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Managing uncertainty in genetic testing: A case report

Genetic test results can confirm a diagnosis, but they can also be ambiguous and lead to uncertainty and anxiety.

ABSTRACT: A 49-year-old woman was found to have primary hyperparathyroidism secondary to parathyroid carcinoma. Investigations led to an incidental finding of renal cell carcinoma and elevated serum gastrin levels. An octreotide scan, endoscopic ultrasound biopsy, and DOPA PET scan found no evidence of gastrinoma. The results of subsequent testing for gene mutations responsible for multiple endocrine neoplasia type 1 and hyperparathyroidism-jaw tumor syndrome were inconclusive. The patient was thus confronted with an unsettling combination of evidence for parathyroid carcinoma, renal cell carcinoma, and elevated gastrin levels, and the uncertainty of the genetic test results. In this case, the patient was counseled and encouraged to contact the genetic testing program again in a few years. As genetic testing becomes increasingly accessible, clinicians must consider the ethical, emotional, and economic consequences of inconclusive test results on the patient and family members.

This article has been peer reviewed.

Case data

In July 2011, a 49-year-old female patient presented to her family physician with worsening of her long-standing dyspepsia. She had a history of gastroesophageal reflux, hypertension, dyslipidemia, and osteoporosis. She was taking hydrochlorothiazide (12.5 mg daily), valsartan (160 mg daily), carvedilol (12.5 mg b.i.d.), simvastatin (80 mg daily), and ranitidine (150 mg b.i.d.). Investigations diagnosed primary hyperparathyroidism with a grossly elevated parathyroid hormone (PTH) level at 119 pmol/L (reference range 1.2-8.4 pmol/L), elevated ionized calcium at 1.88 mmol/L (reference range 1.10-1.30 mmol/L), low phosphorus at 0.67 mmol/L (reference range 0.80-1.40 mmol/L), and low magnesium at 0.36 mmol/L (reference range 0.70-1.10 mmol/L). Her 24-hour urine calcium level was elevated at 7.7 mmol/day (reference range 1.0-7.0 mmol/day). Her estimated glomerular filtration rate was low at 42 mL/min/1.73m^2, and an investigative renal ultrasound revealed bilateral renal masses. A left partial nephrectomy was performed eventually, confirming the presence of a clear cell renal cell carcinoma.

Initial management of the patient's hypercalcemia consisted of discontinuing valsartan and hydrochlorothiazide, and initiating aggressive IV fluid administration, furosemide, pamidronate, and subcutaneous calcitonin. This normalized her ionized calcium level to 1.25 mmol/L. A CT scan of the neck found a well-defined oval mass posterior to the right lobe of the thyroid. A right parathyroidectomy was performed and pathology examination revealed a nonfunctioning parathyroid adenoma. Postresection, the patient's PTH level remained elevated with normal ionized calcium levels. Over the next 3 months, the patient experienced recurrent hypercalcemia that became refractory to conventional treatment, leading to an endocrinology consultation.

Upon consultation, cinacalcet (60 mg daily) was initiated and her ionized calcium level increased from 1.45 mmol/L to 1.50 mmol/L. Under normal circumstances, cinacalcet acts as a calcium-sensing receptor (CaSR) agonist to treat hypercalcemia; how-

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ever, its effectiveness depends on CaSR levels. The patient's poor response to cinacalcet may have been due to chronic hypercalcemia, which caused downregulation of CaSR in the parathyroid gland.

A sestamibi parathyroid scan showed a focus of increased activity in the lower half of the left lobe of the thyroid gland. After the patient underwent a left parathyroidectomy, intraoperative PTH levels decreased from 117.2 pmol/L to 29.3 pmol/L. Pathology examination revealed a parathyroid carcinoma.

Postoperatively, the patient's phosphorous and magnesium levels plummeted immediately, and she was diagnosed with hungry bone syndrome and placed on high doses of calcium supplementation (12 600-mg tablets daily) and calcitriol (0.5 mcg b.i.d.). Follow-up investigations revealed a normal ionized calcium level of 1.22 mmol/L and a high PTH level of 11.8 pmol/L, felt to be a result of hungry bone syndrome with depleted calcium stores. Over the next few months the patient was able to normalize her PTH with decreasing requirements for calcitriol.

The unusual presentation of parathyroid carcinoma in conjunction with bilateral renal masses, including a renal cell carcinoma, was suggestive of a tumor syndrome. An investigation for multiple endocrine neoplasia syndrome was undertaken with a CT scan of the head, which found no intrasellar mass. Prolactin, reproductive hormones, cortisol, and thyroid hormone levels were within normal limits. Insulin-like growth factor was mildly elevated at 301 mcg/L (reference range 107-283 mcg/L) and of uncertain significance. A follow-up glucose suppression test was not performed. Gastrin was found to be elevated at 2140 ng/L (normal value is less than 115 ng/L). An octreotide scan found no evidence of gastrinoma; however, because over 50% of small (less than 1 mm) gastrinomas are not detected by this method the patient underwent endoscopic ultrasound (EUS) to investigate further for gastrinoma. Pathology results from the EUS biopsy were negative for gastrinoma, and results from a DOPA PET scan were also negative for gastrinoma. Genetic tests for hyperparathyroidism-jaw tumor syndrome (*CDC73* gene mutation) and multiple endocrine neoplasia type 1 (*MEN1* gene mutation) were unable to confirm a diagnosis on a molecular basis.

The patient and her husband became anxious when informed of the ambiguous results, and were concerned that their young son could be at risk of disease. They were encouraged to contact the genetic testing program again in a few years to inquire about further developments in genetic testing.

Discussion

The purpose of clinical genetic testing is to provide results that inform medical management. As genetic testing becomes increasingly accessible, clinicians must consider the ethical, emotional, and economic consequences of genetic testing on the patient and family members. Genetic testing can be valuable in confirming a clinical diagnosis; however, results can also be ambiguous and lead to uncertainty and anxiety. As well, inconclusive results may lead to further onerous tests with equally inconclusive results.

For rare diseases such as multiple endocrine neoplasia, sensitivity and specificity of these tests are difficult to determine given the small numbers of patients and the heterogenous genetic findings.

At present, many genetic tests do not identify all of the possible gene mutations that can cause a particular condition. In this case, over 400 mutations have been identified that may lead to multiple endocrine neoplasia type 1, and over 40 mutations have been identified in hyperparathyroidism-jaw tumor syndrome.[1,2] For rare diseases such as multiple endocrine neoplasia, sensitivity and specificity of these tests are difficult to determine given the small numbers of patients and the heterogenous genetic findings. For the *MEN1* mutation, sensitivity is 80% to 90% in patients with a family history, but only 65% in sporadic cases.[3,4] For the *CDC73* mutation, sensitivity is poor at 20% to 29% in patients with sporadic parathyroid carcinoma.[5,6] Furthermore, identification of pathological genetic variants is often carried out in case control trials that do not provide accurate results

for the prevalence of these variants in the healthy population.[7] This creates challenges in interpreting results, as a negative finding does not rule out a genetically determined disease.

For the clinician, the challenge lies in interpreting and disclosing inconclusive results to patients. Interpretation of inconclusive genetic variants found on testing can be approached in various ways. In the case described here, it was not possible to confidently identify a genetic variant as deleterious or benign.

Reviewing a gene-specific mutation database or the literature to see if the variant has been previously identified can guide interpretation. However, when there is ongoing ambiguity, personal and family histories of similar presentations should be used to guide clinical management, including increased medical surveillance.

For health care professionals, frustration is a well-documented reaction to ambiguous results.[4] There is also evidence that health care professionals struggle with delivering news of uncertainty.[4] Many clinicians feel that before performing genetic tests, it is important to prepare the patient by discussing the benefits and risks of genetic testing. The patient must be informed that genetic testing is not 100% sensitive and specific, since there is a public misconception that it is.[8] A trained genetic counselor can be a helpful resource. Genetic testing is of particular importance when there are treatment implications. If a definitive or prophylactic therapy is not available for a given disease, genetic testing may not be the best clinical option.

For the patient, inconclusive results can bring on anxiety, anger, depression, or guilt. Studies have shown that patients would prefer to be told what information is available and deal with the uncertainty rather than not be told.[9] However, strong reactions can lead patients to underuse or overuse preventive measures. Furthermore, a patient's interpretation of probabilistic information may be oversimplified. Evidence has shown that patients often think in the binary form when interpreting statistical information: "I *will* get the disease" or "I *will not* get the disease."[5] This is where the physician and an interdisciplinary team of counselors and geneticists can provide education and emotional support. The most respectful way to treat patients is to disclose what is known openly and candidly and to discuss the uncertainties.

Summary

The case of a 49-year-old woman demonstrates the difficulty of managing uncertainty in genetic testing. The patient was found to have primary hyperparathyroidism secondary to parathyroid carcinoma. After investigations led to an incidental finding of renal cell carcinoma, she underwent genetic testing for multiple endocrine neoplasia type 1 and hyperparathyroidism-jaw tumor syndrome. The results were ambiguous, which made the patient and her husband anxious and raised concerns about their son's risk of disease. The patient was counseled to contact the genetic testing program again in a few years.

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