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CLINICAL CASE

Mucinous carcinoma of thyroid gland with signet ring cells. Case report and literature review

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Abstract

Mucinous carcinoma of thyroid is very rare. We report the 11th case of a mucinous thyroid carcinoma in the reviewed literature. A 68-year-old woman with a history of two types of breast cancer histologically different from each other and unrelated to mucin lakes develops this infrequent entity. By histology, it was compatible with mucinous carcinoma of the thyroid with signet ring cells, with no associated tumors to be considered a possibility of metastases, for which we report it as primary. Only 10 cases have been reported in the literature since its first finding in 1976.

Keywords: *Mucinous carcinoma. Mucin. Thyroid transcription factor 1. Thyroid cancer.*

Carcinoma mucinoso de tiroides con células en anillo de sello. Reporte de caso y revisión de la literatura

Resumen

El carcinoma mucinoso de tiroides es muy raro, se encuentra pocas veces en la literatura. Comunicamos el undécimo caso de un carcinoma mucinoso de tiroides en una mujer de 68 años con antecedentes de dos tipos de cáncer de mama, histológicamente diferentes entre sí y no relacionados con lagos de mucina. Considerado como primario, debido a que no tiene relación patológica con los tumores anteriormente presentados en la misma paciente. Solo 10 casos han sido reportados en la literatura desde su primer hallazgo en 1976.

Palabras clave: *Carcinoma mucinoso. Mucina. Factor de transcripción tiroideo 1 (TTF 1). Cáncer de tiroides.*

Introduction

Mucinous thyroid carcinoma is an extremely rare malignant tumor; Only 10 cases have been described in detail[1,2] with a diagnostic time that ranged from 2 months to 2 years in patients aged 32-82 years (mean 63.1) without a predominance between the sexes[3]. It was first described by Díaz-Pérez in 1976[4], as a tumor that presents nests, trabeculae, and sheets of epithelial cells at the histological level with abundant deposits of intra and extracellular mucin in areas where neoplastic cells are identified[5]. Its evolution is not well defined, so it can have a rapid or slow growth, sometimes presenting painful, "cold" thyroid nodules, with or without palpable regional lymph nodes[1,3]. In our case, we observed the extrathyroid infiltration of tumor cells with the presence of areas of necrosis and mucin lakes with high mitotic rates in addition to their differentiation from signet ring

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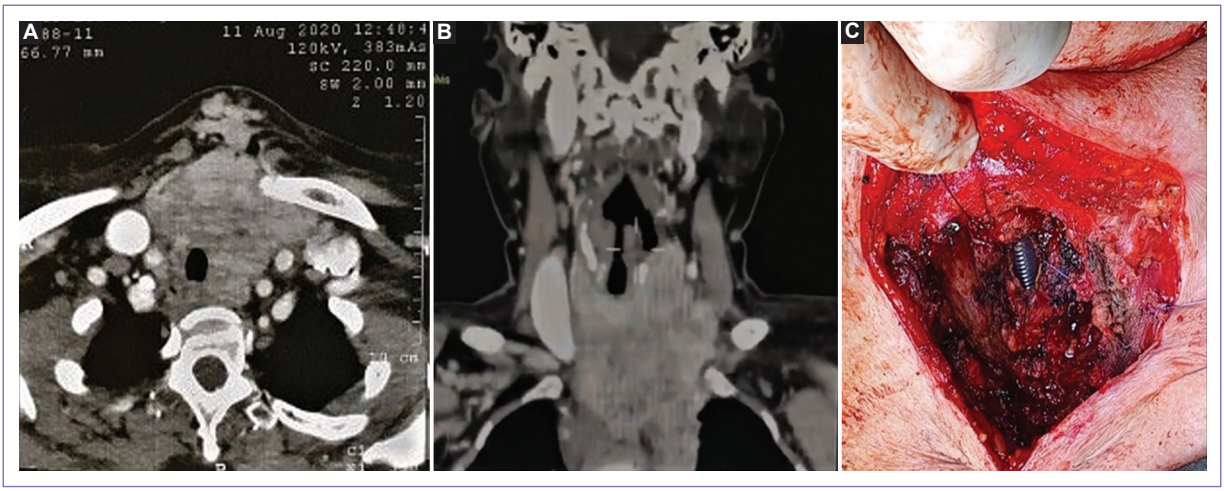

Figure 1. **A-B:** tomography Scan. **C:** tracheal invasion.

cells. Immunohistochemical studies performed through immunostaining techniques on paraffin sections with monoclonal antibodies, using the Maz Polymer Detetion system revealed negative thyroglobulin, PAX8, and thyroid transcription factor (TTF)-1; however, after having investigated and ruled out the primary origin of some other tumor presented in the patient, we classified the cancer as primary due to the clinical and histological characteristics that she presented.

Case report

A 68-year-old woman who was admitted to our hospital due to dyspnea and laryngeal stridor for 1 week that exacerbated the last 48 h, as well as dysphonia and a large cervical tumor of 6 months of evolution. A computed tomography (CT) scan showed a large pretracheal tumor that encompassed the thyroid, surrounding the trachea and esophagus bilaterally (Figure 1A). Heterogeneous image poorly defined in relation to the lower limit of the thyroid gland that extended to the superior frontal mediastinum without cleavage plane, 15 × 12 cm (Figure 1B), no invasion of the tracheal or esophageal lumen was evidenced, which suggested that the symptoms occurred due to compression; abdomen and pelvis did not present pathology. Fibrolaryngoscopy revealed paralysis in the right vocal cord. The fine needle aspiration-biopsy resulted in an undifferentiated neoplasm. In laboratory tests, thyroid stimulating hormone was found elevated to 8423 IU/mL (normal = 0.55-4.78 IU/mL), while T3 and free T4 were at normal levels; antithyroglobulin and antithyroperoxidase antibodies were elevated (antithyroglobulin > 500 U/ml and antithyroperoxidase antibody > 1000 U/ml), and the calcium and calcitonin parameters were within normal values, no relationship was found to medullary carcinoma or metastatic carcinoma. Personal history: in 2000 a quadrantectomy of the right breast was performed for infiltrating ductal carcinoma. Sixteen years later, the patient underwent quadrantectomy of the left breast and ipsilateral axillary dissection; the biopsy was a lobular carcinoma. She continued with follow-up and without tumor recurrence.

The case was interpreted as a thyroid neoplasm versus a breast cancer metastasis. It was decided to perform an emergency tracheostomy using an anterior cervical approach. The patient underwent partial excision of the pretracheal tumor that included thyroid, infiltrated peritracheal soft tissues, mediastinum, and muscles, being unresectable; so we added a tracheostomy (Figure 1C). The histopathology of the 8 × 7 × 8 cm specimen presented mucoid appearance with brown areas; under the microscope, it consisted of a neoplastic epithelial proliferation of round and signet ring cells that arranged in a solid architectural pattern, forming lobes with areas of necrosis, and mucin lakes with high mitotic rates. Extensive infiltration of soft tissues (adipose, muscular, and tracheal fibroconnective), thyroid, and parathyroid tissue being compatible with a mucinous carcinoma with signet ring cells (Figure 2A-C). It was observed by immunohistochemistry: diffuse GATA3 (+++), estrogen receptor (-), progesterone receptor (-), HER2 (-), KI67 (90%), cytokeratin 7 (-), cytokeratin 20 (+++), cytokeratin AE1/AE3 (++), TTF-1 (-),

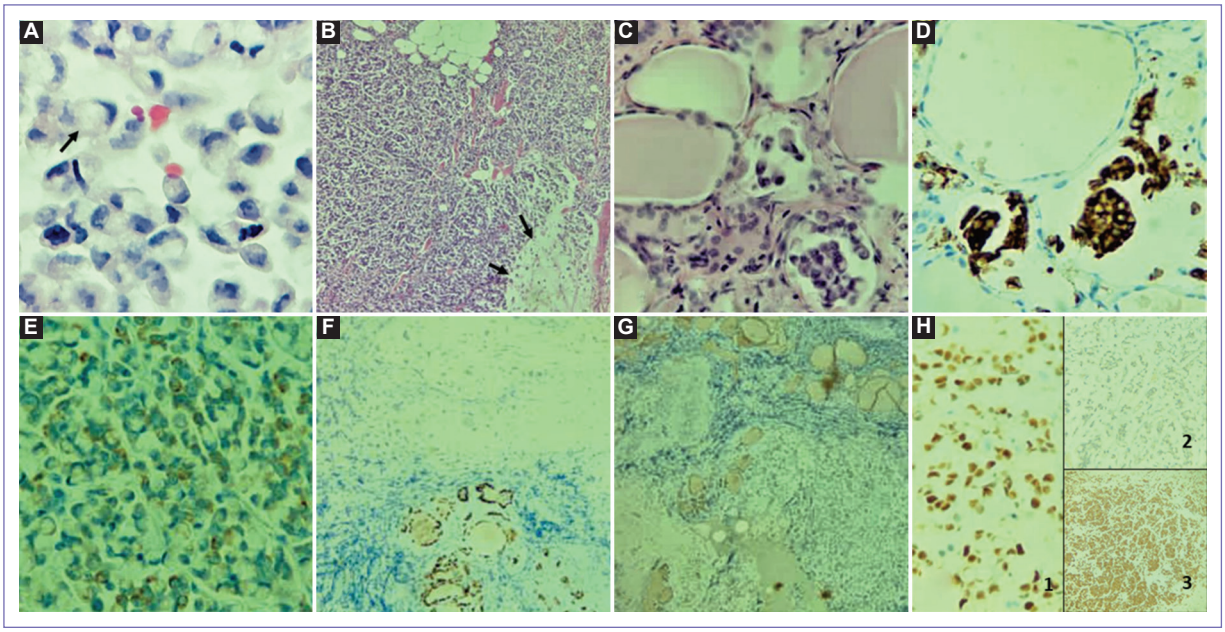

Figure 2. **A:** H&E, ×40. Signet ring cells suspended in mucin lakes (arrow). **B:** H&E, ×20. Mucin lakes (arrows) with adipose and muscle tissue infiltrated by the neoplasm. **C:** H&E, ×10 thyroid follicles infiltrated by the carcinoma. **D:** MUC2 **E:** AE1/AE3 **F:** TTF1 **G:** Thyroglobulin **H:** 1:GATA3, 2: cytokeratin 7, 3: cytokeratin 20.
H&E: hematoxylin-eosin; MUC2: mucin-2 secretory glycoprotein; AE1/AE3: mixture of two monoclonal antibodies AE1 and AE3; TTF1: thyroid transcription factor 1; GATA3: GATA Binding Protein 3 is a protein coding gene.

PAX8 (-), calcitonin (-), thyroglobulin (-), and diffuse MUC2 (+++) (Figure 2D-H). She evolved favorably during the immediate post-operative period until she died 12 days later from a pulmonary embolism despite being anticoagulated.

Discussion

The production of mucin in the thyroid is an infrequent event that, if it occurs, is associated with common neoplasms of the gland such as follicular, papillary, mucoepidermoid or medullary carcinoma, and even adenomas[2,3]. This tumor, first described by Díaz-Pérez in 1976[4], is characterized by presenting a group of neoplastic cells surrounded by extracellular mucin deposits that are mixed with areas of typical thyroid carcinoma[5]. The most common clinical manifestation of this tumor is goiter, depending on the size and aggressiveness, they may present dysphonia or dyspnea[3,6]. The phenomenon of mucin appearance is attributed to the intraplasmic storage of altered thyroglobulin[6]; however, other authors consider that it is due to a double differentiation of tumor cells as a combination of mucin secretion and endocrine function, a cause also described in gastrointestinal mucinous tumors[1,7]. Other possible explanations for its appearance would be the persistent development of the last branchial body, by intrathyroid embryonic remains of salivary glands and remains of the thyroglossal duct, solid cell nests, or overexpression of the gene (RNA MUC1), especially in cases of papillary carcinomas[8]. The diagnosis is made by observing the signet ring cells found in mucin lakes, in addition to confirming the focal expression of thyroglobulin and TTF-1; however, this expression is not always positive, as it occurs in our case. The differential diagnosis arises with metastasis of mucinous carcinomas (lung-breast-colon-pancreas)[9], for which this possibility was studied, reaching the conclusion that the current case is not related to the lobular breast carcinoma that was presented as a history, because of this it is considered a primary tumor. Due to the way the case was presented, an emergency tracheostomy was performed, so there are no previous records of hormonal indications. According to the previously published cases[1,2] (Table 1), it is described that metastases are frequent, the prognosis is unfavorable, there is a poor response to radiotherapy or chemotherapy, and there is a 50% mortality with high recurrence[1,3].

Table 1. Reported primary mucinous carcinomas

Case	Authors	A/S	Tumor size	Treatment	Metastasis	Follow up
1	Diaz-Perez et al. (1976)	44/M	5×4×3 (right)	Hemithyroidectomy, then Total thyroidectomy+ND	NM	7 years, NED
2	Sobrinho et al. (1986)	56/M	8×6×2 (left)	Total thyroidectomy+ND	LN(+), Lung(+), Spine(+)	1 years, recurrence (intestine-lung), Tx: RT y QT. 2 years, DOD
3	Cruz et al. (1991)	32/F	6×2.5×1.5	Total thyroidectomy+ND	LN(+), Lung(+), Skin(+)	2 months, recurrence (thyroid, skin, lung), Tx: I^{131}, RT and QT. 8 months, DOD
4	Kondo et al. (2005)	82/F	3×2×2 (right)	Hemithyroidectomy+ND	LN(+), Skin(+)	2 years, recurrence (LN y skin), Tx: Surgery, I^{131}. 4 years, DOD
5	D' Antonio et al. (2007)	62/F	NM	Total thyroidectomy+ND (incomplete)	LN(+)	6 months, DOD
6	Mnif et al. (2013)	56/M	4×3×2 (left) 3×3×2 (left)	Total thyroidectomy+ND (incomplete)	LN(+)	1 month, DOD
7	Matsuo et al. (2016)	81/F	NM (right)	Thyroidectomy	LN(+)	10 months, recurrence (LN), Tx: re operation+ TSH supression. 6 years, NED
8	Bajja et al. (2017)	74/M	3.5×2.5 (left)	Total thyroidectomy+ND	LN(+), Lung(+)	4 months, DOD
9	Wang et al. (2018)	74/F	5.6×4×2.5 (right) 2.2x1.5x0.8 (left)	Total thyroidectomy+ND	LN(+)	9 months, DOD
10	Puerto L et al. (2019)	66/F	NM	Total thyroidectomy+ND	NM	6 months, NED
11	Present case	68/F	8×7×8	Partial thyroidectomy + tracheostomy	Extra thyroid infiltration (+)	12 days, DOD

A/S: age (years)/sex; M: male; F: female; LN: lymph node; ND: neck disection; NED: no evidence of disease; DOD: died of disease; RT: radiotherapy; QT: chemotherapy; Tx: treatment; NM: not mentioned; TSH: thyroid-stimulating hormone.

Conclusion

We present the case of a mucinous carcinoma of the thyroid with signet ring cells and we highlight that it is rare. The diagnosis is based on the histopathological study and immunohistochemistry with a positive TTF-1 and thyroglobulin; however, it is sometimes negative, with the presence of ring cells and mucin lakes being the main diagnosis, as in our case.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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