Tumor cells were diffusely positive in the plasma membrane for Napsin A

**Figure 3.** Immunohistochemistry images




J. Tumor cells were strongly and focally positive for P63




K. Tumor cells were very strongly and diffusely positive for CK19.

**Figure 3.** Immunohistochemistry images (Next)

## III. DISCUSSION

Mucoepidermoid carcinoma was first described in 1940 and is the most common cancer of the salivary glands. It occurs most frequently in the parotid gland[2] and can also arise in minor salivary glands. This cancer has been rarely reported in the tongue, oral cavity, mucous glands of the lungs, and gastrointestinal tract. In 1977, Rhatigan reported the first case of primary mucoepidermoid carcinoma of the thyroid. Primary mucoepidermoid carcinoma of the thyroid is extremely rare, accounting for only 0.5% of thyroid tumors. Much debate has been about its pathogenesis, prognostic significance, and management[3]. The origin of the disease remains unclear: Some authors suggest ectopic salivary gland tissue in the thyroid, striated muscle, cartilage, and thymus, or remnant thyroglossal ducts. A more convincing explanation for the tumor's origin is metaplastic differentiation of well-differentiated thyroid carcinoma[4].

Similar to thyroid cancer in general, mucoepidermoid carcinoma of the thyroid is more common in females than males, with a ratio of 1.5:1[5]. The average age of onset for thyroid mucoepidermoid carcinoma is 46 years. Clinical presentation is typically a painless mass. All patients are euthyroid. Most patients have no history of radiation therapy. Our patient experienced fatigue and discovered a thyroid nodule on ultrasound during a health check-up, without palpable masses or swallowing discomfort, and thyroid hormone tests were within normal limits. Grossly, the tumor appears as a nodular or partially cystic mass, gray-brown to yellow-orange.

Histological features: Show a variety of architectural patterns (solid, cystic, microcystic, papillary, clear cell, oncocytic, columnar, hyalinized, and sclerosing) Squamous metaplasia can occur in the thyroid, and squamous cell carcinoma was once considered a special variant of papillary thyroid carcinoma[6]. Thyroid cells can produce mucin, detectable by mucin or PAS staining, and may be associated with chronic lymphocytic thyroiditis[6]. In our case, the tumor has structural features including epidermoid cells arranged in cystic or tubular glands containing mucin (Figure 2 C, D), which was mistaken for adenocarcinoma. For prognostic purposes, mucoepidermoid carcinoma is classified into three grades based on histological morphology: Low, high, and intermediate. Generally, well-differentiated or low-grade mucoepidermoid carcinoma has numerous cysts lined by a single layer of mucus-secreting epithelium. Epidermoid and intermediate cells are sparse, with minimal pleomorphism and rare mitotic figures. Intermediate-grade tumors form solid cell clusters, with more cells than low-grade tumors, predominantly epidermoid and intermediate cells, and fewer cystic components. Tumor cells show mild to moderate pleomorphism, with occasional mitotic figures. Our case applied to the intermediate-grade description (Figure 2). High-grade mucoepidermoid carcinoma

tends to have only mucous cells varying in morphology, and intermediate cells are considered dysplastic with more frequent mitotic figures[7]. Most thyroid tumors are mostly low-grade mucoepidermoid carcinoma but bone metastases are also seen[8].

As most tumors are low-grade malignancies, there is still debate about treatment approaches. Surgery is the first-line treatment, typically involving lobectomy of the affected lobe or total thyroidectomy. Recurrence or metastasis time ranges from 1.5 to 15 years (average 8 years)[5, 7, 8]. The survival rate for patients with mucoepidermoid carcinoma is approximately 90%. Surgery based on the current stage of the disease is the preferred method. Additionally, platinum-based chemotherapy, conventional radiotherapy, and iodine therapy may be used but provide little benefit. Recently, HER2 overexpression has been described in salivary gland mucoepidermoid carcinoma[9] which could be useful for targeted therapy, but no reports of this approach for primary thyroid tumors of this type exist.

Differential diagnosis based on immunohistochemical markers: Based on antigen-antibody reactions, immunohistochemical staining helps diagnose the origin and characteristics of cancer cells.

TTF1 (Thyroid transcription factor-1), identified in 1989, is a nuclear-specific DNA-binding protein that interacts with the mouse thyroglobulin gene. TTF-1 regulates gene expression in the thyroid, lungs, and brain during embryonic development. TTF-1, along with PAX8, controls the expression of thyroglobulin, TPO, and thyrotropin receptors. Due to its high specificity for thyroid and lung tumors, TTF-1 is widely used to differentiate the origin of tumors in patients with metastatic cancer of unknown primary[10]. In the thyroid, TTF1 is positive in the nuclei of benign and malignant follicular-derived cells and medullary carcinoma. TTF-1 expression is often reduced in poorly differentiated thyroid cancer and nearly negative in undifferentiated thyroid cancer.

Thyroglobulin is a glycoprotein synthesized in the thyroid, a precursor of T3 and T4 hormones. Thyroglobulin gene expression is coordinately regulated by TTF1, TTF2, and PAX8. Tg is a valuable biomarker for monitoring disease recurrence, metastasis, or persistence after thyroid surgery and radioactive iodine treatment. Compared to TTF1, thyroglobulin is also a highly sensitive marker for detecting follicular cell origin. The positivity rate of thyroglobulin in thyroid carcinomas depends on the degree of differentiation and histological type. Thyroglobulin is 100% positive in differentiated thyroid carcinoma, usually negative in undifferentiated carcinoma cases, or weakly positive or focally positive in a few tumor cells[11]. Thyroglobulin is not positive in medullary thyroid carcinoma. However, thyroglobulin assessment should be cautious due to false-positive staining from diffuse spread to adjacent tissue in medullary carcinoma cases. Thyroglobulin is also expressed in metastatic lymph node lesions but is not a definitive diagnostic marker without CK and TTF1 evaluation[12].

CK19 is a subgroup of cytokeratin (CK), belonging to the low molecular weight group. CK subgroups have been studied for their expression in thyroid parenchyma, benign tumors, and malignant tumors. Papillary thyroid carcinoma expresses CK7, CK18, and CK19 in 66-100% of cases. CK7, CK18, and CK19 have lower positivity rates in poorly differentiated thyroid carcinoma cases, corresponding to 60%, 60%, and 40%[12]. Since CK19 is less expressed in follicular thyroid adenomas, and follicular thyroid carcinomas, and tends to be more focally positive than in papillary thyroid carcinoma, CK19 is considered one of the effective markers for investigating thyroid tumors.

PAX8 is one of 9 members of the paired box (PAX) gene family of transcription factors regulating organogenesis. PAX8 is involved in the development of the central nervous system, eyes, kidneys, thyroid, Wolffian duct-derived organs, and Müllerian duct-derived organs. Therefore, PAX8 is a marker used in diagnosing the origin of thyroid, kidney, and ovarian tumors. Although Napsin A is typically specific for lung adenocarcinoma[10], in our case, tumor cells simultaneously positive for Thyroglobulin and PAX8 allow for the diagnosis of a primary thyroid tumor, differentiating it from rare metastatic tumors to the thyroid.

Due to the different sensitivity and specificity characteristics of each immunohistochemical marker and the dependence on the technique, in our case, although our frontline colleagues had examined the immunohistochemical markers, they were not specialized in thyroid and the positive manifestations of focal or weakly positive cells were overlooked. The final pathological consultation led to the definitive diagnosis of primary mucinous carcinoma of the thyroid. Moreover, screening tests, imaging studies, and endoscopy did not reveal evidence of any other tumors. The patient remained stable for more than 6 months until the case report.

## IV. CONCLUSION

Primary mucoepidermoid carcinoma of the thyroid is a rare malignant tumor, classified as a salivary gland-type carcinoma of the thyroid. Due to its rarity, it can be easily misdiagnosed as a metastatic disease during diagnostic evaluation. Case reports and literature reviews help improve diagnostic capabilities and management strategies. The disease is more common in women and presents as thyroid tumors with vague clinical features. Immunohistochemistry plays a crucial role in differentiating this entity and confirming the definitive diagnosis. Surgery is the primary treatment option, while chemotherapy, radiotherapy, and radioactive iodine treatment may be considered as adjuvant therapies.

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