Primary Hyperparathyroidism and Persistent Peptic Ulcers: A Prelude to a Diagnosis of MEN1 Caused by a Novel Gene Mutation

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INTRODUCTION

Multiple Endocrine Neoplasia 1 (MEN1) is a rare syndrome characterized by a propensity for pituitary, parathyroid, pancreatic, and adrenal tumors.

Over 200 pathologic mutations have been reported. Penetrance is high, but presentation can be highly variable making its diagnosis at times difficult.

CASE PRESENTATION

36-year-old male

Past medical history:

- Type 1 diabetes mellitus complicated by chronic kidney disease and gastroparesis
- Bipolar disorder
- Primary hyperparathyroidism
- Severe peptic ulcer disease

Family history:

- Type 1 diabetes in his mother

CASE PRESENTATION CONTINUED

Regarding his primary hyperparathyroidism:

- Calcium was 11.9mg/dL (ref: 8.4-10.3mg/dL)
- PTH 126.7pg/mL (ref: 9-73pg/mL)
- 24-hour urine calcium was elevated at 332mg/24 hours (ref: 100-300mg/24 hours)
- He never had symptoms of hypercalcemia nor evidence of nephrolithiasis.

His peptic ulcer disease history:

- Multiple ulcers spanning from the esophagus to the jejunum
- 2 episodes of ulcer perforation

Given the multiple widespread ulcers, suspicion was raised for Zollinger Ellison syndrome.

- A gastrin level was elevated at 553pg/mL (ref: <=100pg/mL (while on PPI without gastric pH)
- A somatostatin scan was negative.

CASE PRESENTATION CONTINUED

Regardless, the index of suspicion remained high, and in conjunction with his diagnosis of primary hyperparathyroidism, MEN1 syndrome became a diagnostic possibility.

- Genetic testing which was positive for (arr[hg19] 11q13.1 (64573363_64575254)X1) deletion encompassing a region in exon 4-7 of the MEN1 gene.
- Workup for other manifestations of MEN 1 syndrome were negative, including normal prolactin level and adrenal imaging.

	Patient value	References Range
Calcium (mg/dL)	11.9	8.4-10.3
PTH (pg/mL)	126.7	9-73
24 hour urine calcium (mg/24 hours)	332	100-300
Gastrin (pg/mL)	553	(</=100)
Mutation	(arr[hg19] 11q13.1 (64573363_64575254)X1) deletion encompassing a region in exon 4-7 of the MEN1 gene	

DISCUSSION

Clinical suspicion of MEN 1 syndrome is based on recognition of associated tumors and confirmed with genetic testing. A family history of the disorder is typical, but 10% of cases arise from de novo germline mutations. **Our patient's specific mutation has not been previously described in the literature**; however, similar mutations have established pathogenicity. Most germline mutations in MEN1 syndrome are small insertions, deletions or substitutions. **Large deletions such as this are extremely rare.** Identifying different mutations and their resultant phenotypes helps us further understand the pathogenesis of MEN1 syndrome. The importance of vigilance for small, but often difficult to localize neuroendocrine tumors (NETs) is underscored by the fact that malignant NETs are the primary cause of morbidity and mortality in MEN 1 syndrome. A diagnosis of MEN 1 syndrome is of vital importance for patients and their families, who must be referred for genetic counseling.

REFERENCES

1. Kamilaris CDC, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. Front Endocrinol (Lausanne). 2019 Jun 11;10:339. doi: 10.3389/fendo.2019.00339. PMID: 31263451; PMCID: PMC6584804.

1. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat. 2008 Jan;29(1):22-32. doi: 10.1002/humu.20605. PMID: 17879353.