Case Report

Hirschsprung disease of the colon, a vaginal mass and medullary thyroid cancer – a RET oncogene driven problem

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ABSTRACT

This case report emphasizes the fact that all patients with Hirschsprung disease should be screened for RET Oncogene mutation as there is a well known association between Hirschsprung Disease and Multiple Endocrine Neoplasia (MEN) Type 2A. It also reminds us that Medullary Thyroid Carcinoma is known to cause elevated levels of CEA which does not originate from gastrointestinal tract.

KEY WORDS

Hirschsprung Disease, RET Oncogene, Medullary Thyroid Cancer


Case Report

A 55 year old postmenopausal woman presented with vaginal spotting which rapidly progressed to more severe bleeding.

On examination she was found to have a mass in the vaginal vault which was close to, but not attached to, the cervix. Excisional biopsy of the lesion in the vaginal wall and biopsies of the endometrium, along with cervical conization revealed adenocarcinoma in the vaginal lesion only (Figure 1). Immunostains were performed and these showed a pattern which was most compatible with intestinal differentiation (CK20 and CDX-2 positive, CK7 focally positive (less than 5% of cells), ER and PR both negative, P16 and CEA variably positive) (Figure 2). The Tissue of Origin Test®, run on micro dissected tumor tissue, showed the highest similarity score of 91.1 for a colo-rectal origin. The 14 other tissue types in the panel had similarity scores of less than or equal to 5. CT scan and MRI of the abdomen and pelvis showed several cavernous hemangiomas and cysts in the liver but there was no evidence of any residual or metastatic disease. PET scan was also unremarkable.

Additional history of Hirschsprung disease (HD) as a child, which had required surgical correction (with complications of obstruction and fistula formation at age 19 which were addressed with additional surgery), was obtained. Anorectal examination was grossly unremarkable and random biopsies showed mucosa consistent with a squamous papilloma but with no evidence of malignancy. Colonoscopy was normal. Of note, her CEA level at this time was found to be elevated at 35 ng/ml (normal range 0-5 ng/ml).

Family history was significant for colorectal cancer in her mother and grandfather and endometrial and appendiceal cancer in a cousin. Her brother had also been treated for HD.

At this time she was referred to medical oncology. Physical examination, including a pelvic exam and careful exam of the thyroid, was unrewarding. A repeat PET scan now showed slightly irregular, moderately increased radionuclide accumulation in both lobes of the thyroid. Ultrasound showed a diffusely heterogeneous gland mimicking confluent nodules. TSH was normal but unstimulated serum calcitonin was elevated at 121 pg/mL (Reference Value - Basal: <8) and CEA remained abnormal but stable at 37 ng/ml. Ultrasound guided fine needle biopsy of the thyroid was consistent with medullary thyroid carcinoma (MTC). As a result, she underwent total thyroidectomy and paratracheal lymph node dissection. A 22 gram thyroid revealed a 1.5 cm yellow-tan, firm nodule in the left superior lobe and a 0.7 cm yellow-tan, firm nodule...
in the right inferior lobe. Histologic examination of each of the nodules revealed sheets and nests of monomorphic cells with abundant granular cytoplasm and uniform nuclei with stippled chromatin (Figure 3). Immunohistochemical evaluation of these cells revealed positive staining with calcitonin (Figure 4), chromogranin, and synaptophysin. Staining was negative with thyroglobulin. There was no lymph node involvement. The diagnosis of T1b N0 MTC was thus confirmed. Both CEA and calcitonin levels normalized following surgery.

A subsequent evaluation for MEN (Multiple Endocrine Neoplasia) syndrome included a 24-hour urine collection for metanephrine and normetanephrine and both metanephrine 47 mcg/24hrs (reference range 30-180 mcg/24hrs) and normetanephrine 126 mcg/24hrs (reference range 128 - 484 mcg/24 hrs) were found to be normal. Despite these normal findings, a high suspicion for RET oncogene mutation persisted, given her history of MTC.
as well as a history of HD, with the result that genetic consultation was requested.

Following appropriate counseling, she was tested and found to be positive for a specific RET mutation, C620W, diagnostic of MEN2A. Her sister then also tested positive for the same RET mutation. This particular mutation is known to be associated with familial HD, but in contrast to other RET gene mutations, is less strongly correlated with parathyroid and adrenal disease.

She has continued to have physical examination, blood tests and serial imaging in follow-up, and thus far there has been no evidence of recurrent or new disease. The origin of the adenocarcinoma in the vaginal vault is still unclear. Given the definitive diagnosis of medullary thyroid carcinoma, immunohistochemical staining for calcitonin was performed on the tumor cells and was negative. Therefore, a diagnosis of adenocarcinoma of unknown origin remains and any relationship to the MEN syndrome or the RET germline mutation is undefined. Continued surveillance for a possible primary site continues.

**Discussion**

Germline mutation of the RET (REarranged during Transfection) proto-oncogene (10q 11.2) may result in constitutively activated RET protein. RET protein consists of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain, which contains two tyrosine kinase subdomains (TK1 and TK2) that are involved in the activation of several intracellular signal transduction pathways. There is a correlation between specific mutations and specific disease phenotypes (1). Mutations in RET exons 10 (codons 609, 611, 618, and 620) or 11 (codons 630 or 634), are seen in the majority of MEN2A and FMTC (Familial medullary thyroid cancer) cases resulting in alterations in the cysteine-rich region of the RET protein’s extracellular domain. A mutation in codon 634 in exon 11 is the most common genetic defect in this disorder and is strongly associated with hyperparathyroidism and pheochromocytoma (PC) in MEN2A. Mutations in codons 768 (exon 13), 804 (exon 14) and 891 (exon 15), which result in changes in the intracellular tyrosine kinase domains, are found only in FMTC (2). In MEN 2B patients, the mutation involves codon 918 in exon 16 in 95% of cases and, rarely, codon 883 in exon 15 with resultant change in either methionine or alanine, respectively, in the tyrosine kinase domain of RET (3).

Germaine to our patient and her family, in the rare cases where MEN 2A and HD co-exist, germline RET mutations most often involve exon 10 (1,4), especially codon 618 or 620 (1,5). This association poses a scientific dilemma, as the mutations in MEN are gain of function mutations with RET acting as a dominantly acting oncogene (6,7) and those of HD result in loss of function (8,9). However, a unifying hypothesis has been suggested in that mutations in exon 10 result in a relatively weaker activation of the RET protein kinase, perhaps just sufficient to cause MTC. A concurrent decrease in the total number of receptor molecules on the cell surface possibly results in insufficient numbers of receptors for normal gangliogenesis and migration and/or for the prevention of inappropriate apoptosis, with HD as a result (10,11).

This case teaches us a number of important lessons. Firstly, that all patients with a history of HD should consider screening for RET mutations (it should be noted that RET mutations are the predominant but only one of a number of possible causes of HD) (12,13), as there is a well-established association between HD and MEN2A. If present, this could facilitate early diagnosis of MEN2A with resultant thyroidectomy prior to the onset of MTC or at least prior to the development of metastatic disease. Equally, it is desirable that all patients with MTC should be tested for germline RET mutations in accordance with 2009 American Thyroid Association Guidelines for Management of MTC (14). While somatic mutation of RET gene are limited to C cells with no additional risk of neoplasia in other tissues (approximately 50% of patients with sporadic MTC have somatic RET mutations), germline mutations affect all the tissues derived from neural crest such as neural cells, neuroendocrine cells and urogenital cells, causing MEN syndromes and rarely HD. Secondy, it reminds us that MTC is a potential cause of elevated CEA which does not have its origins in bowel cancer. Unlike calcitonin levels, which are susceptible to stimulation and hence tend to fluctuate on serial measurements, CEA levels are more stable and can be used as a tumor marker for MTC. Elevated CEA levels have been associated with increased tumor aggressiveness, tumor recurrence, and poor prognosis. Thirdly, it illustrates the value of a thorough genetic evaluation in all patients suspected of having a genetic component to their disease. This could have profound implications not only for the index patient but also for family members. Finally, it reconfirms the value of a good history and physical examination, and the therapeutic challenges presented by cancer of unknown origin, even with the sophisticated genome based diagnostics available today (15).
References


