

# Sporadic medullary microcarcinoma in a male patient with concurrent Hashimoto's hypothyroidism and Kikuchi disease

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## *To the Editor,*

Kikuchi disease (KD), also known as histiocytic necrotizing lymphadenopathy, is a rare, benign condition usually characterized by cervical lymphadenopathy and fever [1]. The etiology of KD remains controversial, but autoimmune disorders including systemic lupus erythematosus, tend to develop before, simultaneously, or after an episode of KD [2]. However, only a few KD cases have been reported with autoimmune thyroiditis [1-4]. Here, we report a case of a male patient with concurrent Hashimoto's thyroiditis (HT) and KD.

A 32-year-old Korean male ex-smoker presented to Presbyterian Medical Center with a 4-week history of multiple enlarged right posterior cervical masses (up to 3 cm) that were causing pain and tenderness over the right sternocleidomastoid muscle. He also complained of fever (up to 38.5°C) that was higher in the evening and was associated with chills. He had fatigue, malaise, and weight loss of 4 kg. Physical examination found the ears, nose, and throat to be unremarkable. Laboratory findings showed the following abnormalities: mild pancytopenia (white blood cell count, 2,600/ $\mu$ L; hemoglobin 11.1 g/dL; platelets 103,000/ $\mu$ L); an elevated erythrocyte sedimentation rate of 21 mm/hr (normal range, < 15) and elevated C-re-

active protein of 1.18 mg/dL (normal range < 0.8); increased creatinine kinase 359 U/L (normal range, 50 to 200) and lactate dehydrogenase 507 IU/L (normal range, 124 to 226); mild elevated alanine aminotransferase 61 U/L (normal range, 7 to 38); and aspartate aminotransferase 55 U/L (normal range, 4 to 43). Serum calcium and phosphorus levels were 8.6 mg/dL (normal range, 8.2 to 10.2) and 3.3 mg/dL (normal range, 2.5 to 4.5), respectively. The following investigations were either normal or negative: blood cultures for bacteria, viruses, and fungi along with serology for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, antinuclear antibody test, and rheumatoid factor. However, thyroid function tests revealed the presence of antibodies to thyroid peroxidase (53.71 U/mL, > 0.3 U/mL positive) and antibodies to thyroglobulin (0.9 U/mL, > 0.3 U/mL positive), and a hypothyroid state (elevated thyroid-stimulating hormone of 152.99  $\mu$ U/mL, [normal range, 0.3 to 4]; low free thyroxine of 0.37 ng/dL [normal range, 0.8 to 2.2]).

Computed tomography (CT) scan of the neck revealed multiple enlarged lymph nodes at all cervical levels on the right side without evidence of abscess formation (Fig. 1A). Abdomen, pelvis, and chest CT scans and plain chest ra-

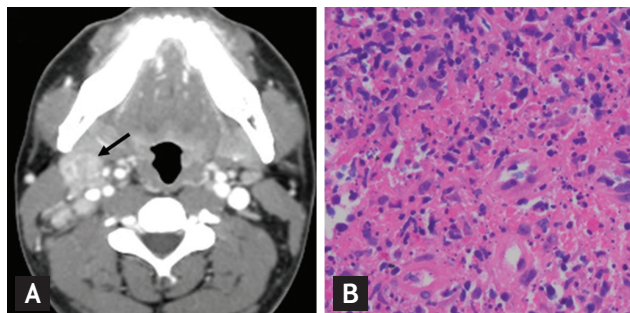
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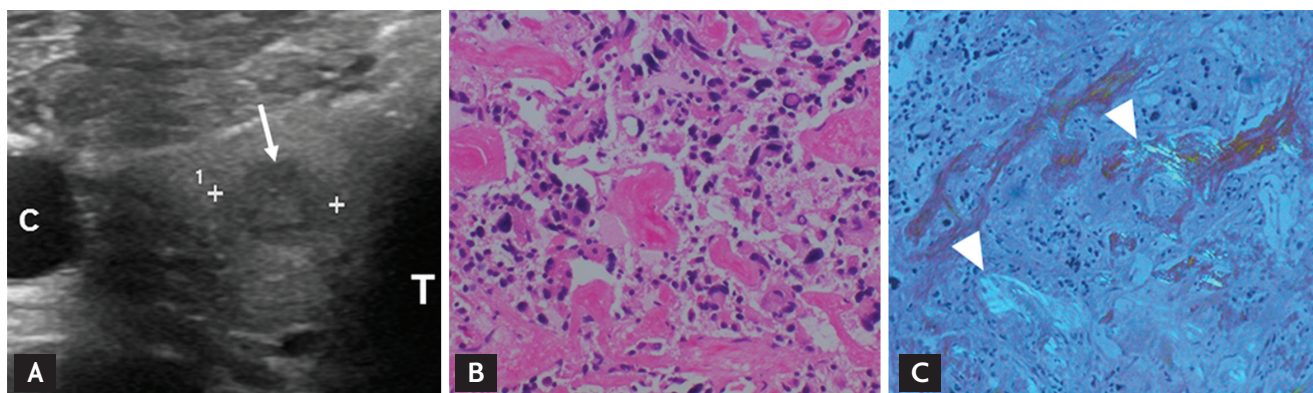
**Figure 1.** (A) Contrast-enhanced computed tomography of the neck showed enlarged right cervical lymph nodes (arrow). (B) Lymph node biopsy demonstrated mixed inflammatory cells including histiocytes and plasmacytoid monocytes with necrotic fibrin debris and karyorrhexis (H&E, ×400).

diography revealed no abnormal findings except for a small pericardial effusion. Pathologic findings from ultrasound-guided core needle biopsies of nodes revealed necrotizing lymphadenitis, which was histologically compatible with KD (Fig. 1B) and polymerase chain reaction was negative for *Mycobacterium*. The patient was put on levothyroxine 100 µg/day, was treated symptomatically for fever, and lymphadenopathy resolved spontaneously. In addition, all abnormal laboratory findings and pericardial effusion had normalized after 2 months.

Thyroid ultrasonography during work-up of KD revealed a 7-mm hypoechoic nodule in the right lobe (Fig. 2A). Fine needle aspiration (FNA) cytology initially found severe atypical cells of uncertain significance, and, after recovery from KD, repeat FNA detected poorly differentiated carcinoma, which prompted surgery. The calcitonin

level measured by chemiluminescence assay was 16.3 pg/mL (normal range in male, < 11.8), which was confirmed on repeat testing. The serum carcinoembryonic antigen of 2.6 ng/mL was within normal limits. Subsequently, bilateral total thyroidectomy and central lymph node dissection were performed. Since RET germline mutation analysis was negative and the patient had no family history of multiple endocrine neoplasm type 2 syndrome, we did not perform presurgical biochemical testing for co-existing tumors (particularly pheochromocytoma and hyperparathyroidism). Histopathology (Fig. 2B and 2C) confirmed a 5-mm medullary thyroid cancer (MTC) via positive immunohistochemical staining of chromogranin A, thyroid transcription factor-1, and synaptophysin and by staining of deposited stromal amyloid with Congo red. Two months after surgery, the patient's calcitonin level was undetectable (< 1.0 pg/mL).

Given the number of clinical cases that describe autoimmune diseases in KD patients, most authors agree that the association between KD and autoimmune diseases cannot be explained by random coincidence [2]. According to an earlier KD case series, work-up of autoimmune diseases in patients with KD is recommended, particularly in women, who are more likely to develop autoimmune manifestations [2]. Further evaluation of these relationships, however, is necessary. To the best of our knowledge, all seven previously reported cases of KD associated with HT occurred in females between the ages of 17 and 30 [1-4]. Three of these patients were diagnosed with HT before an episode of KD, whereas four patients



**Figure 2.** (A) Ultrasonography of the right thyroid lobe revealed a 7-mm hypoechoic nodule (arrow). (B) Surgical section of medullary thyroid cancer (MTC) with polygonal or spindle cells in nests or follicle formation. Tumor cells displayed granular cytoplasm with oval nuclei. The stroma contained amyloid deposits (H&E, ×200). (C) Congo red staining of MTC showed apple green birefringence (arrowheads, ×100). C, carotid artery; T, trachea.

were diagnosed with concurrent HT and KD. However, in contrast to all of the above reported cases, our patient was an adult male. Therefore, this case illustrates that active surveillance for autoimmune diseases including HT, should not be neglected in male patients with KD.

Another unusual feature of this case was the incidental microMTC that coexisted with HT. In addition, the patient's preoperative basal calcitonin level in our case was too low for the observed tumor size, even considering assay-dependent variation. We speculate that the cause of lack of detectable calcitonin may have been (1) tumor dedifferentiation and inability to make calcitonin, (2) preferential production of precursor peptides and aberrant forms of calcitonin, with the concomitant inability to produce mature calcitonin, or (3) a defect in the cellular secretory apparatus of calcitonin [5]. However, further studies including tumor immunohistochemistry for calcitonin, are needed to confirm this. Thus, such a marginal elevation of calcitonin in a patient with MTC can pose a diagnostic challenge for clinicians.

In conclusion, we experienced a unique case of Hashimoto's hypothyroidism with subsequent incidental detection of a microMTC. Due to the distinct cell origins and the paucity of cases with coexistence of these conditions, whether a pathogenic relationship exists among these three diseases remains unclear.

**Keywords:** Thyroiditis; Histiocytic necrotizing lymphadenitis; Neoplasms

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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