Occult medullary carcinoma of thyroid - an unusual clinical and pathologic presentation
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Abstract

Background: Medullary thyroid cancer is a neuroendocrine tumor originating from the parafollicular C cells of the thyroid which secrete calcitonin. MTC accounts for approximately 4% of all clinically detected thyroid malignancies. The prevalence of occult MTC in the general population is not well established.

Case Presentation: We describe a rare patient with occult sporadic MTC who presented with cervical lymphadenopathy and an asymptomatic mediastinal mass, including the mediastinum, is a common occurrence in patients with clinically apparent MTC [2, 3].

Medullary carcinoma grows with a very slow but progressive indolent course; the growth of the primary tumor locally is usually imperceptible compared with its spread and invasion into neck structures and metastasis to cervical lymph nodes and distant nodes. In this report we describe a rare patient with occult sporadic MTC who presented with cervical lymphadenopathy and an asymptomatic mediastinal mass and elevation of calcitonin and carcinoembryonic antigen (CEA) levels.

Case Report

A 29 years old Saudi male patient was evaluated for neck swelling for two years prior to presentation on May 2012. The swelling was small, and gave the patient no discomfort initially. The swelling increased very slowly in size over two years, until May 2012 it had become noticeable enough to seek medical advice. It remained painless and there were no pressure symptoms. The patient was clinically euthyroid and had unremarkable medical history. The family history was negative for thyroid diseases or endocrinopathies.

There was no goiter or palpable thyroid nodules. There was enlargement of the left upper anterior cervical lymph node. Ultrasound and CT scan neck and chest with intravenous contrast revealed a solitary enlarged left upper deep cervical lymphadenopathy just beneath the sternomastoid muscle, showing intense heterogenous enhancement with contrast. The surrounding fat planes were preserved. No abnormal cervical lymph nodes could be identified elsewhere.

The thyroid gland is normal in size, shape and attenuation (Figure 1). Left cervical lymph node fine needle aspiration (FNA) cytology revealed metastatic carcinoma probably medullary carcinoma of the thyroid or nasopharyngeal carcinoma. Right and left ventricular of the larynx, lingual and laryngeal surface of epiglottis, right and left vallecular of the hypopharynx, pyriform fossa of the hypopharynx, base of the tongue and nasopharynx biopsies were obtained and found to be negative for cancer. Ultrasound of the thyroid showed multiple tiny ill-defined nodules in the left thyroid lobe (Figure 2). FNA of the left thyroid lobe showed chronic thyroiditis and benign cystic colloid nodule.

Serum calcium: 2.21 mmol/L (normal=2.15-2.55), parathyroid hormone: 4.09 pmol/L (normal=1.6-6.9), TSH: 7.21 mIU/L (normal=0.27-4.2), Free T4: 20.18 pmol/L (normal=12-22), 25-hydroxyvitamin D: 25.4 nmol/l, CEA: 35 ng/ml (normal=0-3.4), calcitonin: 445 ng/L (normal=0-12). The patient was further investigated for pheochromocytoma in order to exclude MEN 2 syndrome and carcinoid syndrome; 24 hours urine collection showed creatinine: 15.2 nmol (normal=7.0-

Introduction

Approximately 10% of patients with thyroid cancer have the histopathologic subtype termed medullary thyroid cancer (MTC) [1]. An occult primary in MTC is recognized in familial cases. It is rare, and even rarer in sporadic cases. Recognition and diagnosis of the primary lesion is difficult and usually is made only with secondary changes - evidence of local extension or metastases, or from evidence of involvement with other systems associated with this lesion. Metastatic dissemination to both the central and lateral cervical lymph node compartments, including the mediastinum, is a common occurrence in patients with clinically apparent MTC [2, 3].

Medullary carcinoma grows with a very slow but progressive indolent course; the growth of the primary tumor locally is usually imperceptible compared with its spread and invasion into neck structures and metastasis to cervical lymph nodes and distant nodes. In this report we describe a rare patient with occult sporadic MTC who presented with cervical lymphadenopathy and an asymptomatic mediastinal mass and elevation of calcitonin and carcinoembryonic antigen (CEA) levels.

Figure 1(a): Ultrasound of the posterior triangle of the neck shows enlarged posterior triangle lymph node (white arrow). Figure 1(b): Contrast enhanced CT scan of the neck shows enlarged lymph node with significant enhancement (white arrow). Figure 1(c): Mediastinal lymphadenopathy.

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Discussion

MTC is a neuroendocrine tumor originating from the parafollicular C cells of the thyroid which secrete calcitonin. MTC accounts for approximately 4% of all clinically detected thyroid malignancies [4]. The prevalence of occult MTC in the general population is not well established. A systematic review of 24 autopsy series reported a prevalence of 0.14% of occult MTC in unselected autopsies [5]. This prevalence may be an underestimate because of the variability between the series in terms of slice thickness, calcitonin immunostaining, and extent of the pathological exam of the thyroid [5]. Whereas autopsy series report a very low, prevalence of undiagnosed MTC, patients undergoing thyroidectomy for nodular thyroid disease have a rate of approximately 10–15% of cases [5]. The prevalence of MTC in nodular goiter can be estimated from several prospective and retrospective series. For series with more than 100 patients, MTC prevalence ranges from 0.1 to 1.3%. The composite prevalence of MTC is 0.31% across 15,992 patients [5, 6].

MTC is more often located at the junction of the upper third and the lower two-thirds of the thyroid lobes. Metastatic dissemination to both central and lateral cervical lymph nodes occurs frequently like in our case. Cervical lymph node metastases are found in 20-30% of patients with MTC <1 cm in diameter, in 50% of patients with a tumor 1–4cm in diameter and in up to 90% of patients with a tumor >4cm in diameter [7, 8].

Our patient could be spared the nasopharyngeal and hypopharyngeal biopsies if serum calcitonin and CEA were done earlier knowing the limitations of fine-needle aspiration of the thyroid gland to accurately diagnose MTC. Serum CEA, a glycoprotein involved in cell adhesion, is usually elevated when MTC is diffuse and distant metastases are present, but not in preclinical MTC [9]. CEA is a tumor marker in colorectal carcinoma, gastric carcinoma, pancreatic carcinoma, lung carcinoma and breast carcinoma [10].

Serum calcitonin levels are elevated in C-cell disorders, thus making it a sensitive clinical marker for MTC. There has been interest in the routine use of serum calcitonin level screening in the evaluation of nodular thyroid disease [11]. Routine serum calcitonin screening is standard in the initial evaluation of thyroid nodules in Europe based on the 2006 European Thyroid Association guidelines and the 2010 American Association of Clinical Endocrinologists [12, 13]. Conversely, the 2009 American Thyroid Association guidelines for the management of thyroid nodules could not recommend for or against the routine measurement of calcitonin in the initial evaluation of thyroid nodules [14]. This decision was based, in part, on a lack of convincing evidence that screening with serum calcitonin levels decreased MTC-related mortality, improved overall patient outcomes, or demonstrated cost-effectiveness.

There is controversy regarding the sensitivity of FNA for MTC; the diagnostic accuracy of the technique may vary widely in clinical practice. A German study reported that the accuracy of diagnosing MTC by FNA was 89% by experienced cytopathologists; furthermore, in 98.9% of patients, the cytopathology findings indicated a need for thyroidectomy. Combined data for the three largest cytopathology series with surgical ascertainment indicate that 79% of the patients had FNA positive for MTC, and 96% indicated some form of thyroid neoplasm prompting surgery. Variation in sensitivity has been attributed to inconsistent use of calcitonin immunohistochemistry, difficulty in recognizing typical and variant MTC cytomorphology, and especially problems stemming from multiplicity of nodules and the challenges of selecting appropriate nodules for FNA [15]. In a small
fraction of MTC cases, familial inheritance is occult but discoverable. Thus, in 5–6% of cases, a germline RET mutation is present even when the family history is initially judged negative [16]. Subsequent genetic testing typically reveals the presence of less penetrant RET mutations. Very careful attention to family history is sometimes useful in detecting these situations, including an appreciation of when the family history has low information content due to small family size, early death, or lack of contact with biological parents and sibs. In addition to family history, the presence of systemic symptoms pointing to MTC can be informative—especially diarrhea, flushing, and bone pain. 10% of MTC patients had such systemic symptoms at presentation, usually in the setting of widespread metastatic disease.

Given the limitations of history and ultrasound clues to MTC and the potential shortcomings of FNA, preoperative diagnosis can be difficult. In the majority of cases, to reduce the rate of MTC cases diagnosed postoperatively, the preoperative diagnosis could be based on the results of thyroid fine-needle aspiration (FNA), serum calcitonin level, and RET proto-oncogene testing. In the 2009 American Thyroid Association (ATA) guidelines for the surgical management of known MTC, the extent of calcitonin preoperative elevation guides the selection of preoperative imaging studies, which in turn influence the extent of surgery.

Conclusion

Consistent with the above literature review, our practice is to recommend basal calcitonin testing for thyroid nodule patients with increased risk of MTC, including those with a family history of MTC, with a diagnosis of hyperparathyroidism or pheochromocytoma, or symptoms of flushing or diarrhea. We also consider calcitonin testing in patients with FNA results suspicious for malignancy that lack typical features of papillary or follicular neoplasms, and in patients with a metastatic pattern typical of MTC. On the other hand, patients with benign FNA results from a solitary nodule are rarely offered calcitonin testing. If the basal calcitonin level is greater than 80 pg/ml in males or at a lower threshold in females, we generally offer total thyroidectomy, including central neck dissection in patients with marked calcitonin elevation.

Competing interests: The authors declare that no competing interests exist.

References