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Original research

Parathyroid carcinoma and atypical parathyroid neoplasms in MEN1 patients; A clinico-pathologic challenge. The MD Anderson case series and review of the literature

Ioannis Christakis [a], Naifa L. Busaidy [b], Gilbert J. Cote [b], Michelle D. Williams [c], Samuel M. Hyde [d], Angelica M. Silva Figueroa [a], Lily Joy Kwatampora [b], Callisia N. Clarke [a], Wei Qiu [a, e], Jeffrey E. Lee [a], Nancy D. Perrier [a, *]

[a] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Department of Clinical Cancer Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[e] The First Hospital of Jilin University, Hepatobiliary Pancreatic Surgical Department, Changchun, Jilin, China

HIGHLIGHTS

- Parathyroid carcinoma or atypical parathyroid neoplasm can occur Multiple endocrine neoplasia type 1 (MEN1).
- We present 2 cases of parathyroid carcinoma and 1 case of atypical parathyroid neoplasm in a cohort of 291 MEN1 patients.
- The observed genetic mutations in the PC patients were c.703G > A (p.E235K) in exon 4 and c.1378C > T (p.R460X) in exon 10.
- The malignancy potential of parathyroid tumors affects surgical planning for hyperparathyroidism treatment in MEN1 patients.

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ABSTRACT

Background: Multiple endocrine neoplasia type 1 (MEN1) is a genetic disorder characterized by usually benign tumors of the parathyroid glands, pancreatic islet cells, and anterior pituitary. Hyperparathyroidism (HPT) occurs in 90% of MEN1 patients. In rare cases, it is associated with parathyroid carcinoma (PC) or atypical parathyroid neoplasm (APN). We present a cohort of 3 such patients.

Methods: We performed a retrospective review of our institution's MEN1 database to identify patients who underwent operations for HPT and had a histopathologic diagnosis of PC or APN. Clinical features, genetics, and outcomes were summarized.

Results: Of 291 MEN1 patients, 242 had HPT (83.2%). Two of the 242 patients (0.8%) had a histopathologic diagnosis of PC, and 1 (0.4%) had a diagnosis of APN. The patients with PC were male, ages 62 and 56 years at the time of surgery; the patient with APN was female, age 32 years. All patients also had a pancreatic endocrine tumor. The observed genetic mutations in the PC patients were c.703G > A (p.E235K) in exon 4 and c.1378C > T (p.R460X) in exon 10. All 3 patients had recurrence of hypercalcemia, and 2 patients underwent reoperation; pathologic analysis revealed the presence of a hyperplastic gland, not tumor recurrence. No cases had distant metastasis.

Conclusions: This is the first report of APN in an MEN1 patient. Although rare, the presence of PC or APN in MEN1 is noteworthy because it affects the management if hypercalcemia recurs, possibly requiring an open approach rather than the minimally invasive techniques used in the reoperative setting for benign disease.

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal

* Corresponding author. 1400 Pressler Street, FCT 17.6014, Unit 1484, Houston, TX 77030-4009, USA.
E-mail address: nperrier@mdanderson.org (N.D. Perrier).

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dominant Mendelian disorder characterized by the predisposition to tumors involving the parathyroid gland, pancreatic islet cells, and the anterior pituitary [1]. Other endocrine and non-endocrine tumors have also been associated with MEN1 syndrome, including foregut carcinoid tumors (2–8%), thyroid neoplasms (8–27%) and pheochromocytoma (0.5%) [2]. MEN1 has a prevalence of approximately 2–20 per 100,000 individuals and is diagnosed using clinical or genetic criteria [3].

The genetic etiology of MEN1 has been localized to the *MEN1* gene located on the long arm of chromosome 11 (11q13) [4]. Causative mutations in the *MEN1* gene, which encodes the menin protein, have been detected in about 75% of unrelated MEN1 kindreds [5,6]. MEN1 kindreds without detectable *MEN1* mutations are thought to have inactivating mutations in *MEN1* that remain unidentified because they exist outside the coding region or as large deletions. No strong genotype/phenotype relationships have been identified between *MEN1* mutations and clinical outcomes.

Parathyroid tumors have a high penetrance in MEN1, affecting 95% of cases and in most cases consist of multiple benign hyperplastic parathyroid glands, which cause hyperparathyroidism (HPT) [7]. Non-benign parathyroid tumors such as parathyroid carcinomas (PCs) or atypical parathyroid neoplasms (APNs) are extremely rare causes of HPT [8–17]. However, the optimal surgical management of these malignancies is more extensive than that for benign cases. In this study, we present the clinical presentation, genetic background, treatment, and clinical outcomes of 3 MEN1 patients: 2 with PCs and 1 with an APN. To our knowledge, this is the first reported case of APN in an MEN1 patient.

2. Methods

The study complied with ethics guidelines from the local Institutional Review Board. The patient population was identified through a search of prospectively collected data in the MEN1 database of the Department of Surgical Endocrinology at MD Anderson Cancer Center between 2004 and 2015. All cases were reviewed by two expert geneticists at the time of the present analysis to confirm the diagnosis of MEN1 using the clinical practice guidelines described by Thakker et al., in 2012 [1].

From the MEN1 patient database, we identified all patients who underwent surgery for HPT and had a histopathologic diagnosis of PC or APN. The diagnosis of PC was made on the basis of histopathologic criteria, local invasiveness (microscopic or macroscopic), metastasis, or the combination of these criteria [18]. The histopathologic criteria, established by Schantz and Castleman in 1973 include the presence of sheets of tumor cells arranged in a lobular pattern separated by dense fibrous trabeculae, capsular or vascular invasion, necrosis, and/or mitotic figures [19]. The diagnosis of APN was made for parathyroid tumors that had some of the atypical features found in PC but did not meet all of the histologic criteria for diagnosis of PC. All cases were reviewed at the time of the present analysis by an expert pathologist to confirm the diagnosis of PC/APN. Patients with incomplete records were excluded from the study.

Clinical information was obtained from a parathyroid disease-specific patient database and where necessary supplemented with data obtained directly from institutional medical records. Data analyzed included demographics (sex, age), presenting symptomatology, preoperative biochemical workup, type of operation, histopathology results, and follow-up details (outcome of surgery, recurrence, and metastasis). All patients had at least part of their evaluation and treatment at MD Anderson.

Recurrence was defined as disease present [recurrent hypercalcemia with high serum parathyroid hormone (PTH) levels] after a disease-free period of at least 6 months. Persistent hypercalcemia was defined as the presence of elevated serum calcium levels that did not drop after the surgery for HPT. Patients with a diagnosis of PC or APN were followed up initially every 6 months and then yearly.

2.1. Statistical analysis

Demographic and clinical characteristics were summarized using descriptive statistics. Analysis was conducted using GraphPad Prism version 5.00 (GraphPad Software).

3. Results

From the MD Anderson patient database, 291 patients with a genetic and/or clinical diagnosis of MEN1 were identified. HPT was diagnosed in 242 (83.2%) of these patients. Two of the 242 cases (0.8%) had a histopathologic diagnosis of PC, and 1 (0.4%) had a diagnosis of APN.

Both PC patients had a clinical and genetic diagnosis of MEN1. Genetic testing was not performed for the patient with APN. The demographic and clinical characteristics of these 3 patients are summarized in Table 1. All 3 patients had pancreatic endocrine tumors, 1 had a pituitary adenoma, and 2 had carcinoids (1 thymic and 1 bronchial) (Table 1). Both of the PC patients were male; the APN patient was female.

Two of the 3 patients required a second parathyroid surgery because of HPT recurrence after the removal of the PC/APN tumor (not because of tumor recurrence). In both reoperative cases, histopathology revealed only the presence of benign hyperplastic glands. There was no evidence of metastasis in any of the patients, and the 2 PC patients were alive at 70.7 and 6.3 months after PC diagnosis. The APN patient died of metastatic disease from a thymic carcinoid 16.2 months after APN diagnosis.

Tables 2 and 3 summarize the clinical presentation of the PC/APN patients at the time of the parathyroid tumor diagnosis, their pre- and intraoperative laboratory findings, their histopathologic features, and the genetic testing results. The cases are described in brief below; for more detail, see the Supplementary Appendix.

4. Case reports

4.1. Patient 1

This male patient was 54 years old when he was diagnosed with mild hypercalcemia in 1999. In March 1999, the patient underwent a subtotal 3.5-gland parathyroidectomy. The postsurgical histopathology report revealed the presence of a well-differentiated right superior PC (1.8 cm) extending into the adipose tissue and abutting the adjacent thyroid. The tumor was positive for chromogranin and PTH immunostains and negative for thyroglobulin, CEA, gastrin, and calcitonin. The patient was diagnosed with MEN1 in early 2009 using clinical criteria (Table 1) and had confirmatory genetic testing in July 2009 [c.703G > A (p.E235K)] (Table 3). The patient presented at MD Anderson with recurrent hypercalcemia, mild HPT, and worsening osteoporosis in January 2013. He underwent reoperation in January 2014 and had a right inferior and a left superior parathyroid gland removed; both of the excised glands were hyperplastic with no evidence of malignancy. Since that time, the patient has remained eucalcemic with a detectable PTH level of 16 pg/ml.

4.2. Patient 2

The patient was a 55-year-old man with a history of nephrolithiasis beginning at age 30 years and with peptic ulcer disease