









# New-onset thyrotoxicosis in a patient with anaplastic thyroid carcinoma: a diagnostic challenge

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## Summary

Anaplastic thyroid cancer (ATC) is the type of thyroid cancer that has the worst prognosis. It usually presents as a rapidly growing cervical mass that generates compressive symptoms. Its association with thyrotoxicosis is rare. A 76-year-old woman, with no contributory history, presented with a 3-month course of fast-growing cervical tumor, associated with tenderness, cough, and weight loss. Physical examination revealed goiter, localized erythema, and a painful and stone tumor dependent on the right thyroid lobe. Due to the malignant findings of the thyroid ultrasound, the patient underwent a thyroid core needle biopsy, which indicated ATC. Laboratory tests revealed leukocytosis, decreased thyroid-stimulating hormone, elevated free thyroxine (fT4), and increased thyroperoxidase (TPO) antibodies. At the beginning, we considered that the etiology of thyrotoxicosis was secondary to subacute thyroiditis (SAT) after SARS-CoV-2 infection, due to the immunochromatography result and chest tomography findings. The result of markedly elevated TPO antibodies left this etiology more remote. Therefore, we suspected Graves' disease as an etiology; however, thyroid histopathology and ultrasound did not show compatible findings. Therefore, we suspect that the main etiology of thyrotoxicosis in the patient was the destruction of the thyroid follicles caused by a rapid invasion of malignant cells, which is responsible for the consequent release of preformed thyroid hormone. ATC is a rare endocrine neoplasm with high mortality; it may be associated with thyrotoxicosis, whose etiology can be varied; therefore, differential diagnosis is important for proper management.

## Learning points:

- Anaplastic thyroid cancer is the thyroid cancer with the worst prognosis and the highest mortality.
- The association of anaplastic thyroid cancer with thyrotoxicosis is rare, and a differential diagnosis is necessary to provide adequate treatment.
- Due to the current pandemic, in patients with thyrotoxicosis, it is important to rule out SARS-CoV-2 as an etiology.
- Anaplastic thyroid cancer, due to its aggressive behavior and rapid growth, can destroy thyroid follicular cells, generating preformed thyroid hormone release, being responsible for thyrotoxicosis.

## Background

Anaplastic thyroid cancer (ATC) is one of the most aggressive endocrine neoplasms. It has the worst prognosis, with a specific mortality rate close to 100% (1). Usually, its clinical presentation is a rapidly growing cervical mass in patients over 50 years of age, associated with compressive symptoms such as dyspnea, dysphonia, and dysphagia. Distant metastases are found in 50% of cases at the time of diagnosis (1). Case reports associated with thyrotoxicosis are rare (2, 3).

Thyrotoxicosis is a state of inappropriately high levels of circulating thyroid hormones in the body. The clinical presentation varies from a subclinical state to a life-threatening thyroid storm. Typical symptoms are due to a hypermetabolic state and include weight loss, heat intolerance, and palpitations. Differential diagnosis requires a complete physical examination, laboratory studies, and imaging to determine the etiology (4).

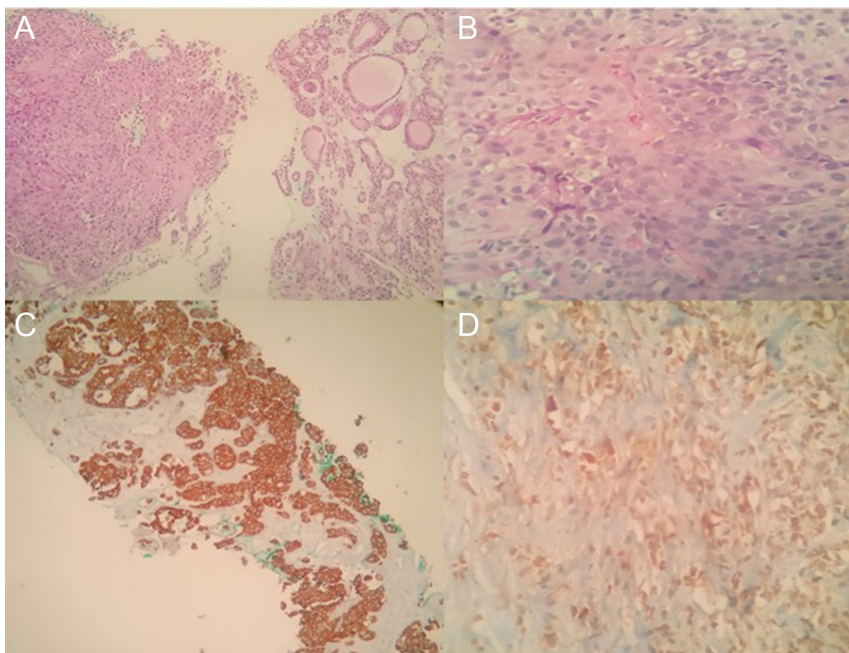
In this study, we present a case report of a patient diagnosed with ATC, who developed new-onset thyrotoxicosis, being the etiology, a challenge for endocrinologists.

## Case presentation

A 76-year-old female Peruvian patient, with noncontributory pathological, surgical, and family history, was brought by her relatives to the emergency room (ER) of Social Security Hospital in Peru. The patient

stated that she noticed a palpable painless neck mass of 2 × 3 cm on the right side associated with a demanding dry cough for the last 3 months; nevertheless, she decided not to go to the hospital due to quarantine regulations caused by the current COVID-19 pandemic. Two months before admission to ER, the size of the cervical tumor increased, becoming visible; she was associated with hyporexia, chills, and night sweats. Then, 1 month later, the patient had cervical pain of moderate-intensity, radiating to her ipsilateral jaw, and she also lost weight of up to 5 kg.

The patient attended to a private doctor who requested a thyroid ultrasound. The findings showed that the entire right thyroid lobe was found to have a mixed solid mass measuring 72 × 62 × 53 mm, with lobulated edges and thick calcifications, whose anteroposterior axis was greater than the transverse axis, with Doppler flow present. In the left thyroid lobe, four irregular solid nodules were found, with lobulated edges, without Doppler flow, and of sizes 16 × 9, 6 × 3.6, 8 × 6, and 4 × 5 mm, respectively. Likewise, loss of the fatty hilum was found in ganglion groups 3, 4, and 5. Given these findings, a thyroid core needle biopsy was requested. The cytological results (Fig. 1) were as follows: high-grade epithelioid malignancy, abundant cytoplasm, and nuclear pleomorphism. The immunohistochemical results were as follows: positive for vimentin, cytokeratin 7, and cyclin D1; weakly positive for thyroglobulin; and negative for CK20, TTF1, P53, calcitonin, chromogranin, synaptophysin, and embryonal carcinoma antigen. Finally, the diagnosis was ATC. Due to these new findings, the patient was referred to us.



**Figure 1**

Cytological findings of thyroid core needle biopsy. In image (A), hematoxylin–eosin staining of two totally different areas of the same organ is observed: on the right side, normal thyroid tissue, and on the left side, loss of integrity of the thyroid morphology compatible with neoplastic tissue. Image (B) shows the proliferation of epithelioid cells, irregular organization, nucleus, and pleomorphic cytoplasm. Immunohistochemistry was positive for cytokeratin 7 (C) and weakly positive for thyroglobulin (D). All these findings confirm the diagnosis of anaplastic thyroid cancer.



## Investigation

Upon admission to the ER, the patient had a blood pressure of 100/60 mmHg, heart rate of 98 b.p.m., respiratory rate of 20 breaths/min, body temperature of 36.8°C, and oxygen saturation at 98% (FiO<sub>2</sub>, 21%). Her physical exam results were as follows: non-exophthalmos, poor general condition and nutritional status, a height of 170 cm, and a body weight of 50 kg (17.3 kg/m<sup>2</sup>). At the cervical region, a grade III goiter was found with localized erythema and increased local temperature (Fig. 2), as well as a 7 × 6 cm painful stone tumor, with irregular borders, adhered to deep planes and dependent on the right thyroid lobe. The remainder of the physical examination was noncontributory. Blood tests (Table 1) and immunochromatography for SARS-CoV-2 were requested; the result was reactive for IgG.

## Treatment

Due to the initial suspicion of an infectious process of soft tissue at the cervical level, antibiotic treatment was started with ceftriaxone 2 g per day and clindamycin 600 mg q8h IV, as well as metamizole 1 g q8h IV, propranolol 40 mg q12h PO, and enoxaparin 40 mg subcutaneously every 24 h without improving symptoms.

## Outcome and follow-up

To clarify the etiology of thyrotoxicosis, immunological tests were requested (Table 1). In addition, for the staging of the background disease, we requested a neck and chest CT scan with contrast (shown in Figs. 3 and 4), in which a right thyroid mass was found with characteristics of malignancy and extension to the mediastinum, as well as cervical lymphadenopathy, thrombosis of the right internal jugular vein, bilateral metastatic pulmonary nodules, 'ground-glass' areas, mediastinal lymphadenopathy, pericardial



**Figure 2**  
Ectoscopy of the neck region. Size of the thyroid gland increases and erythema over the skin, attributable to cervical cellulitis.

effusion, and thrombosis in the superior vena cava and right pulmonary artery. In the cerebral and abdominal pelvic CT scan with contrast, no significant alterations were found. Thus, the clinical stage of the disease was IV C.

Unfortunately, she had a torpid evolution requiring high oxygen requirements without criteria for mechanical ventilation due to underlying disease. She died of acute respiratory failure 3 days after hospital admission.

## Discussion

ATC is responsible for the majority of deaths associated with thyroid carcinoma. It arises from the thyroid follicular cells, which do not retain their normal functions, such as iodine absorption and thyroglobulin synthesis, and also lose their dependence on TSH. The incidence is estimated at one to two cases per million per year. The incidence is estimated at one to two cases per million per year. Peak incidence is in the sixth and seventh decades of life, with most affected patients over 50 years of age and with a female to male ratio of 1.5:2 (5).

With regard to the immunohistochemical diagnosis of ATC, thyroglobulin and thyroid-lineage markers such as thyroid-transcription factor 1 are expected to be absent. Also, expression of another thyroid-lineage marker, such as PAX8, is retained in 40–60% of ATCs. Similar to papillary thyroid cancer, the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) somatic mutations are present in 40–70% of cases of ATC. Immunohistochemical detection of the most common *BRAF* mutation (*BRAF*-V600E) is specific and sensitive. Positive immunoreactivity for *BRAF*-V600E can support the diagnosis of ATC and can also serve as a surrogate for molecular testing preoperatively and in the immediate post-diagnostic period and thus can be used theranostically for targeted *BRAF* inhibition (6). However, detection of the PAX8 marker and the *BRAF*-V600E mutation was not available in our hospital.

Its clinical course is characterized by aggressive local invasion, a high rate of metastasis, and rapidly fatal outcomes. These patients are considered to have a systemic disease at the time of diagnosis. Almost all patients die within 6 months of the diagnosis of the disease, as in the case presented (5). The clinical presentation of ATC is characterized by a rapidly growing neck mass, which occurs in 85% of patients. Tumor enlargement can cause neck pain and tenderness and compression of the upper aerodigestive tract, resulting in dyspnea (35%), dysphagia (30%), dysphonia (25%), and cough. Constitutional symptoms, such as anorexia, weight loss, fatigue, and fever, may be present (7). The skin over the tumor may



**Table 1** Laboratory characteristics of the patient.

CBC on admission	Hemoglobin: 12.3 g/dL, platelets: $207 \times 10^3/\mu\text{L}$ , white blood cells: $23.84 \times 10^3/\mu\text{L}$ , band neutrophils: 0%, lymphocytes: 11%
Biochemical profile	Glucose: 147 mg/dL, creatinine: 0.6 mg/dL, ALT: 12 (VR: 10–49 U/L), AST: 08 (VR: 0–34 U/L), ALP: 462 (VR: 45–129 U/L), HSA: 3.06 g/dL.
Thyroid profile	TSH: 0.02 (VR: 0.55–4.78 $\mu\text{UI}/\text{mL}$ ), ft4: 4.766 (VR: 0.89–1.76 ng/dL), Tg: 346.6 (VR: 5–55 ng/mL)
Immunological test	TgAb: 35 (VR: <60 IU/mL), TPOAb: 2600 (VR: <35 IU/mL)

Data obtained from the Division of Endocrinology of Hospital Nacional Guillermo Almenara Irigoyen.

ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; CBC, complete blood count; ft4, free thyroxine; HSA, human serum albumin; Tg, thyroglobulin; TgAb, antithyroglobulin antibodies; TPOAb, thyroperoxidase antibodies; TSH, thyroid-stimulating hormone; VR, values of reference.

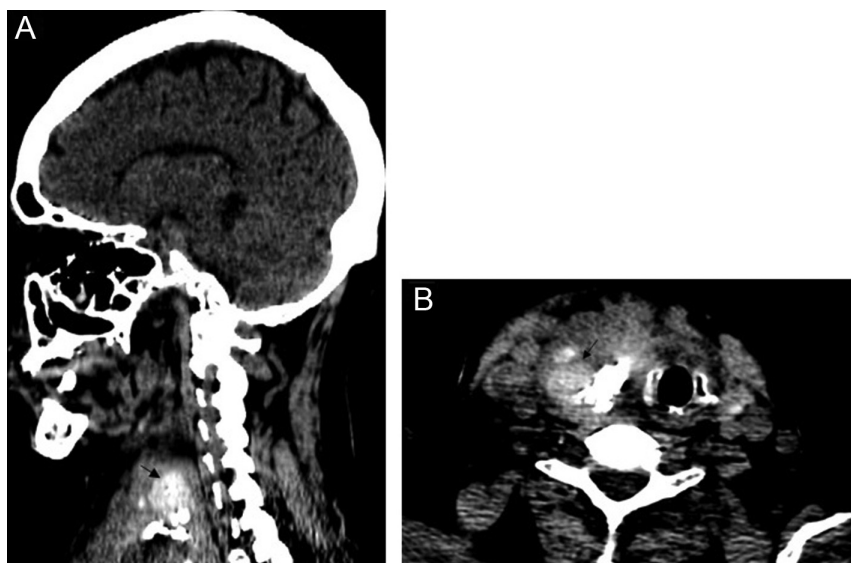
be erythematous or even ulcerated, which was evident in our patient. In rare cases, rapid tumor growth within the thyroid gland causes thyrotoxicosis symptoms, pain, and tenderness in the neck (8).

In the presented case, the patient developed clinical and biochemical characteristics of thyrotoxicosis, within the evolution of ATC, due to the finding of increased free T4 and decreased TSH, leukocytosis, and elevated thyroglobulin. Performing a radioactive iodine uptake test (thyroid scintigraphy) was not possible due to the clinical condition of the patient, which could have contributed to ruling out thyroiditis. The erythema over the skin was attributed to a soft tissue infectious process compatible with cervical cellulitis, influenced by the previously performed thyroid biopsy procedure, justifying antibiotic treatment.

The work team aims to determine the etiology of thyrotoxicosis in a patient with ATC, which was initially unclear. In the current context, we proposed subacute thyroiditis (SAT) by SARS-CoV-2 (thyrotoxic phase) as a first diagnostic hypothesis, due to clinical findings

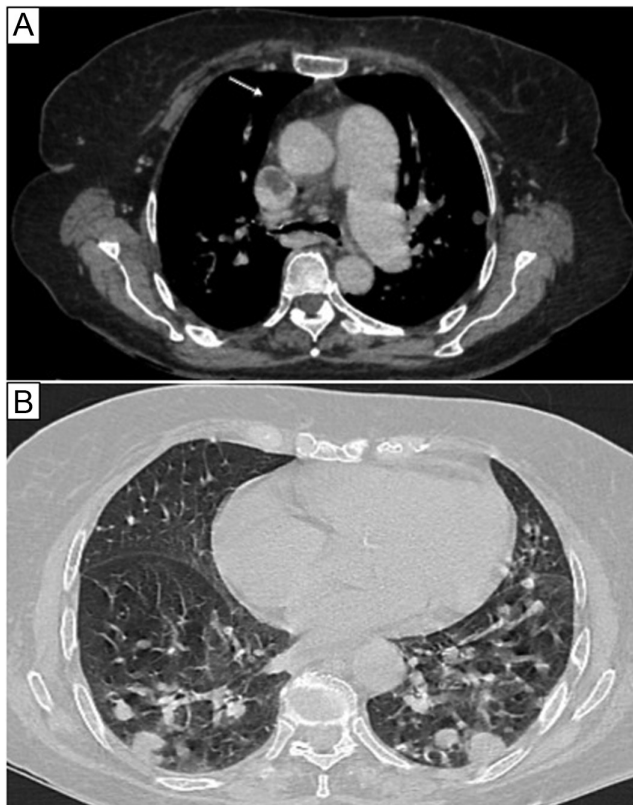
of painful thyroiditis, in addition to classic ground-glass lesions in the chest tomography and the positive immunochromatography test for IgG antibodies against COVID-19, as there are already reported cases of this disease in the world (9, 10, 11), all of which were diagnosed by RT-PCR test that was not performed on our patient, because it was not available. It is postulated that the pathogenesis of SAT by SARS-CoV-2 results in direct infection of the thyroid gland or a postviral inflammatory reaction in genetically predisposed individuals (11). However, there are several important issues that are related to the use of serological tests, being currently unclear whether a positive serological test indicates a previous encounter with the virus, expresses only a false-positive laboratory result or indicates a cross-reaction with other endemic coronaviruses (12).

The marked elevation of TPO antibodies leaves the possibility of SARS-CoV-2 infection as etiology more remote because like the rest of subacute thyroiditis, TPO antibodies are usually negative (11), with only one case reported with a slight elevation of these antibodies (13). Therefore, we suspected Graves-Basedow disease as a diagnostic



**Figure 3**

Neck CT scan with contrast. In the sagittal plane (A) and axial plane (B), an irregular and heterogeneous mass measuring  $76 \times 68 \times 58$  mm is observed (black arrow), with thick calcifications, alteration of the adjacent fat planes, and areas of central necrosis in the right thyroid lobe, extending to the mediastinum.



**Figure 4**  
CT scan of the chest with contrast. In the mediastinal window (A), mediastinal lymphadenopathies and thrombosis of the superior vena cava (white arrow) are observed. In the pulmonary window (B), multiple and bilateral irregular nodules of random distribution, some cavities (the largest of 20 mm) findings suggestive of malignancy; likewise, ground-glass opacity is identified in both lungs.

hypothesis because it can present elevated TPO antibodies in 80% of cases (14). However, thyroid ultrasound findings were not suggestive, and histopathology of the thyroid showed an area of normal thyroid, and not findings reported in Graves' disease such as diffuse papillary and follicular hyperplasia and lymphocytic infiltration into the thyroid stroma (15). Also, TSH receptor antibodies were not carried out, a test that has a sensitivity of 90–99% (16). The free T3/free T4 ratio is another useful tool that could have helped us differentiate Graves–Basedow disease from other causes of thyrotoxicosis, since a cutoff point  $>2.96$ – $3.6$  has been established, with a sensitivity of 71% and specificity of 88–99%. However, in our case, the free T3 test was not available at that time (17).

On the other hand, it cannot be ruled out that non-evaluated areas of thyroid tissue, without histological characteristics of ATC, may have findings of Hashimoto's thyroiditis, although it has not been found associated with ATC (18).

There are reported cases of thyrotoxicosis associated with ATC, which show that the etiologies are nonspecific, such as ATC associated with Graves' disease, autonomous thyroid nodules, and silent thyroiditis (19). Due to the clinical and radiological characteristics of our case report, we postulate that the rapid invasion and destruction of normal thyroid follicle cells by malignant tumor cells, resulting in the leakage of preformed hormones into the circulation, was the main etiology of thyrotoxicosis, a finding that has been previously reported in patients with rapidly growing ATC (4, 19, 20, 21), cases in which TPO antibody results have been negative. However, Heyman *et al.* reported a 74-year-old man who was presented with left-sided neck pain and a rapidly enlarging neck mass. Thyroid function tests revealed the following: TSH, 0.03 IU/mL; free thyroxine, 1.28 ng/dL; and total triiodothyronine, 119 ng/dL. Remarkably, TPO antibodies were elevated: 322 IU/mL (normal, 0–34). Pathology examination of the neck mass disclosed anaplastic thyroid carcinoma. Thyrotoxicosis was managed with  $\beta$ -adrenergic blockade and ATC with external beam irradiation. Two months later, he developed hypoparathyroidism, later dying from complications of the ATC (20). The thyrotoxicosis in our patient could have worsened the short-term prognosis.

In conclusion, ATC is rare, with poor prognosis and high mortality; it may be associated with thyrotoxicosis, which etiology can be varied; therefore, differential diagnosis is important for proper management.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Patient consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

#### Author contribution statement

Marcio Jose Concepción-Zavaleta, Maria Alejandra Quispe Flores and Laura Esther Luna Victorio: Part of the treating team, written contribution to body of text, and case reviewer. Sofia Ildefonso Najarro and Esteban Alberto Plasencia-Dueñas: Part of the treating team, written contribution to body of text, and literature overview. Diego Martin Moreno Marreros: Case reviewer, translating, editing and preparing the manuscript. Luis Alberto



Concepción Urteaga: Literature overview. Freddy Valdivia Fernández Dávila: Part of the treating team and case reviewer.

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