

Medullary Thyroid Carcinoma with Hepatic Metastasis Presenting as Watery Diarrhea for about 1.5 Years: A Case Report

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Abstract

Medullary thyroid carcinoma (MTC) is a rare cause of chronic diarrhea. When systemic symptoms such as diarrhea occur, distal metastasis often exists. The most common clinical presentation of MTC is solitary thyroid nodule. It was uncommon that chronic diarrhea as initial presentation of MTC without visible thyroid nodule. A 66-year-old woman suffered from watery diarrhea for 4 months. Irritable bowel syndrome was impressed initially. Water diarrhea persisted for another one year under medical treatment. Abdominal echography showed a 6.9cm non-cirrhotic hepatic tumor unexpectedly. Finally, core-needle biopsy for the hepatic tumor revealed metastatic medullary thyroid carcinoma. Physical examination revealed a palpable nodule in left thyroid lobe. Further thyroid ultrasonography disclosed multiple nodular goiter and the largest left thyroid nodule had punctate microcalcification. Fine needle aspiration cytology confirmed the diagnosis of MTC. Palliative surgery with total thyroidectomy, and liver bi-segmentectomy were done. After palliative surgery, watery diarrhea was partially improved. (J Intern Med Taiwan 2014; 25: 25-29)

Key Words: Medullary thyroid carcinoma, Chronic diarrhea, Liver metastasis

Introduction

Medullary thyroid carcinoma (MTC) accounts for 5-10% of all thyroid cancers. It arises from parafollicular or C cell of thyroid gland. There are sporadic (80%) and hereditary (20%) forms of MTCs. The latter is associated with either familial MTC, multiple endocrine neoplasia (MEN) 2A, or

MEN2B^{1,2,3}.

Palpable hard thyroid nodules or enlargement of regional lymph nodes is usually the first presentation of MTC. Distal metastases may arise in the liver, lungs, bones and less frequently in the brain and skin¹. Systemic symptoms including bone pain, flushing and diarrhea usually present while there is distal metastasis^{2,3}. Occasionally, distal metastasis

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may be first noted². The systemic symptoms of MTC are not specific, so, it is more challenging for clinical doctor to diagnose MTC when systemic symptoms are the first presentation.

We report a 66-year-old woman with MTC and hepatic metastasis presenting as chronic diarrhea for about 1.5 years.

Case report

A 66-year-old woman with no history of systemic diseases presented due to watery diarrhea more than 10 times daily for 4 months. She denied abdominal pain, fever or vomiting. There were not any aggravating or relieving factors associated with her diarrhea. As her stool examination was negative, colonoscopy was done which showed only mixed hemorrhoid. Irritable bowel syndrome was impressed at that time, and anti-spasmodics and anti-diarrheals were prescribed to her.

However, watery diarrhea persisted for another one year, and body weight loss of 7 kg occurred during this period of time. She later visited a general practitioner. Unexpectedly, her abdominal ultrasonography revealed a 6.9 cm non-cirrhotic hepatic tumor. Furthermore, her virological markers of HBsAg and anti-HCV were negative, and the serum alpha-fetoprotein level was normal (1.45 ng/ml). She was referred to our gastroenterologist clinic for further investigation. Tumor markers revealed high CEA (208.5 ng/ml) and normal CA19-9 (35.6U/ml) levels. Tri-phase abdominal CT scan displayed three non-cirrhotic hypervascular lesions and the largest one is about 6.5 cm in diameter at S4 of liver with central necrosis (Fig. 1). Admission was arranged for further investigations.

She was 154 cm tall and weighted 46.2 kg. Her sclera was anicteric. Grade I left nodular goiter was noted. Her abdomen was soft and hepatomegaly without tenderness. Liver function test showed normal level of albumin (3.8 g/dL), total bilirubin (0.4 mg/dl) and ALT (22 IU/L), but elevated AST

(74 IU/L). Core-needle biopsy for the largest hepatic tumor was done.

Pathology revealed metastatic carcinoma, and immunohistochemical stains showed positive TTF-1, calcitonin, and synaptophysin (Fig. 2). A metastatic medullary carcinoma from the thyroid is highly suspected. Thyroid ultrasonography showed multiple nodular goiter. The largest left nodule measuring about 3.44 x 2.73 x 2.43 cm had micro-calcifications (Fig. 3) and fine needle aspiration cytology confirmed the diagnosis of MTC (Fig. 4). Her serum calcitonin level was more than 10,000 pg/ml. 24-hour urine VMA and catecholamine were checked to screen for pheochromocytoma, and the



Figure 1. A 6.9 cm non-cirrhotic hepatic tumor at S4 was disclosed by abdominal CT scan.



Figure 2. Immunohistochemical stain of liver biopsy specimen showed positive calcitonin.

results were all within normal limit.

Palliative surgery with total thyroidectomy and liver bi-segmentectomy were done. Amyloid accumulation was noted in the pathological specimens of thyroid (Fig. 5) and liver. The post-operative serum calcitonin level decreased to 3736 pg/ml, and diarrhea only partially improved.

Discussion

When MTC is diagnosed, it is not only to evaluate disease extent, but also to screen for pheochromocytoma and hyperparathyroidism to find out whether MTC is sporadic or hereditary. RET proto-oncogene should be studied in patient with

hereditary form^{2,3}. Our patient had sporadic MTC, so no further gene study was done.

Palpable hard thyroid nodules or enlargement of regional lymph nodes is usually the first presentation of MTC. Ipsilateral lymph nodes in level II to VI area of neck are the most common pattern of lymph node metastasis in MTC³. In patient with an MTC less than 1cm, there are about 20-30% of nodal metastasis. If it is bigger than 4cm, there are up to 90% of nodal metastasis². Distal metastasis may arise in the liver, lungs, bones and less common in the brain and skin¹. About 10-15% of patients have distal metastasis at the time MTC is diagnosed⁴. Distal metastasis to lungs, bone and liver may present initially in 15-25% of patients of MTC⁵. While there is distal metastasis, systemic symptoms including bone pain, flushing and diarrhea usually present^{2,6}.

Calcitonin and CEA are the most reliable tumor markers of MTC. The level of calcitonin correlates with tumor size. If preoperative calcitonin level is within 10-40 pg/mL, it may predict nodal metastasis. Distal metastasis may occur if preoperative calcitonin level is higher than 150 pg/ml and is frequently higher than 1,000 pg/ml. Besides, if preoperative CEA level is higher than 30 ng/ml, it highly predicts that MTC is incurable by operative intervention. If CEA levels is higher than

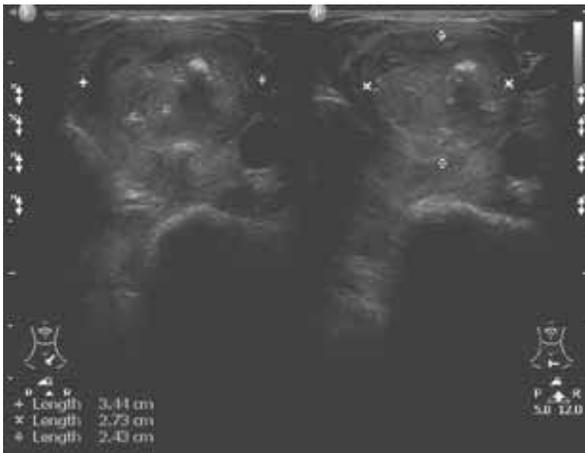


Figure 3. The largest left thyroid nodule measuring about 3.44 x 2.73 x 2.43 cm had microcalcifications.

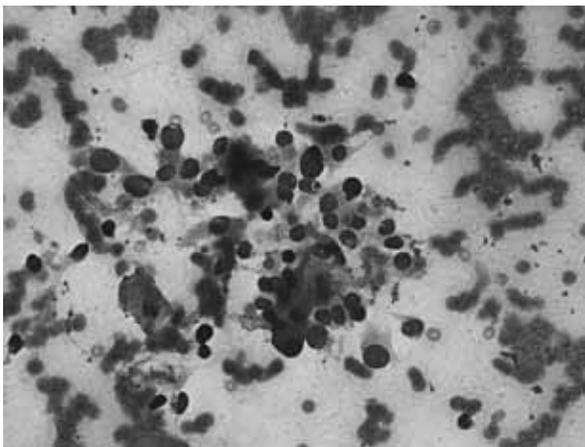


Figure 4. Thyroid fine needle aspiration cytology disclosed medullary thyroid carcinoma.

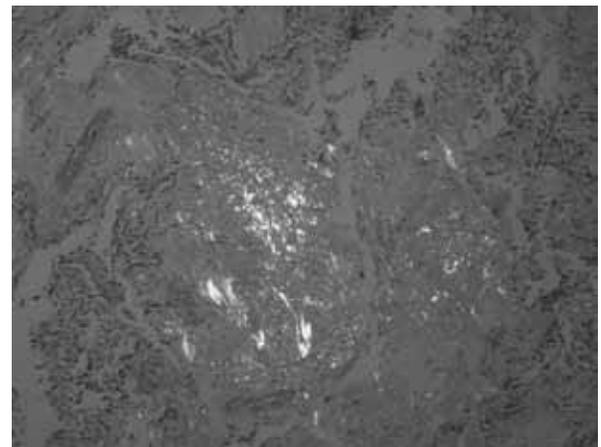


Figure 5. Thyroid tissue showed apple green appearance under polarized light.

100 ng/ml, it highly predicts extensive lymph node and distant metastasis⁴. Our patient's preoperative calcitonin and CEA level are >10,000 pg/ml and 208.5 ng/ml respectively.

The only curable treatment of MTC with or without any local and regional metastases is complete surgical removal of all neoplastic tissue. Total thyroidectomy with bilateral central neck lymph node dissection is recommended in patient without distal metastasis⁶. In patient with distal metastasis, the survival rate is about 20% at 10 years¹. The treatment goal in such patients is palliative and strategically prophylactic. Less aggressive neck surgery may be recommended according to the patient's clinical situation⁶. There is no evidence that current treatments for advanced MTC such as external beam radiation therapy, palliative surgery, palliative chemotherapy and clinical trials-- tyrosine kinase inhibitors have improvement in overall survival, but they can improve the local or systemic symptoms^{3,8}. If the patient can't tolerate external beam radiation therapy and palliative surgery, tyrosine kinase inhibitor may be a choice for patient with advanced MTC.

MTC is a rare cause of chronic diarrhea. There are many secretory products of MTC which cause diarrhea, including calcitonin, CEA, chromogranin-A, dopa-carboxylase, histaminase, somatostatin, gastrin-releasing peptide, thyrotropin-releasing hormone, and ACTH¹. The mechanism between these secretory products and diarrhea is not well known, except calcitonin-induced secretory diarrhea. This mechanism may be direct activation of

calcitonin receptor by calcitonin in intestinal epithelial cells which induce Cl⁻ secretion⁹. Therefore, further target therapy at calcitonin receptor may treat calcitonin-induced diarrhea in advanced MTC patients.

In conclusion, MTC is a rare cause of chronic diarrhea, MTC should be kept in mind if no definite gastrointestinal cause accounts for the chronic diarrhea.

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甲狀腺髓質癌併肝轉移以慢性水瀉為表現

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摘 要

腸胃科門診遇見慢性腹瀉的病患，由於其原因很多，病患如果沒有明顯的甲狀腺腫大，甲狀腺髓質癌是不容易被列為起初的鑑別診斷中。我們所報告的這位66歲女性，起初因水瀉四個月到腸胃科門診求診。當時安排的大便以及大腸鏡檢查並沒異狀。病患被診斷為大腸狂躁症。再經過一年多，水瀉並沒有改善。腹部超音波檢查意外發現一顆6.9公分大小的肝腫瘤。B型及C型肝炎檢查都呈陰性，胎兒蛋白數值正常。肝腫瘤穿刺病理報告為轉移性甲狀腺髓質癌。此時理學檢查發現病人有一顆看不明顯但摸得到的左側甲狀腺腫瘤。甲狀腺超音波發現左葉有一顆有鈣化的節結。細胞刺針結果確診為甲狀腺髓質癌。甲狀腺髓質癌併肝轉移以慢性腹瀉為最初表現，在臨床上病患卻沒有明顯的甲狀腺腫大是較少見的，這也增加了診斷的難度。若慢性腹瀉不是由腸胃道問題造成的，甲狀腺髓質癌要被列為鑑別診斷中，仔細的頸部理學檢查是必須的。