Letter to the Editor

Filipe Miguel Montes de Jesus and Luca Giovanella*

Unexplained increase of serum carcinoembryonic antigen: don't forget the thyroid!

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To the Editor,

Carcinoembryonic antigen (CEA) is glycoprotein associated with various functions of endothelial cells, including adhesion, proliferation, and migration. As a serum biomarker, it is commonly employed in the diagnosis and post-treatment surveillance of colorectal cancer patients [1]. Nevertheless, it may also be elevated in other malignancies such as breast, lung, ovarian or medullary thyroid cancers, as well as other nonmalignant conditions (i.e., liver disease, inflammatory gastro-intestinal disorders, renal failure, smoking) [1–3]. Although CEA testing is a cost-effective and widely available diagnostic tumor marker, its lack of sensitivity and specificity precludes any pathognomonic diagnosis. Ultimately, a combination of clinical findings, biochemical testing and imaging are necessary to guide clinical decisions [4]. When faced with elevated CEA measurements, clinicians and clinical pathologists must recognize its ambivalence and thoroughly exclude any important pathology and interferences as well. We present a case of a 60-year-old female patient with persistent CEA elevation after the diagnosis and therapy of invasive ductal carcinoma in 2012 (pT1b pN0 cM0). Patient underwent tumor resection with adjuvant radiotherapy and maintenance with letrozole until 2017. An elevated CEA was initially detected in 2012 during the diagnostic work-up for her primary malignancy. Particularly, a serum CEA concentration of 20.6 µg/L (reference <5 µg/L) was measured by the Elecsys® CEA immunoassay on the eCobas e601 fully automated platform (Roche Diagnostics, Rotkreuz, Switzerland). Throughout follow-up, periodic CEA measurements remained unchanged without any other clinical symptoms or biochemical abnormalities. In 2018, due to further increase in the CEA levels (34.1 µg/L), gastro- and colonoscopy exams were performed, revealing a gastritis and few diverticula in the colon. In the absence of any other pathological findings, including normal mammogram and breast ultrasound, persistent CEA elevation was attributed to the heavy smoking habitus of the patient. In 2021, neck ultrasound was performed due to supraclavicular adenopathy after COVID-19 vaccination. It revealed an unsuspicious, reactive, supraclavicular enlarged lymph node and an unknown small goiter with a suspicious nodule (i.e. hypoechoic, heterogeneous, with irregular margins and intensely vascularized, EUTIRADS-5) in the left thyroid lobe further characterized as an area of low uptake on ^{99m}Tc-pertechnetate scintigraphy (i.e. "cold" nodule). Serum calcitonin levels were found to be elevated (279 pmol/L, reference range <1.9 pmol/L) by using the Elecsys® Calcitonin immunoassay on the eCobas e601 fully automated platform (Roche Diagnostics, Rotkreuz, Switzerland) and the diagnosis of medullary thyroid cancer (MTC) was corroborated by increased procalcitonin levels (3.4 µg/L, reference range <0.1 µg/L). A total thyroidectomy with central neck dissection was performed, after which a steep decrease in calcitonin (0.3 pmol/L), procalcitonin (<0.1 µg/L) and CEA (2.5 µg/L) levels was observed (Figure 1). The diagnosis of MTC was confirmed by surgical pathology examination and immunohistochemical calcitonin staining (TNM stage: pT1b pN0, cM0). Our patient is currently in complete remission (i.e. excellent response to treatment). The present case illustrates potential clinical challenges in using serum tumor markers, namely CEA, to monitor cancer patients. Although most commonly used in colorectal cancer patients, clinicians should retain a broad differential diagnosis when faced with persistently elevated CEA results [1]. In our case, clinical efforts were focused on the detection of early relapse giving the patient's history of breast cancer [2]. Part of the difficulty when

***Corresponding author: Luca Giovanella**, MD, Clinic for Nuclear Medicine and Molecular Imaging, Imaging Institute of Southern Switzerland – Ente Ospedaliero Cantonale, Via Ospedale 12, CH-6500 Bellinzona, Switzerland; and Clinic for Nuclear Medicine, University Hospital of Zürich, Zürich, Switzerland, Phone: +41-91-811 86 72, Fax: +41-91-811 82 50, E-mail: luca.giovanella@eoc.ch. https://orcid.org/0000-0003-0230-0974
Filipe Miguel Montes de Jesus, Clinic for Nuclear Medicine and Molecular Imaging, Imaging Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

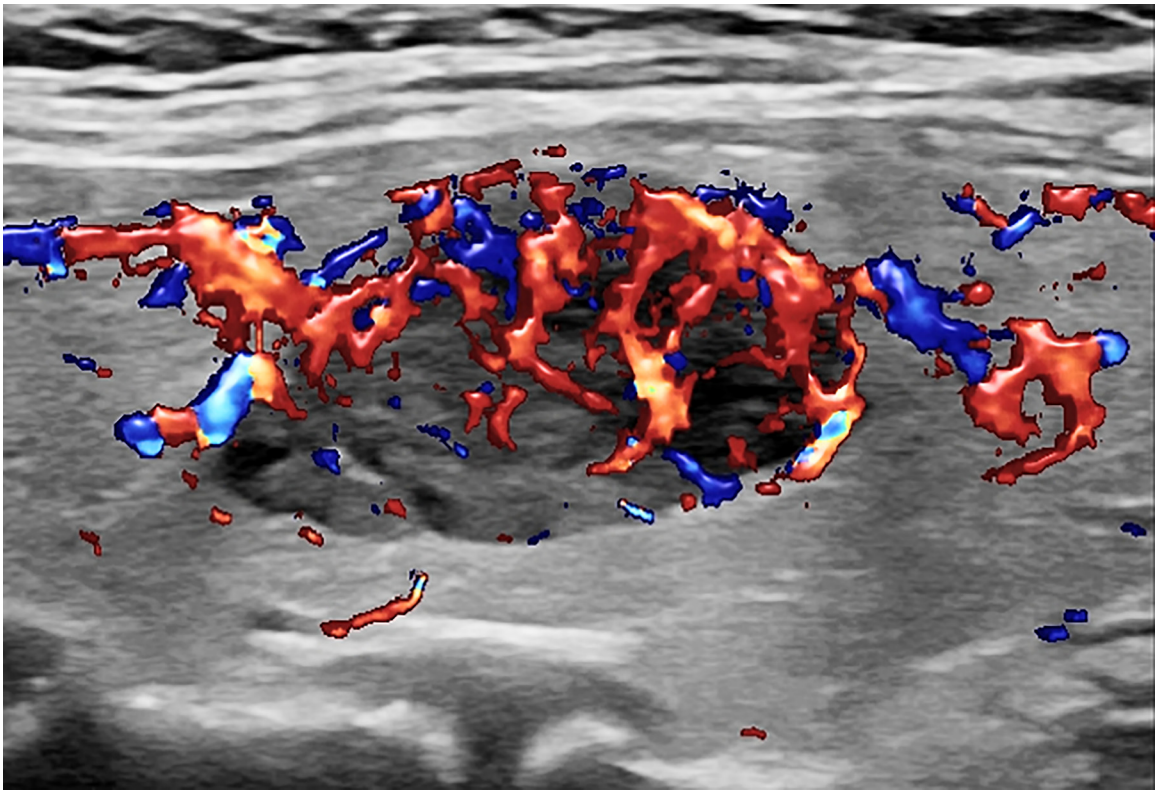

Figure 1: Thyroid ultrasound: medullary thyroid carcinoma presenting as an hypoechoic and heterogeneous nodule with irregular margins and intense vascularization.

interpreting such a case, may be attributed to CEA being expressed in the epithelial cells across multiple organ systems. It is also implicated in several biological functions, not only in cell to cell adhesion, regulation of cellular differentiation and apoptosis but also tumorigenesis and inflammatory response [5–7]. Smoking and other non-malignant conditions may also be associated with elevated CEA levels but values >10 µg/L particularly with a upwards trend, should raise the concern for malignancy and prompt additional examinations [3]. Accordingly, gastrointestinal malignancies were ruled out, but due to the lack of accuracy of this biomarker, other diagnostic avenues should have been be pursued. A complementary panel of blood-based tumor biomarkers has been suggested to increase sensitivity and help narrow down the differential diagnosis. These are dependent on clinical assessment and may include: α-fetoprotein, prostate-specific antigen (PSA), CA19-9, CA125, CA15-3, squamous cell specific antigen and cytokeratin 19 fragment [4]. Medullary thyroid cancer is rare, with an estimated prevalence of 1 in 30,000 in the general population and may be not screened in such cases. However, calcitonin measurement is a simple and cost-effective way to increase diagnostic sensitivity and prompt targeted diagnosis in patients with unexplained increased CEA [8]. In patients with thyroid nodules, the diagnostic performance of calcitonin has been reported to have a sensitivity of 99.7 % and a specificity of 96.6 % for the diagnosis of medullary thyroid cancer, at a threshold of 2.9 pmol/L [9]. In addition, as demonstrated also in our case, serum procalcitonin measurement, a widely available test in clinical laboratories, can complement or even replace calcitonin as a new standard of care in diagnosis and management of medullary thyroid carcinoma [10]. Considering the slow growth rate of medullary thyroid cancer, the elevated, more or less stable, CEA levels over time and dramatic CEA decrease after surgery, the increased CEA levels may have already been an indication of medullary thyroid carcinoma in our patient. Accordingly, a simple calcitonin or procalcitonin measurement could have anticipated the diagnosis by several years. In conclusion, CEA is a serum biomarker may alert the clinician for a potential pathology and it is a useful tool for monitoring patient with colon cancer. However, it lacks specificity and in patients without any directing clinical symptoms, diagnosis remains challenging. In this context, when faced with persistently elevated CEA levels, clinicals should pursue further testing in attempt to refine their

differential diagnosis, refer to laboratory specialists to properly screen for interferences (i.e. smoke, heterophilic antibodies, biotin …) and discuss rare diagnosis and appropriate reflexing strategies (i.e. calcitonin test in the present case). Then, as a final message, in front of an unexplained high CEA level please don't forget medullary thyroid cancer.

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