# High serum levels of calcitonin are not pathognomonic of medullary thyroid carcinoma and may indicate polyglandular autoimmune syndrome III

**To the Editor:** Nuclear medicine plays a major role in the diagnostic assessment and postoperative work-up of medullary thyroid carcinoma (MTC) by measuring serum calcitonin (CT) by either radioimmunoassay (RIA) or by immunoradiometric assay (IRMA). Calcitonin is a polypeptide hormone composed of 32 aminoacids secreted by thyroid C-cells [1]. A number of radiopharmaceuticals are available to detect either primary or metastatic MTC sites before or after primary surgery [2-6]. Increased serum CT is a highly sensitive tumour marker for the detection of MTC, but has a low specificity for this tumour [1]. Several physiologic and pathologic conditions other than MTC have been associated with increased levels of CT, such as sex, age, physical activity, chronic use of omeprazole or omeprazole-like drugs, of glucocorticoids, of beta-blockers, etc, and also hypercalcemia, hypergastrinemia, neuroendocrine tumours, renal insufficiency and papillary and follicular thyroid carcinoma [1].

We had a case of a 38 years old Greek woman with type I diabetes mellitus and Hashimoto's thyroiditis, and serum CT 110pg/mL measured by RIA (normal value: <10pg/mL). The patient did not have MTC. Her medical history included a single thyroid nodule with 4mm diameter which had been diagnosed 9 months earlier. Her family medical history was unremarkable. The patient underwent a careful investigation in order to rule out pathologic conditions associated with increased levels of CT other than MTC [1]. This investigation revealed autoimmune gastritis with high fasting serum gastrin levels (480pg/mL), measured by RIA (normal value: <100pg/mL), positive serum autoantibodies to parietal cells and also to intrinsic factor, vitamin B12 deficiency measured by RIA (154pg/mL) and atrophy of the gastric corpus and fundus on gastroscopy. A low serum pepsinogen I concentration, and macrocytic anaemia with Hb 10.3g/dL due to vitamin B12 deficiency, were also detected. Serum thyroid stimulating hormone (TSH), free thyroxine and free triiodothyronine measured by RIA were normal, but serum antithyroid peroxidase and anti-thyroglobulin antibodies were remarkably elevated (>1000 IU/mL). Tumour markers (carcinoembryonic antigen-CEA, alpha-fetoprotein-AFP, CA 19-9) and 24h urine metanephrines and vanillylmandelic acid levels were normal. The computerized tomography scan of the thorax and the abdomen (Tomoscan SR 7000 Philips, Netherlands) was normal. A further investigation of a possible association of autoimmune gastritis with other organ-specific or organ-nonspecific autoimmune diseases was also performed [7]. The basal levels of plasma adrenocorticotropic hormone and serum follicle-stimulating hormone, luteinizing hormone, growth hormone, estradiol, prolactin, parathormone, fasting morning cortisol measured by RIA were all within the normal range. Antinuclear antibodies, antibody to double-stranded DNA, antineutrophilic cytoplasmic antibodies were negative, and rheumatoid factor, complement-3 and -4 were normal.

High levels of gastrin stimulate the synthesis and secretion of CT, thus raising its serum levels. It is known that gastrin, in the form of pentagastrin, is used as a stimulatory test evaluating the capacity of C-cells to secrete CT. Consequently, hypergastrinemia due to autoimmune gastritis in our diabetic patient was the cause for increased serum CT. Autoimmune gastritis and pernicious anaemia in our case were accompanied by other autoimmune diseases, including type I diabetes mellitus and autoimmune thyroid disease (Hashimoto's thyroiditis), therefore our patient had polyglandular autoimmune syndrome type III (PAS III) [8, 9]. This syndrome in contrast to PAS I and II, does not involve the adrenal cortex [9]. In PAS III, autoimmune thyroiditis occurs with some other organ-specific autoimmune disease (excluding Addison's disease and/or hypoparathyroidism), but the syndrome cannot be classified as PAS I or II [10]. PAS III is classified into the following three subcategories: 1) PAS IIIA: autoimmune thyroiditis with immune-mediated diabetes mellitus (type I diabetes mellitus) 2) PAS IIIB: autoimmune thyroiditis with pernicious anaemia, and 3) PAS IIIC: autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease. Autoimmunity, environmental factors, and genetic factors are the main factors in the pathophysiology of PAS III [10]. In particular, it is considered that human leukocyte antigen (HLA) complex on chromosome 6p is one of the most important genetic factors affecting many autoimmune disorders [11]. The exact international prevalence of PAS III is unknown, but the morbidity and mortality of PAS III is determined by the individual components of the syndrome. No racial or ethnic difference in frequency of PAS III has been reported, but PAS III is more common in middle-aged females than in males. Medical care of patients with PAS III includes monitoring of glandular functions for early detection of glandular failure, lifelong hormone replacement treatment for established glandular failure(s), and familial screening.

*In conclusion,* differential diagnosis of hypercalcitoninemia as in our case shall avoid misdiagnosis of MTC, an incorrect recommendation for thyroid surgery, and shall draw attention to screening patients with type I diabetes mellitus for other autoimmune disorders which can affect prognosis.

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## Hercules knot

Macedonians considered as one of their ancestors the hero Hercules. The first Macedon according to Isiodos - 7th century b.C., had Jupiter as his father and Hellina the Greek as his uncle.