

Elevated serum CA 19-9 in association with Hashimoto thyroiditis

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ABSTRACT

Tumour markers are widely used in clinical practice. Elevated tumour markers can be observed in both malignant and benign conditions. Therefore, it is important for clinicians to be aware of the association of tumour markers with various disorders so that unnecessary investigations can be avoided without missing the malignant disorders. A 58-year-old woman who presented with weight loss and elevated carbohydrate antigen 19-9 (CA19-9) was referred to our hospital for evaluation and was diagnosed with Hashimoto thyroiditis. Investigations for underlying malignancy were negative. The CA19-9 level normalised subsequently, with restoration of the euthyroid state.

Keywords: Hashimoto disease, hypothyroidism, tumour markers

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INTRODUCTION

Tumour markers are widely used in clinical practice for the diagnosis and monitoring of treatment response or tumour recurrence.⁽¹⁾ Carbohydrate antigen 19-9 (CA 19-9) has been widely used for the diagnosis of pancreatic cancer. Elevated tumour markers, including CA 19-9, can be seen in both malignant and benign conditions.⁽¹⁻³⁾ Therefore, clinicians need to be aware of these rare associations so as to avoid unnecessary investigations without missing the malignant disorders. We present the case of a patient with elevated CA 19-9 levels who was referred for gastrointestinal evaluations and was later diagnosed with Hashimoto thyroiditis.

CASE REPORT

A 58-year-old Chinese woman was referred to our hospital from a private practice general practitioner for the evaluation of weight loss and elevated serum CA 19-9 (103 IU/ml; normal range < 37 IU/ml). The rest of the tumour markers, including serum carcinoembryonic antigen (CEA), alpha foetoprotein (AFP), CA 125 and

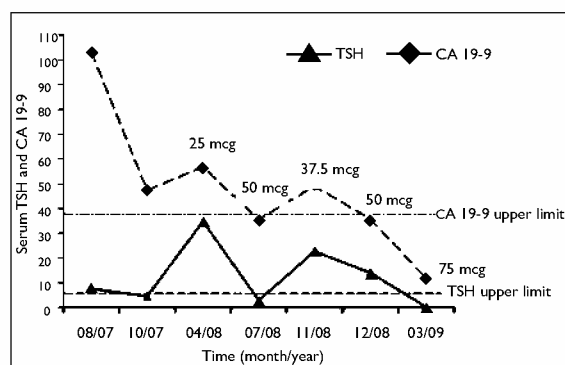


Fig. 1 Graph shows the serum carbohydrate antigen (CA) 19-9 level, serum thyroid stimulating hormone (TSH) level and thyroxine replacement dose at different timelines.

CA 15.3, were all within the normal limit. The initial concern was that of an underlying pancreatic neoplasm. At the same time, the serum thyroid stimulating hormone (TSH) was also mildly elevated at 7.71 mIU/L (normal range 0.40–4.70 mIU/L), with normal free T3 and T4 levels. Erythrocyte sedimentation rate (ESR) was mildly elevated, while the rest of the blood investigations were normal.

The patient's past medical history was relevant for having undergone treatment for tuberculous lymphadenitis (18 years ago) and hepatic haemangioma. Apart from one episode of bleeding per rectum, she denied any other gastrointestinal symptoms. There was no family history of any gastrointestinal malignancy, except for a brother who also had a thyroid disorder. On examinations, the patient seemed well, was thin-built and had no goitre or any hypothyroid features. Based on the thyroid function test, she was diagnosed to have sub-clinical hypothyroidism. However, as she did not have overt hypothyroid features, treatment was not started, and the situation was monitored with repeat blood evaluations.

Upper and lower gastrointestinal endoscopy showed gastritis and mild proctitis, respectively. Biopsies from the stomach showed chronic gastritis and *Helicobacter (H.) pylori* infection, whereas the rectal biopsies only showed nonspecific colitis. Computed tomography imaging of the abdomen and pelvis showed hepatic haemangioma. The pancreas and the biliary

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Table I. Association of elevated serum CA 19-9 with benign and malignant disorders.

	Benign disorders	Malignant disorders
Pulmonary	Bronchiectasis, fibrosis, emphysema, smoking, bronchiolitis, sequestrated lung, effusion, cystic fibrosis, interstitial pneumonia, tuberculosis	Lung cancer, mediastinal teratoma
Gastrointestinal	Obstructive jaundice, cholangitis, Mirizzi's syndrome, cirrhosis, primary sclerosing cholangitis, splenic cyst, ulcerative colitis	Hepatoma, cholangiocarcinoma, pancreatic, gastric and colorectal cancers
Genitourinary	Pyonephrosis, ureteric stones, hydronephrosis, tubo-ovarian, ovarian dermoid cyst	Prostate cancer, transitional cell carcinoma, ovarian cystic teratoma, bladder paraganglioma
Endocrine	Hashimoto thyroiditis, De Quervain's thyroiditis, thyroid adenoma	Thyroid carcinoma*
Rheumatological	SLE, rheumatoid arthritis, systemic sclerosis, dermatomyositis, Sjögren's syndrome, mixed connective tissue disease	
Others	Gravid macromastia	

* Includes anaplastic carcinoma, anaplastic transformation of papillary carcinoma and papillary carcinoma.
SLE: systemic lupus erythematosus

systems were normal. The *H. pylori* infection was successfully eradicated with our standard eradication therapy (omeprazole 20 mg bid, clarithromycin 500 mg bid and tinidazole 500 mg bid). Due to the history of previous tuberculosis (TB) infection and elevated ESR, the patient was also referred for respiratory evaluation. Chest radiography showed changes in previous TB infection, and three sputum smears were negative for acid fast bacilli. Bronchoscopy and alveolar lavage were negative for TB infection.

At the subsequent review, the patient complained of cold intolerance, and had a hoarse voice and slow relaxing reflexes. Repeat serum TSH was 34.6 mIU/L (normal range 0.35–5.5 mIU/L), free T3 3.09 pmol/L (normal range 2.61–5.67 pmol/L) and free T4 8.03 pmol/L (normal range 9.03–19.09 pmol/L). Serum CA 19-9 was also raised at 56.8 IU/ml. The patient was started on thyroxine 25 mcg daily, which was increased to 50 mcg one week later. Six weeks later, both the TSH and serum CA 19-9 levels had normalised. Serum thyroglobulin IgG was markedly elevated (> 1,100 IU/ml; normal range > 80 IU/ml; strongly positive), which was consistent with Hashimoto thyroiditis.

Both the serum CA 19-9 and TSH levels of the patient were again elevated six months later. It was found that the dose had been decreased to 37.5 mcg by the respiratory physician. The dose was subsequently increased, resulting in the normalisation of the serum CA 19-9 and TSH levels. The time trends of both the serum CA 19-9 and TSH levels are shown in Fig. 1. The patient remained well on follow-up.

DISCUSSION

CA 19-9 is synthesised by normal human tissue, including

pancreatic and biliary ductular cells as well as gastric, colonic, endometrial and salivary epithelia.⁽⁴⁾ Therefore, it is not unexpected that elevated serum CA 19-9 levels have been reported in many disorders, both benign and malignant. However, the levels tend to be high with malignant disorders. The associations that have been reported with elevated serum CA 19-9 are shown in Table I.

There have been several reports of elevated serum CA 19-9 in association with benign thyroid disorders, especially thyroiditis.⁽⁴⁻⁸⁾ In our case, the CA 19-9 level was only mildly elevated. In view of our patient's history of weight loss, underlying pancreatic neoplasm was initially suspected. The correlations of CA 19-9 with the thyroid status in our patient indicated a direct association. Associations with thyroid tumours, both benign and malignant, have also been reported.⁽⁹⁻¹²⁾

The exact underlying pathogenesis for elevated CA 19-9 with these thyroid disorders is unknown, although it is likely to be multifactorial. A recent study found that the mean serum CA 19-9 levels were increased in Hashimoto thyroiditis patients compared to those in hyperthyroid and euthyroid patients.⁽⁵⁾ In another study, the elevated mean serum levels of other tumour markers (AFP, CEA, CA 125 and CA 15-3) but not CA 19-9 were correlated with the hypothyroid states.⁽⁸⁾ This suggests that the hypothyroidism state itself, where the metabolic rate is reduced, may be important. However, the reasons certain markers are affected while others are not and why differences between different individuals exist remain unknown. Two studies have shown that CA 19-9 is expressed by inflamed thyroid tissue on immunohistochemical staining.^(4,7) Schmid et al have observed that the staining was strongest in

cases of late stage subacute thyroiditis.⁽⁴⁾ However, not all inflammatory thyroid disorders are associated with elevated serum CA 19-9. Elevated serum CA 19-9 levels and staining of CA 19-9 in neoplastic thyroid conditions, such as anaplastic thyroid carcinoma, anaplastic transformation from papillary carcinoma and papillary carcinoma, have also been reported.⁽⁹⁻¹²⁾ Similarly, not all patients with thyroid cancers have been found to express CA 19-9 in the cancer tissue.⁽¹²⁾

In conclusion, our case highlights the importance of awareness of the associations of elevated tumour markers with not just malignant conditions but also benign ones. False positives can lead to over-investigations and cause unnecessary anxiety to patients. Patients with elevated CA 19-9 should also be evaluated for underlying thyroid disorders that may be sub-clinical.

REFERENCES

1. Loi S, Haydon AM, Shapiro J, Schwarz MA, Schneider HG. Towards evidence-based use of serum tumour marker requests: an audit of use in a tertiary hospital. *Intern Med J* 2004; 34:545-50.
2. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; 24:5313-27.
3. Kim HR, Lee CH, Kim YW, Han SK, Shim YS, Yim JJ. Increased CA 19-9 level in patients without malignant disease. *Clin Chem Lab Med* 2009; 47:750-4.
4. Schmid KW, Ofner C, Ramsauer T, et al. CA 19-9 expression in subacute (de Quervain's) thyroiditis: an immunohistochemical study. *Mod Pathol* 1992; 5:268-72.
5. Parra JL, Kaplan S, Barkin JS. Elevated CA 19-9 caused by Hashimoto's thyroiditis: review of the benign causes of increased CA 19-9 level. *Dig Dis Sci* 2005; 50:694-5.
6. Takahashi N, Shimada T, Ishibashi Y, Oyake N, Murakami Y. Transient elevation of serum tumor markers in a patient with hypothyroidism. *Am J Med Sci* 2007; 333:387-9.
7. Tekin O. Hypothyroidism-related CA 19-9 elevation. *Mayo Clin Proc* 2002; 77:398.
8. Hashimoto T, Matsubara F. Changes in the tumor marker concentration in female patients with hyper-, eu-, and hypothyroidism. *Endocrinol Jpn* 1989; 36:873-9.
9. Leães CG, Sperb D, Garcia E, et al. Elevated CA 19-9 associated with thyroid follicular adenoma. *Endocrinologist* 2008; 18:176-7.
10. Hoshi S, Yoshizawa A, Arioka H, et al. [Anaplastic thyroid carcinoma with lung metastasis producing CA 19-9 and GM-CSF]. *Nihon Kokuyuki Gakkai Zasshi* 2000; 38:391-7. Japanese.
11. Ogawa M, Hori H, Hirayama M, et al. Anaplastic transformation from papillary thyroid carcinoma with increased serum CA19-9. *Pediatr Blood Cancer* 2005; 45:64-7.
12. Kamoshida S, Ogane N, Yasuda M, et al. Immunohistochemical study of type-1 blood antigen expressions in thyroid tumors: the significance for papillary carcinomas. *Mod Pathol* 2000; 13:736-41.