CASE REPORT

Incidental diagnosis of medullary thyroid microcarcinoma in COVID-19 patient with elevated procalcitonin levels

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ABSTRACT

A 38-year-old male patient was admitted to the Medical Intensive Care Unit during the second wave of the coronavirus disease (COVID-19) pandemic presenting with fever, headache, muscle pain, and cough. The low-dose chest computed tomography (CT) result was normal, but an increased serum level of procalcitonin (PCT) was detected. Due to COVID-19, pronounced symptoms, and increased inflammatory markers, empiric antibiotic therapy was started. PCT level remained elevated despite 7 days of antimicrobial treatment. Hence, the diagnostic evaluation of the patient was expanded, and we identified medullary thyroid microcarcinoma. After diagnosis, a total thyroidectomy with cervical lymph node resection was performed, and the patient was discharged with oral levothyroxine. Control measurements of serum calcitonin and 18F-fluorodihydroxyphenylalanine positron emission tomography (18F-PET/CT) showed cervical and mediastinal lymph node metastases. Beside surgical treatment, the patient was not motivated for any adjuvant therapy and no new lesions were detected on control PET/CT two years after. In conclusion, clinicians should also consider malignancies such as medullary thyroid carcinoma as a potential cause of increased PCT levels, and as a next step should measure serum calcitonin level and perform neck ultrasound.

KEYWORDS: medullary thyroid microcarcinoma; procalcitonin; basal calcitonin; stimulated calcitonin; PET/CT

INTRODUCTION

Procalcitonin (PCT) is a 116-amino acid peptide widely used in clinical practice as a biomarker for bacterial infection, sepsis, and treatment guidance since its serum concentrations correlate with the severity of microbial infection [1]. It is formed from preprocalcitonin, a product of thyroid C-cells, and it is transformed into calcitonin, a hormone responsible for regulating calcium and phosphorous serum levels. Under physiological conditions, serum PCT levels are very low (0.05 ng/mL), but they tend to increase during inflammation [2]. Besides the thyroid gland, almost all other tissues throughout the body including the liver, kidney, lung, intestine, etc. contribute to its production. Elevated serum levels of PCT can be observed in various conditions, such as trauma, surgery, burns, cardiopulmonary bypass surgery, cardiogenic shock, heat stroke, immunomodulator pharmacotherapy, the first day of a neonate's life, and malignant disease (especially neuroendocrine tumors and tumors with metastases) [3,4].

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CASE PRESENTATION

A 38-year-old man was admitted to the Department of Medical Intensive Care at the University Clinical Centre of the Republic Srpska in Banja Luka (the Subunit for outpatient examinations) during the second wave of the coronavirus disease (COVID-19) pandemic. The patient had complaints of headache, muscle pain, fever, and dry cough for 3 days before admission. The patient's medical history was unremarkable. Physical examination on admission showed fever of 38.5°C and the oxygen saturation of 95% on ambient air, with all other parameters within normal ranges. A polymerase chain reaction (PCR) test on a nasal swab for COVID-19 was positive, and abnormalities were found in serum levels of calcium: 2.18 (reference range, 2.20 to 2.65 mmol/L), phosphorus: 0.62 (reference range, 0.81 to 1.45 mmol/L), interleukin-6: 21.9 (reference range, 0 to 7 pg/mL), platelets: 1.21 (reference range, 1.58 to 4.27 x 10*12/L), lymphocytes: 0.57 (reference range, 1.19 to 3.35 x 10*12/L),

and PCT: 9.75 (reference range <0.5 ng/mL). The low-dose chest computed tomography (CT) scan was normal. Due to the diagnosis of COVID-19, pronounced symptoms, and increased inflammatory markers, empiric antibiotic therapy was started. However, control tests revealed persistent abnormalities in PCT serum levels (11.4 to 12.4 ng/mL). In consideration of the differential diagnosis, a neck ultrasound showed the presence of a hyperechoic nodule in the right thyroidal lobe (Figure 1). Due to suspicion of a thyroid tumor in a patient, additional laboratory tests were performed, and abnormal calcitonin serum levels of 1051 pg/mL were detected (reference range, 0 to 9.52 pg/mL), while the other results of the hormonal status remained within the reference ranges. Calcitonin levels were measured at baseline and after the calcium gluconate stimulation test, and all results were abnormal: calcitonin basal 1542 pg/mL, calcitonin 1-minute 1840 pg/mL, calcitonin 2-minute 1675 pg/mL, calcitonin 3-minute 1933 pg/mL, calcitonin 5-minute 1807 pg/mL, and calcitonin 10-minute 1752 pg/mL (reference range, 0 to 9.52 pg/mL). A neck CT scan showed a 3 mm hyperechoic nodule in the lower part of the right thyroidal lobe and an enlarged lymph node of II group 7mm without lipomatous hilus (Figures 2 and 3). A CT scan of chest and abdomen showed ground-glass opacities in the left upper lobe of the lungs, suggesting the effects of COVID-19. After all analyses, the patient was transferred to the Department of Thoracic Surgery, and a multidisciplinary team, including maxillo-facial and thoracic surgeons, performed a total thyroidectomy with simultaneous dissection of the central cervical lymph nodes (VI group). The tumor size measured in the pathology specimen was 4.5 mm, and the pathology report confirmed the diagnosis of the medullary thyroid microcarcinoma (Figure 4) with metastases in 3 of 12 examined lymph nodes (pT1aN1a). After recovery, the patient was

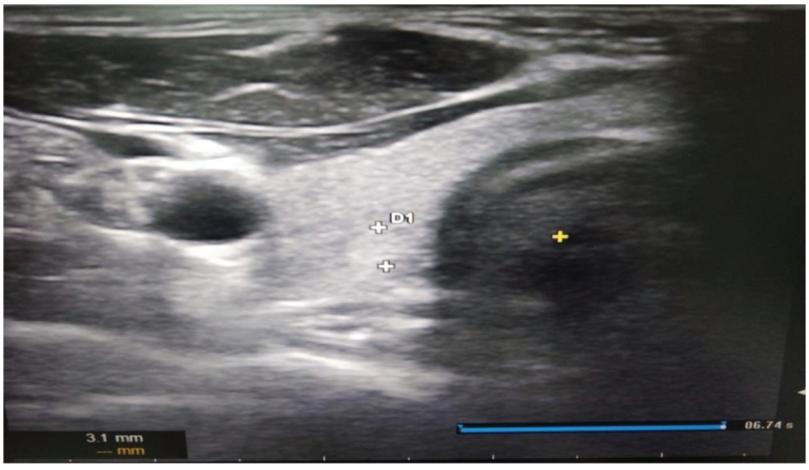

Fig. 1. Neck ultrasound. A 3mm hyperechoic nodule in the right thyroidal lobe.

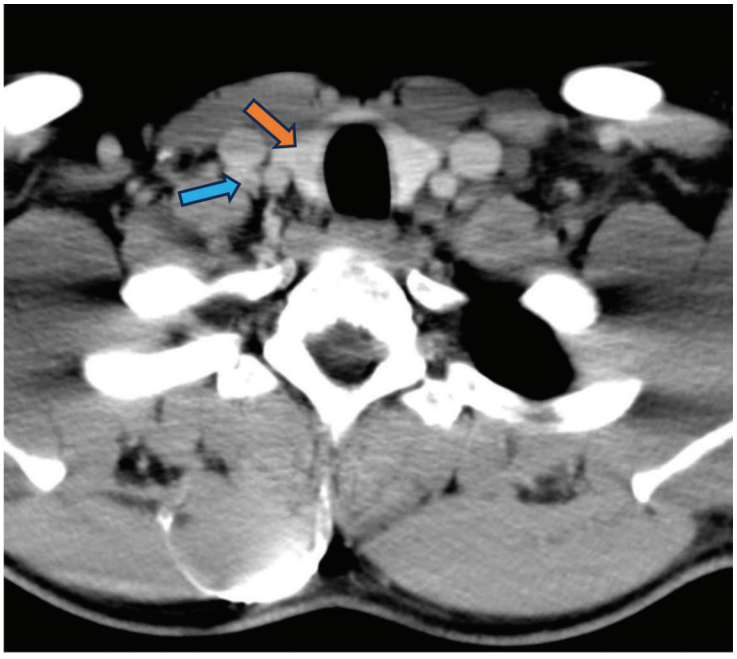

Fig. 2. Neck CT scan (transverse view). A small hypodense nodule in the right thyroidal lobe (orange arrow) and an enlarged lymph node (blue arrow).

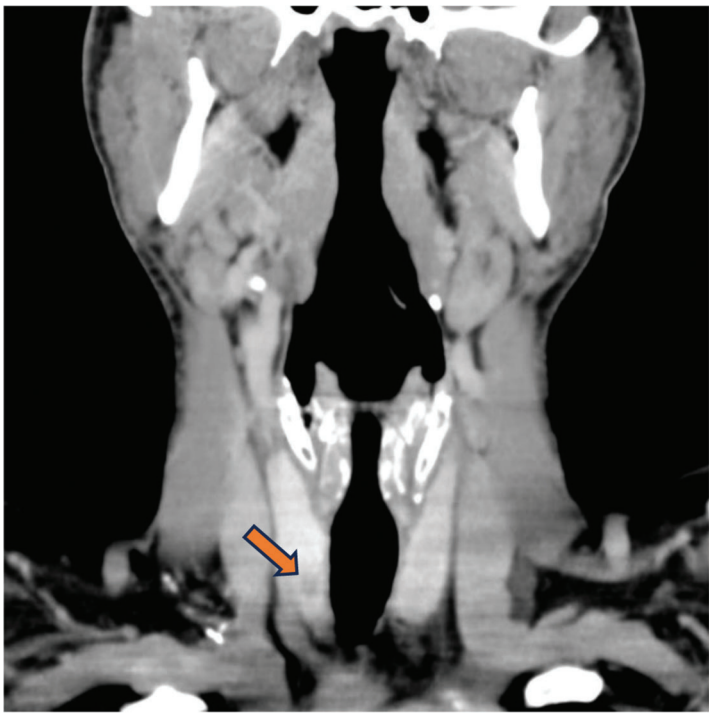

Fig. 3. Neck CT (coronal view). A small hypodense nodule in the right thyroidal lobe (arrow).

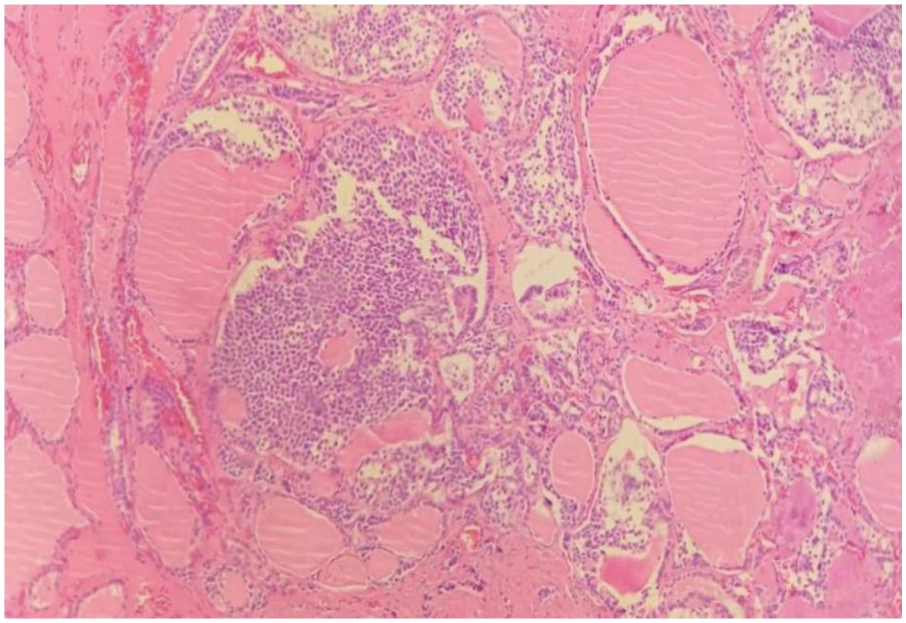

Fig. 4. Microscopical image of the medullary thyroid microcarcinoma (HE, x200).

discharged with oral levothyroxine (100 μg/day), and mild right facial nerve palsy that occurred postoperatively. One month after surgery, control calcitonin serum level was elevated (971 pg/mL), and metastatic disease with further calcitonin production was suspected. The 18F-fluorodihydroxyphenylalanine positron emission tomography (18F-PET/CT) was performed, and metastases were detected in the cervical and anterior mediastinal lymph nodes. After that, an extended resection of the lymph nodes was performed: extirpation of the lymph nodes of the II group, as well as the lymph nodes adjacent to right internal jugular vein (groups III, IV, V). The pathology report confirmed MTC metastases, identifying involvement in 7 out of the 23 examined lymph nodes. After surgical resection, the endocrinologist scheduled follow-up visits for 3 to 6 months. The follow-up calcitonin was again elevated (571 pg/mL) and follow-up 18F-PET/CT showed moderate tracer uptake in the right paratracheal lymph nodes and superior mediastinum,

but despite findings, the patient was not motivated for any further surgical or adjuvant therapy. Adjuvant therapy (chemotherapy or radiotherapy) was not recommended. The test result for the RET protooncogene was negative. Two years later, the follow-up PET/CT scan revealed no new lesions, the patient is in good clinical condition, and is still not subject for any adjuvant therapy.

DISCUSSION

Medullary thyroid carcinoma (MTC) is a rare and aggressive neuroendocrine tumor originating from the parafollicular or C-cells of the thyroid gland that produces calcitonin. It may be sporadic form (75% of cases) or is familial and associated with multiple endocrine neoplasia (MEN) type 2 (25% of cases) [5]. A solitary asymptomatic thyroid nodule is the most common presentation of MTC, and diagnosis is mainly based on fine needle aspiration (FNA) biopsy and immunohistochemical staining for calcitonin. This tumor metastasizes to the lymph nodes, lungs, liver, and bones. The mainstay therapy is a total thyroidectomy with a surgical resection of locoregional metastases [5].

The initial assumption in this case report was that the elevated PCT was associated with a secondary superinfection due to primary coronavirus infection. The value of PCT did not decrease after antibiotic therapy, indicating that another underlying cause was responsible. Due to previous similar case, to assess the differential diagnosis, we performed a neck ultrasound, which revealed a 3 mm hyperechoic nodule with calcification. This nodule was identified as a high-suspicion nodule with a malignant risk. FNA of the thyroid nodule and cytologic examination could not be performed due to its size (< 1 cm), so we did further laboratory and radiological analyses. There are two serum biomarkers for MTC, calcitonin (specific) and carcinoembryonic antigen (CEA), which should be measured upon diagnosis of MTC. These biomarkers help in detection of the hypersecreting tumor, and calcitonin values after total thyroidectomy represent a marker for detection of recurrences. Basal calcitonin concentration higher than 60-100 pg/mL strongly indicate the diagnosis of MTC, and calcium-stimulated serum calcitonin concentrations exceeding the cutoff values may enhance diagnostic accuracy [6]. In the present case, basal and stimulated calcitonin concentrations were significantly increased, suggesting the diagnosis of MTC. For further evaluation, in addition to the neck ultrasound, we performed a CT scan of the neck, lungs, and abdomen, and a 3 mm thyroid tumor was found with locoregional metastases in the II group of the cervical lymph nodes, followed by a PET/CT scan to detect MTC metastases in the neck and upper chest. Recommended imaging studies for the diagnosis of primary MTC and metastases include neck ultrasonography, CT of mediastinum and lungs, magnetic resonance imaging (MRI) which gives excellent visualization of metastatic lesions in soft tissues, intraabdominal lymph nodes, liver and bones, and nuclear medicine techniques (e.g. PET/CT, bone scintigraphy) [7]. Additionally, all patients should be evaluated for hyperparathyroidism and pheochromocytoma, as well as genetic testing for RET germline mutation (evaluation for MEN2A or MEN2B). In this case, the test result for the RET protooncogene was negative, which indicate less aggressiveness of the disease [8]. Currently, total thyroidectomy is the first treatment option for patients with MTC and can be combined with neck dissection (central only or central and lateral) due to frequent cervical lymph node metastases [9]. Post-thyroidectomy, the patient needs to take a lifelong thyroid hormone replacement therapy. MTC does not respond to radioactive iodine or conventional chemotherapy, but one more option for patients with advanced disease is a treatment with a multikinase inhibitors (vandetanib or cabozantinib) or with RET inhibitors (selpercatinib or praseltinib).

CONCLUSION

We frequently encounter elevated PCT in our daily practice, but we seldom consider a malignant disease. MTC is a thyroid tumor that produces PCT, so in case of its elevation, we should measure serum calcitonin, to perform a thyroid ultrasound, and do an FNA if it is possible. Early identification and surgical treatment are the mainstay of therapy, but multidisciplinary team discussion and treatment can improve patient outcome and survival.

Disclosure

The authors have no conflicts of interest to declare.

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None to declare.

Patient consent for publication

The patient provided written informed consent for the publication of this case report.

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