

# Advanced medullary thyroid carcinoma uncovered by persistently elevated procalcitonin in a patient with COVID-19

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## Summary

We report the case of an 88-year-old man hospitalized for COVID-19 with persistently very high procalcitonin (proCt) levels despite infection resolution. Since proCt is an adjunct tumor marker in the diagnosis of medullary thyroid carcinoma (MTC), serum calcitonin (Ct) was also measured showing very high levels. Computed tomography (CT) scan showed the presence of a thyroid mass and neck ultrasound revealed a solid isoechoic, inhomogeneous, 50 mm nodule in the right thyroid lobe, extended into the mediastinum. Fine needle aspiration (FNA) of the thyroid nodule confirmed the diagnosis of MTC. An <sup>18</sup>F-fluorodopa positron emission tomography/computed tomography (PET/CT) scan revealed the presence of distant metastases in ribs, vertebrae, in the right iliac wing and the liver. Since surgery was not feasible, the patient was started on cabozantinib 40 mg/dL. After 16 months the patient is still on cabozantinib at the same dose, he reports complete autonomy in daily life activities, and serum Ct is still elevated; however, the imaging evaluation does not show signs of disease progression.

## Learning points

- High procalcitonin serum values despite the absence of infection are suggestive of MTC.
- Advanced MTC with multiple metastases can have an indolent course and can go unrecognized for years.
- Cabozantinib is a valuable option for the treatment of advanced MTC.

## Background

Medullary thyroid carcinoma (MTC) accounts for 1% to 2% of all thyroid carcinomas. MTC originates from parafollicular or C-cells which produce calcitonin (Ct), as well as other peptides such as carcinoembryonic

antigen (CEA). Measuring Ct allows early detection of MTC in patients with thyroid nodular disease; Ct serum levels directly correlate with the C-cell mass and have high diagnostic, predictive and prognostic value as an MTC tumor marker (1). Ct is a 32-amino-acid hormone biosynthesized as part of a larger prohormone, called procalcitonin (proCt). Because prohormones are not

secreted in the bloodstream, proCt levels are very low in healthy subjects (2). On the contrary, during acute bacterial infection, elevated levels of proCt are observed due to the secretion of the peptide by the neuroendocrine cells of the lungs and intestine. Therefore, proCt is a biomarker with an established role in the diagnosis and prognosis of bacterial sepsis, and in the decision-making of antimicrobial therapy showing accuracy and specificity higher than that of C-reactive protein (CRP) (3). There is also increasing evidence regarding proCt-guided therapy in patients with coronavirus disease 2019 (COVID-19) (4). proCt has been also proposed as an adjunct tumor marker in the diagnosis and follow-up of MTC since, compared to Ct, it offers some preanalytical advantages (longer half-life, more thermal stability, standardized cut-off, less circadian variability). Further, proCt, like Ct, correlates with tumor size and progression (5). Therefore, when proCt elevation is unexplained in the clinical context, serum Ct assay should be advised to exclude MTC. Here, we report the case of an 88-year-old man hospitalized for COVID-19 with a large thyroid mass and persistently very high proCt levels despite infection resolution who was subsequently diagnosed with advanced MTC.

## Case presentation

An 88-year-old man was admitted to the COVID Hospital in Pescara, Italy, for the onset of fever, diarrhea, nausea and respiratory distress in August 2022. A nasal/oro-pharyngeal swab for real-time polymerase chain reaction tested positive for SARS-CoV-2. He had a medical history of hypertension, mild chronic renal failure and transient ischemic attack. At the age of 52, he had undergone a vertical frontolateral laryngectomy for squamous carcinoma of the right vocal cord. He reported good health in subsequent years. At the age of 80, he underwent an emergency tracheostomy and laser surgery for the sudden onset of severe dyspnea due to laryngeal mucosal flap, after that he refused the decannulation and two further laser treatments for mucosal flap were performed in the two following years. Later on, the patient discontinued follow-up appointments at the otolaryngology division. The patient reported complete autonomy in daily life, good health and an active lifestyle for his age. Just a few months before the hospitalization he had begun to complain about dysphagia and weight loss which had led him to arrange an appointment at the otorhinolaryngology unit. Fibrolaryngoscopy was unremarkable and the patient was referred to dietitians and speech-language pathologists for clinical assessment and treatment; a dysphagia diet was recommended. On admission at the COVID Hospital, a computed tomography (CT) chest scan demonstrated typical bilateral pulmonary 'ground-glass' areas, it also showed thyroid enlargement due to a right lobe mass extending into the upper mediastinum with

tracheal and esophagus compression. Laboratory tests showed high levels of CRP (32.9 mg/dL, normal range (NR): < 5 mg/dL), proCt (> 97.89 ng/mL, NR: < 0.1 ng/mL) and interleukin 6 (IL-6) (24.68 pg/mL, reference range: 5.3–7.5 pg/mL), anemia and neutrophilia. The patient received intravenous antibiotics and low-molecular-weight heparin with good clinical response. There was no need for O<sub>2</sub> therapy.

## Investigation

On hospital day 8, while CRP (5.88 mg/L) and IL-6 (2.95 pg/mL) significantly decreased, proCt persisted high (> 97.89 ng/mL). Considering the clinical and laboratory context (thyroid right lobe mass and elevated proCt) serum Ct was measured and it was found to be very high (29 000 pg/mL, NR: < 9.52 pg/mL); carcinoembryonic antigen (CEA) was slightly elevated (5.3 ng/mL, NR: < 4 ng/mL), thyrotropin and free thyroxine were in the normal range.

Repeated CT chest and neck scans confirmed an enlarged thyroid with the extension of the right lobe to the mediastinum causing compression over the esophagus. The trachea appeared displaced to the left; however, it was of regular caliber due to the presence of a tracheostomy tube. No enlarged lymph nodes were found (Fig. 1). Neck examination was notable for a painless, right laterocervical swelling, and neck ultrasound revealed a solid isoechoic, inhomogeneous, 50 mm nodule in the right thyroid lobe, extended into the mediastinum. Fine needle aspiration (FNA) of the thyroid nodule showed isolated cellular elements, some with spindle cell morphology, with pleomorphic and dysmorphic nuclei. The cells showed strong immunoreactivity for Ct and synaptophysin. Ct in the FNA washout fluid



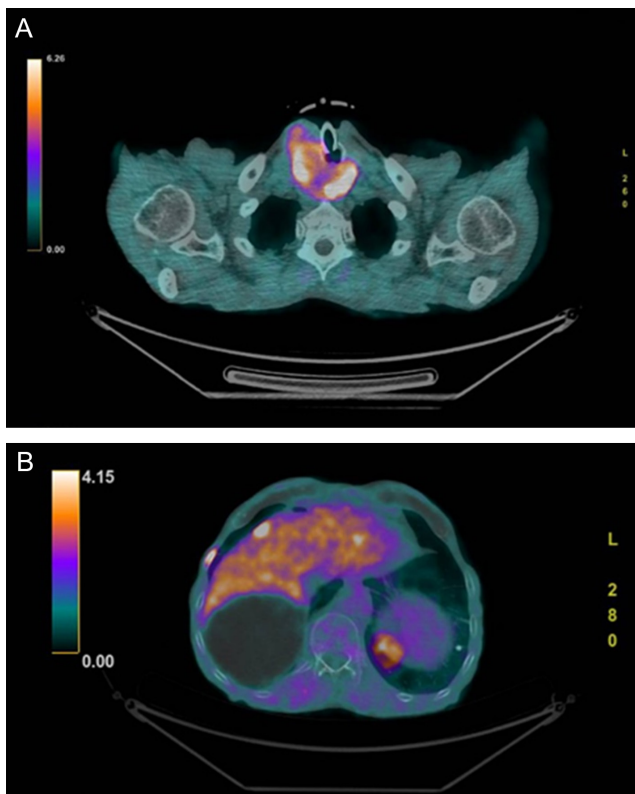
**Figure 1**

Computed tomography chest and neck scan. Large inhomogeneous thyroid right lobe mass with mediastinal extension in the right retro- and paratracheal area; the presence of a tracheostomy tube.

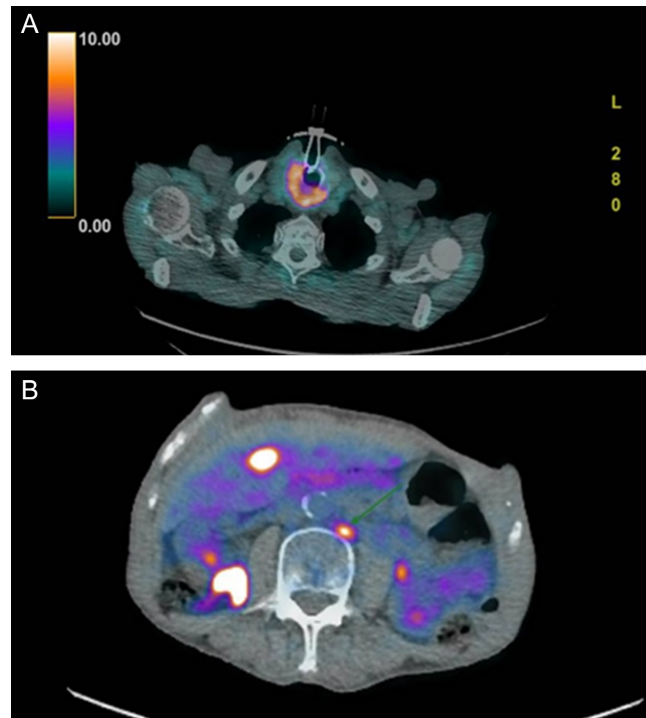
was > 10 000 pg/mL. An  $^{18}\text{F}$ -fluorodopa positron emission tomography/computed tomography (PET/CT) scan showed an increased tracer uptake (SUVmax 18.82) of the anterior cervical region with caudal, mediastinal and paratracheal, posteromedial and contralateral, extension with probable infiltration of the right thyroid shield, of the laryngeal wall and the proximal esophagus. Increased tracer uptake was also found in multiple ribs and vertebrae and the right iliac wing as well as in the liver (Fig. 2A and B).

## Treatment

The patient was referred to a multidisciplinary tumor board; members agreed that debulking surgery was not feasible, and systemic therapy with targeted agents was suggested since the presence of dysphagia was considered clinically significant and suggestive of the progression of a locally advanced disease. In November 2022, the patient was started on cabozantinib 40 mg/day. The patient did not experience significant adverse effects; at each follow-up visit his ECOG performance status was between 0 and 1.



**Figure 2**  
 $^{18}\text{F}$ -Fluorodopa positron emission tomography/computed tomography scan. A. Increased tracer uptake in the right thyroid lobe with caudal, mediastinal and paratracheal, posteromedial and contralateral extension. B. Increased tracer uptake in ribs and liver.



**Figure 3**  
(A and B) Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan. No signs of disease progression.

## Outcome and follow-up

After 16 months, the patient is still on cabozantinib at the same dose; he reports complete autonomy in daily life activities; serum Ct is still elevated (22 000 pg/mL) and the imaging evaluation ( $^{18}\text{F}$ FDG-PET/CT) does not show signs of disease progression (Fig. 3A and B). The multidisciplinary tumor board agreed to continue the treatment with cabozantinib to avoid even a minimal increase of the tumor mass that could worsen the swallowing dynamics since the patient adheres to a dysphagia diet.

## Discussion

proCt is one of the acute phase reactants widely employed in the assessment of the inflammatory response. proCt has also emerged as a biomarker of MTC (5). We report the case of an 88-year-old man who was diagnosed with advanced MTC due to persistently high levels of proCt despite clinical resolution of a COVID-19 pneumonia. During the COVID-19 pandemic, three cases of MTC uncovered by persistently elevated proCt have been reported, Table 1 (6, 7, 8). The three patients were younger than 50 years, for all of them regional lymph node metastasis was found at surgery. In one patient bone metastases, barely suspectable at the

**Table 1** Cases of MTC uncovered by persistently elevated proCt in patients with COVID-19.

	Study			
	Sira <i>et al.</i> (8)	Gianotti <i>et al.</i> (6)	Saha <i>et al.</i> (7)	Present study
Age, years	46	43	43	88
Sex	Male	Male	Female	Male
CT, pg/mL	89	2120	406	29 000
proCt, ng/mL	6	84	11.6	97
CEA, ng/mL	7.5	108	Normal	5.3
Pathological staging	pT1a (m), pN1b	T1b-N1a	pT2N1M0	Not available
Stage	IVA	III	III	IVC*
Treatment	Total thyroidectomy, central and left lateral neck dissection	Total thyroidectomy, bilateral neck dissection	Total thyroidectomy, central + radical neck dissection	Cabozantinib
Follow-up	4 weeks post surgery, no evidence of recurrence	6 months post surgery, bone metastases	6 months after first surgery, no evidence of recurrence	2 years, no evidence of progression

\*Defined on the basis of imaging studies.

pre-surgery workup, were evident 6 months after surgery (6). Compared to the previously described cases ours is peculiar due to the age of the patient. MTC biologic behavior varies widely; from indolent in some cases, to rapidly progressive in others (9). Up to 15–20% of patients will present with distant metastatic disease at diagnosis, and retrospective series report a 10-year survival of 10–40% from the time of the first metastasis. MTC mostly occurs in the 5th or 6th decade of life when sporadic, but earlier in the cases of hereditary disease. In a large series of sporadic MTC, the median age at diagnosis was 54 years (interquartile range (IQR): 43–63 years), the median tumor size was 1.5 cm (IQR: 0.8–2.7 cm) and distant metastasis was found in 11% of patients. It is conceivable that in our patient the MTC had an indolent course. However, it is necessary to underline that some factors may have delayed the clinical diagnosis of such an advanced cancer. Indeed, it is likely that the presence of the cannula prevented the occurrence of tracheal compression phenomena. On the other hand, the dysphagia, a symptom reported by the patients in the last few months before hospitalization for COVID-19, was initially attributed to the altered swallowing dynamics linked to the cannula and the previous hemilaryngectomy. A multidisciplinary team of physicians deemed the patient a poor candidate for surgery and recommended systemic therapy. The multi-tyrosine kinase inhibitor (TKI) cabozantinib has been approved for the treatment of progressive and metastatic MTC due to the ability to inhibit several TK receptors: MET, c-KIT, VEGFR2, and RET (10). Two years of treatment with cabozantinib resulted in the absence of disease progression without significant side effects. Our case suggests the need to consider the presence of MTC when proCt levels are discordant with the clinical scenario and with other markers of inflammation/infection; all this also in very elderly patients due to the slow and insidious course of MTC. Persistently high proCt may be useful for non-endocrinologists to uncover MTC

in patients not undergone endocrinological assessment. However, since using proCt routinely in patients with thyroid nodule(s) was not fully investigated, and considering that proCt correlates with Ct, the latter remains the standard blood test to diagnose MTC and the former has a role in rare clinical scenarios. The use of TKIs is a valuable option for the treatment of advanced MTC to slow the progression of the disease.

#### Declaration of interest

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

#### Funding

This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

#### Patient consent

Written informed consent for publication of its clinical details and clinical images was obtained from the patient. A signed copy of the consent form is collected in the patient's archive.

#### Author contribution statement

IB, GDD, CG, PR, BC, GN: clinical and endocrinological evaluation, conception and design of the study, literature review, drafting the work, approval of the final version of the manuscript; CA: oncological evaluation and follow-up, conception and design of the study, approval of the final version of the manuscript; PG: ENT evaluation and follow-up, conception and design of the study, approval of the final version of the manuscript.

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