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Case Report

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A Case of Medullary Thyroid Carcinoma Diagnosed With Sustained High Level of Procalcitonin in a Critically Ill Patient. The Importance of Clinical Suspicion

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1. Introduction

Medullary thyroid carcinoma (MTC) is a thyroid cancer that originates from the parafollicular C cells and accounts less than five percent of all thyroid cancer cases [1]. It can be sporadic or part of a familial syndrome [2]. Diagnosis in the routine clinical practice is difficult since the detection rate is low with fine needle aspiration and the ultrasonographic features are not reliable [3]. Although serum calcitonin is the most accurate marker for the diagnosis there is no specific cut off for excluding MTC with certainty and different potential cutoff values have been reported in literature [4]. There are also few cases of MTC without calcitonin elevation in the literature [5]. Serum calcitonin levels can vary during the day because of its pulsatile secretion [6]. Calcitonin also can be in different immunoreactive isoforms leading different results with different assays. Moreover, calcitonin is an unstable peptide and is rapidly degraded by protease enzymes in the room temperature. Even it is refrigerated 23% decays in the first twelve hours that can lead a false test result [7].

For that reasons, there is need for new marker that can be used for diagnosis and to make the initial treatment plan. MTC cells do not only release calcitonin but they also synthesize, store, and release other neuroendocrine substances such as calcitonin gene-related peptide, procalcitonin, chromogranin A and B, and/or synaptophysin [6]. Procalcitonin is the precursor peptide which is derived from PR procalcitonin. Procalcitonin is more stable than calcitonin with a half-life of 20-24 hours.

Recently determination of procalcitonin was investigated for the diagnosis of MTC in several studies and revealed comparable utility. Measurements were similar with different antibody assays. There are some advantages of measuring procalcitonin such as not requiring cold chain during the entire process. Herein this report we represented a case of medullary carcinoma who was admitted to our center with post renal acute kidney failure and urinary tract infection and diagnosed with medullary thyroid carcinoma which was suspected because of persistently elevated procalcitonin despite the improvement of infection.

2. Case

60 years old male patient was referred to internal medicine ward and hospitalized due to post renal acute renal failure. He had history of nephrostomy applied for nephrolithiasis, chronic myelocytic leukemia, stroke, and hypertension. At the time of admission his symptoms were anorexia and nausea. In the physical examination he had pale extremities, tachycardia, and subfebrile fever (body temperature was 37.7 °C). Regarding to possible infection focus, his pharynx was normal, there were rales at both lung bases and there was no cellulitis or decubitus on the skin. Chest x-ray was compatible with hypervolemia and mild pulmonary edema. Since he was hospitalized during Covid-19 pandemics and had subfebrile fever, we performed reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs two times to exclude Covid-19 and the results were both negative. Biochemistry revealed a partly compensated metabolic acidosis (pH 7.27 and pCO2: 22.5), elevated blood urea nitrogen (46 mg/dl; normal range: 7–18 mg/dL) and creatinine (4.6 mg/dl; normal range 0.7-1.3 mg/dl) with normal liver function tests and electrolytes. In the urinary culture there was E. Coli proliferation and antibiotic (ceftriaxone) was started. After application of proper hydration, diuretics and 1 week of antibiotic treatment serum creatinine level decreased to 2.6 mg/dl and serum c-reactive protein and sedimentation rate returned to normal range. However, his procalcitonin level was persistently high without any sign of infection or sepsis. Since his procalcitonin remained high, we suspected a possible thyroid malignancy and ordered thyroid function tests with autoantibodies, serum calcitonin and thyroid ultrasonography. Thyroid gland physical examination which had been omitted at the first place was performed and a firm palpable thyroid nodule was detected on the right lobe. In the detailed anamnesis for nodular thyroid disease, he did not report dyspnea, hoarseness, difficulty in swallowing or any symptom that could be related to hypo or hyperthyroidism. There wasn't any family history of tjyroid cancer. His thyroid function tests were normal (TSH: 0.89 mIU/L, free T4:1 ng/dl and free T3: 2 pg/ml). Thyroid autoantibodies were negative whereas serum calcitonin was markedly elevated (1536

pg/ml, normal range; <8 pg/ml). The ultrasound examination confirmed the presence of a 12.8x18x26 mm sized solid isoechoic thyroid nodule with cystic degenerations and calcifications. There was not any suspicious lymph node in the central or both lateral parts of the neck. Fine needle aspiration was performed due to the size and suspicious appearance of the nodule and cytopathology revealed oval cell aggregates with elongated nuclei that were arranged in syncytia. And groups of tumoral cells separated by thin fibrous bands (Figure 1). In the cytoplasm of some cells there were thin metachromatic granular material immunohistochemical staining was performed and revealed positive staining with calcitonin and chromogranin on the cell blocks (Figure 2A, 2B).

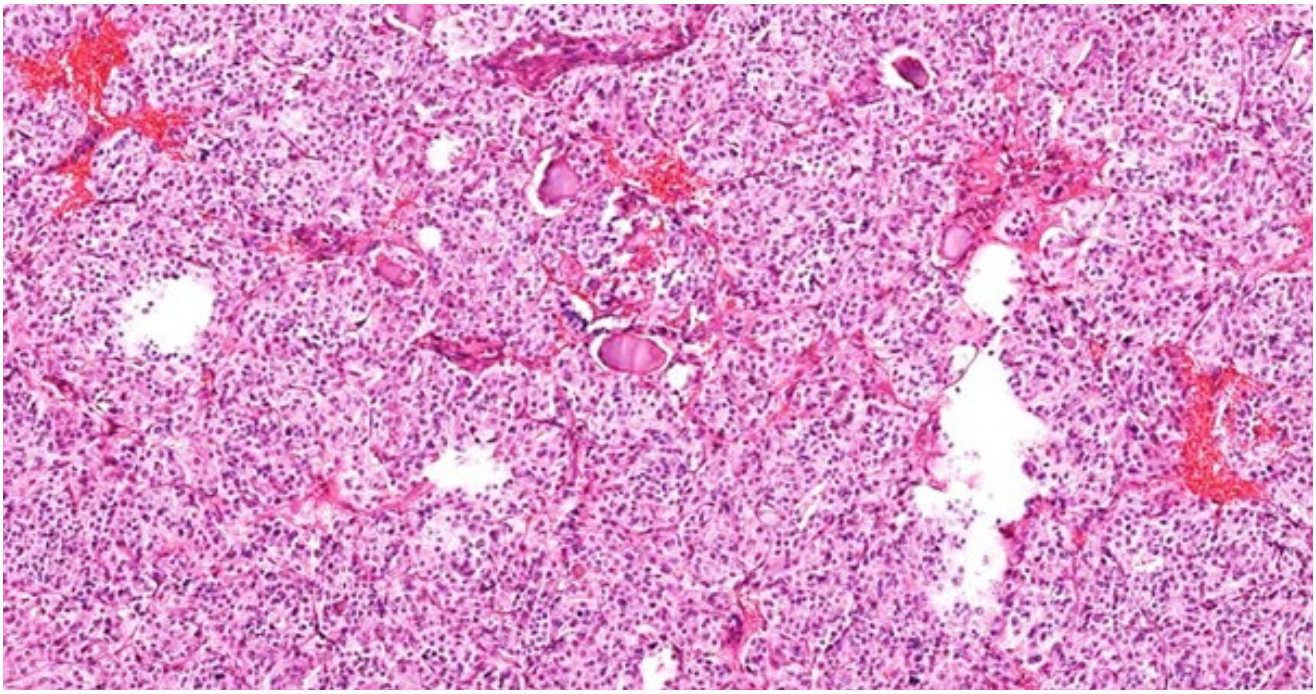

Figure 1: HEx100 Groups of tumoral cells separated by thin fibrous bands

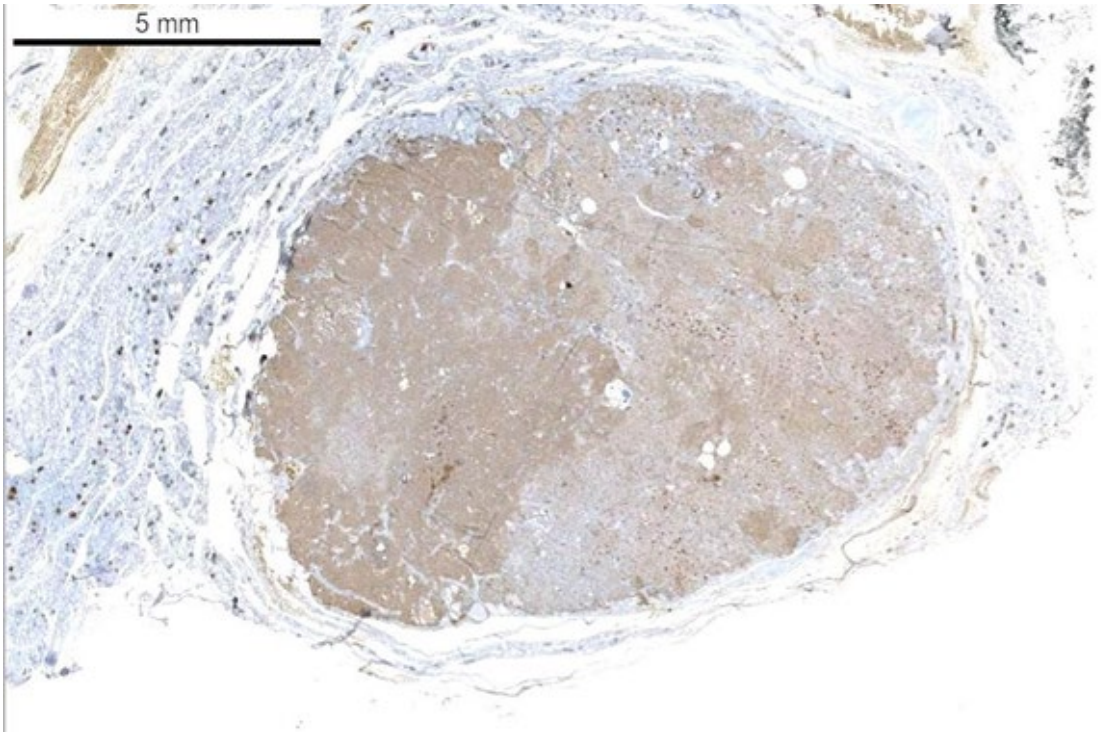

Figure 2A: Immunohistochemical staining was performed and revealed positive staining with calcitonin

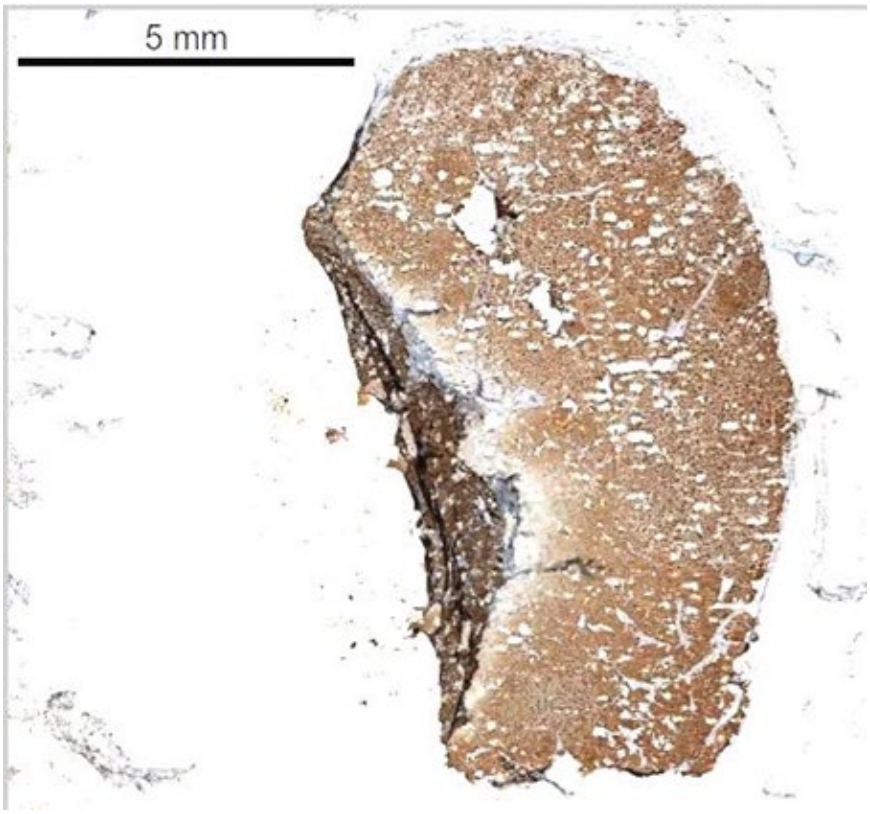

Figure 2B: Immunohistochemical staining was performed and revealed positive staining with chromogranin

The Bethesda classification was reported as 'suspicious for malignancy'. Since the elevated calcitonin level and cytology were compatible with medullary thyroid cancer, screening for familial disorders were made including RET oncogene screening, serum and urinary fractionated metanephros's and serum PTH together with calcium. Work-up for hyperparathyroidism and pheochromocytoma were negative. Exons 1–20 of the RET proto-oncogene were sequenced, and revealed no deleterious mutations, ruling out the presence of a germline mutation or a diagnosis of Multiple Endocrine Neoplasia. The thorax CT and abdominal MRI were negative regarding to metastasis. He underwent total thyroidectomy and central lymph node dissection. The histopathology revealed 1.1 cm sized medullary thyroid cancer without any lymph node metastasis.

3. Discussion

MTC is an aggressive cancer of the thyroid gland. At the time of diagnosis, cervical lymph node and distant metastases are present in up to 50% and 10% of patients [8]. Therefore, it is crucial to suspect and screen it in a patient with thyroid nodule. The gold standard marker for the diagnosis of MTC is calcitonin with certain pitfalls such as variable half-life and unstable nature. There is a debate about the cost effectiveness of routine calcitonin measurement for MTC screening in patients presented with a thyroid nodule. The previous reports suggest that there is a large reservoir of undiagnosed micro MTC that can be uncovered by calcitonin screening [9]. In contrary there are studies showed that benefits of screening may be overestimated, and the risk of observation may be acceptable [10]. At our hospital serum calcitonin measurement is routinely applied for all patients who are admitted with thyroid nodules requiring FNA. However, it is reported that depending on the assay used, 56%-88% of subjects without thyroid disease usually show a calcitonin level below the functional sensitivity, while 3%-10% have CT levels >10 pg/mL [11]. Falsely elevated levels can lead unnecessary surgeries so there is need for extra tests to increase sensitivity and specifity such as pentagastrin or calcium stimulation which are either impractical or unavailable.

Another tool that is being used widely to diagnose thyroid malignancy is US in the last decade. There are well known ultrasonographic features for determining the risk of papillary thyroid carcinoma such as presence of microcalcifications, hypoechoic appearance with irregular margins or increased anteroposterior diameter [11]. Because of the low prevalence of MTC a few papers analyzed US characteristics associated with this cancer in small series with controversial results [12].

Procalcitonin is a precursor peptide which is usually present in low amounts in healthy individuals. The level is increased in severe systemic inflammation, infection, or sepsis. In the recent years it has been evaluated as a potential biomarker for MTC. In one study enrolled 2705 patients with nodular thyroid disease procalcitonin could detect 7 MTCs in these that basal calcitonin measurements were concordantly positive [11]. In the study by Machens et al.

procalcitonin level was correlated with MTC recurrence, primary tumor size, presence of lymph node metastasis or distant metastasis as serum calcitonin [13]. In another study 1236 patients with thyroid nodules were enrolled. Calcitonin, and precalcitonin measurements were performed. On those 14 patients with abnormal calcitonin level (>10pg/ml) pentagastrin stimulation test was also performed. Four of those fourteen patients had thyroid malignancy, one had C cell hyperplasia ang 9 had benign thyroid disease. In all patients with MTC basal calcitonin was >100 pg/ml and procalcitonin was 0.1 µg/L. The main results of that study were that basal and pentagastrin-stimulated CT had some false-positive results, whereas all patients without MTC had undetectable levels of both basal and stimulated procalcitonin with a 100% positive predictive value (PPV) and a 100% negative predictive value (NPV), respectively [14].

In this case the patient admitted to our hospital's emergency room and hospitalized for acute exacerbation of renal failure. He had urinary tract infection and therefore high procalcitonin level. To suspect the sustained high levels of procalcitonin despite clinical relief of infection with antibiotics led the clinician to diagnose completely irrelevant but very mortal condition. That is art of diagnosis which should remind the clinicians to look at the patient's whole clinical picture and see the details. Another important point in this case is high calcitonin level without any distant or lymph node metastasis due to chronic renal failure.

4. Declarations

- **Ethics approval and consent to participate:** Not applicable.
- **Consent for publication:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
- **Availability of data and materials:** All the data generated and/or analyzed during this study are included in this published article.
- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** Not applicable
- **Authors' contributions:** BCC collected data and drafted the initial manuscript, written the main body of the text. MC and IA critically reviewed the manuscript. All authors have read and approved the manuscript.
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