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Anaplastic thyroid cancer with prolonged survival. Report of a clinical case

Carcinoma anaplásico de tiroides con supervivencia prolongada. A propósito de un caso

Anaplastic thyroid cancer (ATC) is an uncommon and extremely aggressive undifferentiated tumour derived from the follicular epithelium. It has an annual incidence of one to two cases per million inhabitants and represents 1%–2% of all thyroid cancers.[1] It generally manifests in a person's fifties and sixties, with a higher incidence in women. The risk factors for the diagnosis of ATC are, on the one hand, low educational level and previous goitre (both factors probably related to iodine deficiency), blood group B and obesity.[2,3]

We present the case of a 76-year-old woman with personal history of interest of a sliding hiatal hernia and gastro-oesophageal reflux, who was admitted to the intensive care unit in June 2020 due to a 15-day history of progressive dyspnoea associated with a non-productive cough and dysphagia for solids. The patient's vital signs at the time of admission were blood pressure 190/120 mmHg, heart rate 135 bpm and basal oxygen saturation 65%, for which she required orotracheal intubation and connection to a mechanical ventilation system. After ruling out SARS-CoV-2 infection, computed tomography angiography was performed, which excluded pulmonary thromboembolism, revealing the presence of a hypodense mass that seemed to be attached to the right thyroid lobe, suggestive of a neoformative process. The study was completed with computed tomography (CT) of the neck, where a solid, hypodense, heterogeneous mass was observed with calcifications measuring 43 × 34 × 44 mm that caused invasion of the tracheal lumen by infiltration of the right posterolateral wall of the trachea without lateral cervical lymphadenopathy of significant size. In view of the clinical suspicion of ATC, it was decided to perform a core needle biopsy (CNB), with tissue fragments composed predominantly of avascular necrosis obtained, with small foci of plasmacytoid-type tumour cells, with abundant cytoplasm and nucleus displaced to the periphery. In the immunohistochemical study, weak nuclear positive expression was observed for PAX-8 and TTF 1 and weak expression for CD56, with absence of expression for thyroglobulin, calcitonin, synaptophysin and chromogranin. The Ki-67 proliferation index score was low, but the interpretation was doubtful due to the presence of intense necrosis in the sample. With these findings, ATC was diagnosed. An ^{18F}-fluorodeoxyglucose positron emission tomography (FDG PET) scan was performed, revealing a right cervical mass with increased metabolic activity with an SUV_{max} of 28.5 and images suggestive of multiple bilateral pulmonary, lymph node (in the right supraclavicular and left axillary area), muscular and right atrium metastases (Fig. 1A).

After the diagnosis of ATC and awaiting the molecular study to detect the $BRAF^{V600}$gene mutation, which was positive, in June 2020 the patient received two cycles of systemic chemotherapy with carboplatin and paclitaxel and two cycles of palliative radiotherapy (RT) on the thyroid lesion, adding a margin of 1 cm for active bleeding from the tracheostomy, with a total dose of 16 Gy. She also received nutritional support with percutaneous endoscopic

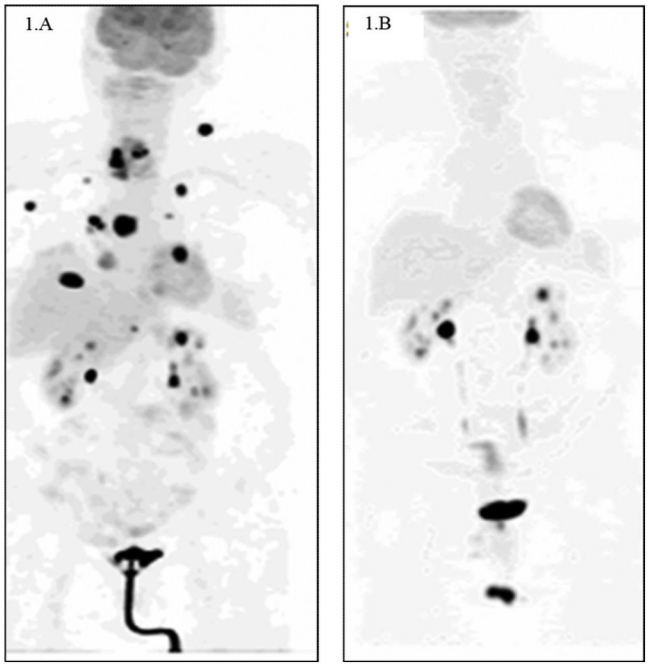

Figure 1 A) ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) on diagnosis. A right cervical mass with increased metabolic activity with an SUV_{max} of 28.5 and images suggestive of multiple bilateral pulmonary, lymph node (in the right supraclavicular and left axillary area), muscular and right atrium metastases. B) FDG PET after 11 months of treatment with BRAF/MEK inhibitors (dabrafenib-trametinib). Morpho-metabolic involution of the right cervical mass with disappearance of the metastatic lesions at all levels is observed.

gastrostomy (PEG). In July 2020, treatment was started with dabrafenib 300 mg daily + trametinib 20 mg daily in a PEG-adapted liquid formula, with a favourable clinical response. After 11 months of treatment with BRAF/MEK inhibitors, the control FDG PET showed a morpho-metabolic involution of the right cervical mass with disappearance of the metastatic lesions at all levels (Fig. 1B). In August 2021, a total thyroidectomy was performed without complications, with a pathology result of a total thyroidectomy specimen with areas of fibrosis without evidence of residual neoplasia. At the present time, the patient is stable, with no evidence of recurrence of her underlying process and she does not require PEG or tracheostomy.

ATC is a tumour that has classically had a very poor prognosis, with an overall survival of 20% one year after diagnosis,[4] and that used to cause more than half of the deaths associated with thyroid cancer despite its low incidence. Survival two years after diagnosis is very rare, although there are case series published prior to the use of BRAF/MEK inhibitors that describe 10-year survival ranging from 3% to 10% in patients without metastatic disease, unlike our case.[5,6]

The great advances made in our understanding of ATC have led to a paradigm shift in the management of this disease that has been reflected in the guidelines published in recent years.[7,8] Firstly, in stages IVa and IVb, if the tumour is considered resectable, a surgical approach should be taken, with a total thyroidectomy performed with prophylactic or therapeutic central-lateral lymphadenectomy,[7,8] taking into account that more aggressive surgeries including laryngectomy or tracheal or oesophageal resections are not routinely recommended.[8] In stage IVc ATC, palliative surgery can be considered in selected cases such as preventive procedures in which there is an imminent compromise of the airway, or resections of locoregional disease due to symptomatic metastatic disease or in cases with few distant metastases.[8] Finally, in those cases with unresectable ATC during the initial evaluation, if, after the administration of RT, systemic chemotherapy or BRAF/MEK inhibitors, there is a possibility of surgery, surgical treatment should be reconsidered,[8] as happened in our case, in which the tumour was initially considered unresectable due to extensive locoregional and metastatic involvement, with a total thyroidectomy performed after 13 months of systemic treatment due to the patient's excellent clinical response. This therapeutic regimen of starting systemic therapy with BRAF/MEK inhibitors and subsequent surgery has been associated with an increase in overall survival.[9]

In stage IVc ATC, systemic chemotherapy with doxorubicin, taxanes (including paclitaxel) and platinum derivatives has been considered the treatment of choice, either alone or in combination with intensity-modulated RT.[8] In our case, pending the results of the genetic study, treatment with systemic chemotherapy was started and palliative RT was administered due to tumour bleeding. Before starting systemic treatment, all patients with ATC should be evaluated for the $BRAF^{V600}$ mutation, which is present in more than 70% of cases,[10] in order for targeted therapy with BRAF/MEK inhibitors (dabrafenib and trametinib), approved since 2018 by the US Food and Drug Administration (FDA), to be considered for the treatment of $BRAF^{V600}$-mutated ATC patients. As stated in the Clinical Practice Guidelines published in 2021 by the *American Thyroid Association*,[8] this treatment is indicated as first choice in $BRAF^{V600}$-mutated patients with unresectable stage IVb and stage IVc ATC, rejecting RT with a strong strength of recommendation.

In conclusion, the multidisciplinary approach and the therapeutic advances in recent years in the management of patients with ATC have contributed to improving overall survival in these cases, even in patients with advanced stages of the disease.

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Active surveillance in lymph node small cell neuroendocrine carcinoma

Vigilancia activa de carcinoma neuroendocrino de celulas pequeñas de ganglio linfático

While most small cell neuroendocrine carcinomas (SCNEC) arise from the bronchopulmonary tree, some have other origins. Primary SCNECs of lymph nodes are extremely rare. To date, only a few cases have been reported. Management of this condition is quite challenging since no clinical guidelines are available or published, and good-quality evidence is lacking.

A 61-year-old male presented with a left inguinal mass of 4 months' evolution. Past medical history was unremarkable, except for urolithiasis, and he denied taking any medication. No risk factors were present (no exposure to tobacco) and there was no family history for neoplastic disease. He was asymptomatic, and at physical examination nothing relevant was found. Laboratory workup (complete blood cell count, renal function and electrolytes, hepatic tests, calcium-phosphorus metabolism, high sensitivity c-reactive protein, sedimentation rate, serum protein electrophoresis) was normal. Left inguinal ultrasonography showed a 4-cm well-circumscribed hypoechoic lesion, suggestive of adenopathy. Fine needle aspiration cytology revealed small to medium-sized blue cells with scant cytoplasm, pleomorphic nuclei, and molding. Surgical excision was performed, and anatomopathological analysis established the diagnosis of small cell neuroendocrine carcinoma: immunohistochemistry showed positivity for synaptophysin, CK AE1/AE3 (perinuclear dot-like stain), CAM5.2, chromogranin and was negative for TTF-1 and CK20, with a Ki-67 score of 80–90% (Fig. 1).

A metastasis of SCNEC was suspected, and a thorough search for primary tumor was conducted: repeated dermatological assessment of inguinal region and left inferior limb showed no abnormalities; upper and lower endoscopic studies were normal; computed tomography (CT) and magnetic resonance imaging (MRI) of neck, thorax, abdomen and pelvic region did not reveal any suspicious lesion; 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) study had no abnormal radiopharmaceutical uptake. Heterogeneous radiopharmaceutical hypercaptation at prostate topography on 68Ga DOTA-TOC PET was found (Q.SUVmax = 7.5). In face of this finding, multiple prostate biopsies were performed, revealing bilateral atrophy and chronic inflammation, with no evidence of malignancy or prostatic intraepithelial neoplasia. Serum chromogranin A was 23 ng/mL (RR < 102), and every other hematological, biochemical, and immunological studies were normal. Chemotherapy, radiation therapy, or other adjuvant treatments were not performed. An active surveillance strategy was decided with patient agreement. He remains disease-free after a 40-month follow-up period. We opted, in a multidisciplinary team setting, to conduct follow-up with clinical and analytical evaluations, including inflammatory markers, and yearly CT/MRI imaging and 18F-FDG PET-CT scan.

Extrapulmonary small cell carcinoma are uncommon malignancies with a reported incidence between 2.5–5.0% of small cell carcinoma cases and 0.1–0.4% of all malignancies.[1] They can occur in almost all sites of the body, mainly gastrointestinal and genitourinary systems.[2] SCNEC usually present as aggressive high-grade tumors with dismal prognosis. Small cell carcinoma located exclusively in a lymph node or multiple lymph nodes without any evidence of a primary tumor are even rarer, our comprehensive literature review yielded less than 20 cases reported to date.

Lymph node SCNEC's origin is very peculiar since, in normal circumstances, neuroendocrine cells are absent from lymph nodes. It could arise from a multipotent stem cell or due to a primary cancer elsewhere in the body with secondary metastases to the lymph node and spontaneous regression of the primary lesion.

Everson and Cole first described, in 1956, spontaneous cancer regression.[3] Should our patient's primary tumor had undergone spontaneous regression, diagnosis could have been established from the metastatic lesion. However, given the tumor's extremely high grade (Ki67 80–90%), it's likely that recurrence would have to become obvious after surgical resection.

Merkel cell carcinoma (MCC), an aggressive primary neuroendocrine malignancy of the skin, disseminates frequently to regional lymph nodes. MCC has also been found in inguinal lymph nodes in the absence of a primary site[4]. In our case, physical examination did not reveal any suspicious primary skin lesion and there was an absence of reactivity of malignant cells for cytokeratin 20, so a MCC is rather improbable.

Our first approach was to rule out an occult primary tumor. Exhaustive investigation was innocent and included clinical, analytical, and radiological evaluations, as well as functional exams (including 18F-FDG PET and a somatostatin receptor PET tracer). Also, after 40 months, our patient maintains an excellent general condition with a normal CT scan and absence of uptake in 18F-FDG PET.

The main difference between extrapulmonary SCNEC located in other organs compared with lymph node SCNEC seems to be the latter's better prognosis.[5,6] Despite being a very rare entity, its identification is crucial because adequate treatment can lead to favorable clinical outcomes.

Although there's no standard treatment, several approaches have been proposed according to the site and stage of the tumor, the patient, and the physician. In the literature, surgery, radiotherapy, chemotherapy, or a combination of these treatments remain the therapeutic options available.[6] Immune checkpoint inhibitors were used with a favorable clinical response in other extra-