CLINICAL CASE

Intrathyroidal thymic carcinoma misdiagnosed as a medullary thyroid carcinoma

Carcinoma tímico intratiroideo diagnosticado erróneamente como carcinoma medular de tiroides

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Abstract

The intrathyroidal thymic carcinoma is a rare neoplasm. The probable origin of this neoplasm is the presence of ectopic thymic tissue or remnants of the third and fourth branchial arch. The case of a 49-year-old female with an initial diagnosis of medullary thyroid cancer is presented. When she was operated for regional recurrence, 16 years later, the pathology report demonstrates the presence of a intrathyroidal thymic carcinoma. Intrathyroidal thymic carcinoma is considered an independent type of thyroid carcinoma because this entity has specific clinical-pathological characteristics similar to thymic carcinomas and different prognosis than known thyroid carcinomas. We present the case of a patient initially treated as having a medullary thyroid carcinoma who, upon presenting recurrence, the presence of intrathyroidal thymic carcinoma was demonstrated.

Key words: *Intrathyroidal thymic carcinoma. Carcinoma showing thymus-like differentiation. Thyroid cancer. Carcinoma showing thymus-like differentiation. Case report*

Resumen

El carcinoma tímico intratiroideo es una neoplasia rara. El origen probable de esta neoplasia es la presencia de tejido tímico ectópico o de restos del tercer y cuarto arcos branquiales. Se presenta el caso de una mujer de 49 años con diagnóstico inicial de cáncer medular de tiroides. Cuando fue operada por recurrencia regional, 16 años después, se demostró la presencia de un carcinoma tímico intratiroideo, que se considera un tipo independiente de carcinoma tiroideo debido a que tiene características clínico-patológicas específicas similares a los carcinomas tímicos y un pronóstico diferente a los carcinomas de tiroides conocidos. Este caso se trató inicialmente como carcinoma medular de tiroides y al presentar recurrencia se demostró la presencia de un carcinoma tímico intratiroideo.

Palabras clave: *Carcinoma tímico intratiroideo. Carcinoma tiroideo con diferenciación similar al carcinoma tímico. Cáncer de tiroides. CASTLE. Reporte de caso.*

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Introduction

Intrathyroidal thymic carcinoma or carcinoma showing thymus-like differentiation (CASTLE) is a rare neoplasm, first described in 1985 as an intrathyroidal thymoma similar to squamous cell carcinoma[1,2]. It has been recognized as an independent clinic pathologic entity by the WHO. The probable origin of this neoplasm is the presence of ectopic thymic tissue or remnants of the third and fourth branchial arch[3,4]. This pathology has not been adequately characterized due to its rarity and difficult diagnosis, currently < 100 cases have been reported in the literature. In this sense, we describe the case of a 49-year-old female with an initial diagnosis of medullary thyroid cancer. When operated on for regional recurrence, 16 years later, the pathology report demonstrate the presence of a intrathyroidal thymic carcinoma.

Case report

A Peruvian 49-year-old female patient, with no relevant medical history, who had a total thyroidectomy back in 1997 for a medullary thyroid cancer. Subsequently, she maintained periodic controls without evidence of recurrence. In 2013, she complained about the appearance of a mass in the cervical region and mild pain. The preferential physical examination of the neck showed a 6 cm tumor in the left supraclavicular region with extension to the ipsilateral pre and paratracheal region, the rest of the examination was negative.

The neck computed tomography scan showed a 6 cm neoformative lesion, located at the level of the left IV to VII groups which displaced the trachea toward the right side and remodeling it's left lateral wall. Laboratory tests reported thyroid-stimulating hormone: 47.88 uU/mL, T4: 0.72 ng/dL, and calcitonin: 2.6 pg/mL. Fine-needle aspiration biopsy was compatible with medullary carcinoma. However, due to the incongruence between the low values of calcitonin during the patient's follow-up and the pathology reports, pathology and cytology slides were reviewed concluding that it was a poorly differentiated thyroid carcinoma.

The patient underwent cervical exploration and partial tumor resection due to vascular and soft-tissue involvement. The pathology report of the operative specimen reported on this occasion lymph node metastasis from thyroid CASTLE, it was associated with extracapsular extension and the immunohistochemistry analysis showed positivity for pankeratin, CD117, CD5, and negativity for thyroglobulin, thyroid transcription factor (TTF1), calcitonin, and chromogranin. The laminae from the first surgery (total thyroidectomy) were reviewed concluding that they had the same immunophenotype as the resected metastasis (Figs. 1 and 2).

The patient received adjuvant external beam radiotherapy in cervical and mediastinal field. She received the dose of 4500 cGy in 25 sessions, 5000 cGy at the neck, and boost in oblique fields until reaching 6000 cGy, with adequate tolerance. At present, 5 years after the recurrence treatment, the patient is asymptomatic in periodic follow-ups and free of disease recurrence. Figure 3 summarizes the timeline on the patient's treatment.

Discussion

Intrathyroidal thymic carcinoma is a rare tumor of the thyroid gland and soft tissues of the neck[5]. The etiology of this neoplasm is little known, however, it is known that during embryological development, the primordial thymic tissue that derives from the third and fourth branchial sac migrates through the neck to the mediastinum. Then, the persistence of thymus remanents along this path of migration can manifest as ectopic tissue[6]. It is believed that these tumors arise from this ectopic tissue and retain the potential to differentiate along the thymic line, but it is unknown how it acquires the potential to develop into malignant neoplasms[7].

This neoplasm usually affects middle-aged adults, with a slight preponderance by the female sex (M:F ratio of 1:1.3), as the reported 49-year-old patient[1]. Intrathyroidal thymic carcinomas are generally indolent and less aggressive than squamous cell carcinoma of the thyroid, with better survival curves reported in the literature[8]. This type of carcinomas is characterized by slow growth but may present recurrent and metastatic disease. Ge et al. reported the presence of cervical lymph node metastasis in 22 of 81 evaluated patients with CASTLE[1,9].

The pre-operative diagnosis of thyroid tumors is based on physical examination, imaging, and aspiration cytology. The physical examination usually demonstrates the presence of hard, non-mobile thyroid masses, and extrathyroidal extension may be present[10]. Yamamoto et al. reported that ultrasound findings in patients with CASTLE are similar to other thyroid neoplasms, in their report, they described solid, hypoechoic tumors with heterogeneous echoes, without cystic components or calcifications[9]. In tomographic studies, the tumor usually shows a soft-tissue density, is well defined, with slight uptake of the

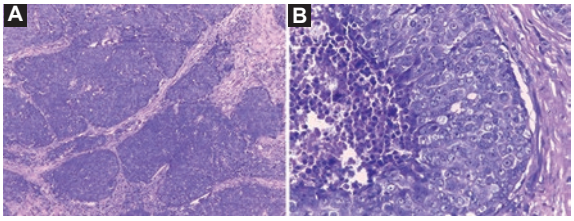

Figure 1. *Microphotography, hematoxylin-eosin stain.* **A:** *accumulation of squamous epithelial cells of scaly appearance delimited by bands of fibroconnective stromal tissue.* **B:** *presence of lymphocyte and plasma cell infiltrate in the tumor tissue.*

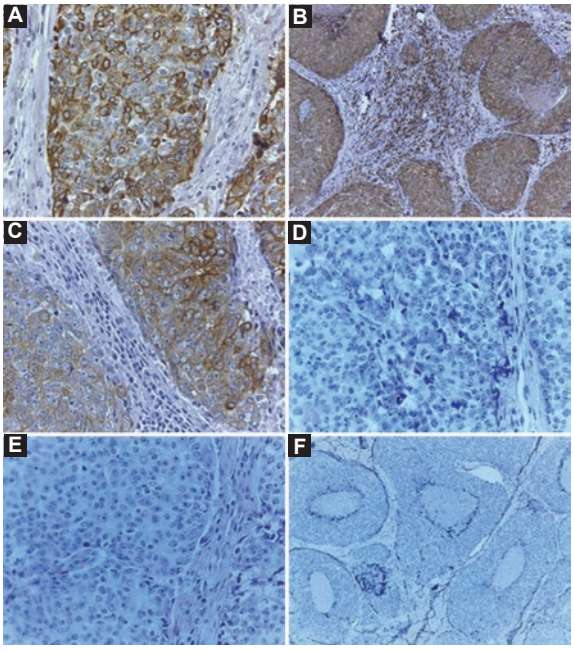

Figure 2. *Immunohistochemistry.* **A:** *positive pankeratin,* **B:** *positive CD5,* **C:** *positive CD117,* **D:** *negative thyroid transcription factor 1,* **E:** *negative thyroglobulin,* **F:** *negative calcitonin.*

contrast substance, similar characteristics as the findings of the presented case. Magnetic resonance images show isointensity in the T1-weighted images and hyperintensity in the T2 enhanced images[7].

The pre-operative cytological diagnosis of intrathyroidal thymic carcinoma has not been widely described in the literature, so there is no reliable criteria[6]. Hirokawa et al. described the cytological characteristics of eight cases of thyroid carcinoma with pseudothymic differentiation; of which six had an initial cytological diagnosis of poorly differentiated carcinoma[7]. Some reports indicate that intrathyroidal thymic carcinoma should be suspected in the differential diagnosis of poorly differentiated thyroid carcinomas and this was established with immunohistochemistry in our case[9,10].

Histologically, different names have been used to describe intrathyroidal thymic carcinomas, among which are carcinoma showing pseudothymic elements (CASTLE), carcinoma with pseudothymic differentiation, primary thymoma of the thyroid, CD5-positive thyroid carcinoma, and thyroid carcinoma-like lymphoepithelioma. Macroscopically, this tumor has undefined lobulated edges, fibrous septa, hard consistency, and grayish-white color. Microscopically, the cells have different shapes and sizes, they have elongated nuclear vesicles and the epithelial cells are separated by fibrous septum, as well as the infiltration of lymphocytes and plasma cells[10]. The tumor cells show characteristics similar to squamous cells and have eosinophilic cytoplasm. In the presented case, the pathology study of the cervical recurrence revealed accumulations of squamous epithelial cells of scaly appearance delimited by strips of fibroconnective stromal tissue with the presence of lymphocytes (Fig. 1). The differential diagnosis should include squamous cell thyroid carcinoma, papillary thyroid carcinoma, medullary thyroid carcinoma, and anaplastic thyroid cancer. The final diagnosis should include immunohistochemistry studies, in which the tumor cells stain were positive for CD5, cytokeratin, p63, and p53 and were negative for TTF1, thyroglobulin, and calcitonin. The expression of CD5 is given by Hassall's corpuscles being an important characteristic of this type of tumors[10]. In the reported case, the immunohistochemistry study showed positive CD5, positive pankeratin, positive CD117, negative thyroglobulin, negative TTF1, negative calcitonin, and negative chromogranin (Fig. 2), this supports the final diagnosis of CASTLE.

Due to the rarity of this neoplasm, there is no consensus for treatment, however, in majority of reported cases, surgical treatment is important for loco regional control, and adjuvant treatment with chemotherapy and radiotherapy is not frequently used. In this case, the patient had initial surgical treatment in the context of a thyroid cancer, when the disease recurred, he was treated with surgery and radiotherapy due to the presence of unresectable disease, achieving good loco regional control until now.

There are no guidelines for the post-operative management and follow-up of intrathyroidal thymic carcinoma. However, clinical examination and imaging studies have been used in the cases reported. One study reported a disease recurrence rate of 18.57% in 82 patients with intrathyroidal thymic carcinoma[9], these being more frequent when lymph node involvement at diagnosis[8]. In the reported case, the follow-up

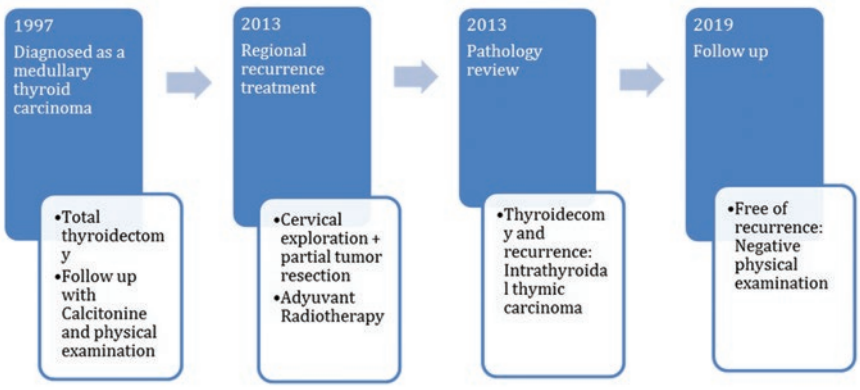

Figure 3. *Timeline: patient's diagnosis, treatment, and follow-up.*

was carried out by physical examination, ultrasound, and cervical tomography, which were negative for disease recurrence. The monitoring of tumor markers such as thyroglobulin was not taken into account since they are not characteristic of this neoplasm[1,2].

Some limitations in the handling of this case can be considered: the lack of clinical suspicion and limited immunohistochemistry in 1997. However, due to the high grade of suspicion, and diagnosis confirmation, a timely treatment was made. This was reflected in a total survival of 23 years and an optimal quality of life, as reported by the patient in her last control of December 2019.

Conclusions

Intrathyroidal thymic carcinoma is considered an independent type of thyroid carcinoma according to the WHO. It should be included in the differential diagnosis of thyroid tumors that clinically appear to be undifferentiated. This entity of difficult diagnosis has specific clinicopathological characteristics similar to thymic carcinomas, therefore, a different prognosis to known thyroid carcinomas, which is good despite not expressing a classic differentiated component.

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 the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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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