Published in final edited form as:

Endocr Pathol. 2008 ; 19(4): 289–293. doi:10.1007/s12022-008-9049-8.

First Description of Parathyroid Disease in Multiple Endocrine Neoplasia 2A Syndrome

James C. Sisson, MD, Thomas J. Giordano, PhD, MD, Victoria M. Raymond, MS, Gerard M. Doherty, MD, and Stephen B. Gruber, PhD, MD

University of Michigan Health System, Ann Arbor, Michigan. Department of Radiology, Division of Nuclear Medicine (JCS); Department of Pathology (TJG); Department of Surgery, Division of Endocrine Surgery (GMD); and Department of Internal Medicine and Department of Human Genetics (VMR and SBG)

Abstract

Context—Hyperparathyroidism and/or parathyroid hyperplasia, medullary thyroid carcinoma (MTC) and pheochromocytomas compose the hallmarks of the multiple endocrine neoplasia type 2A (MEN 2A) syndrome. Revisiting a report in 1939 of a patient with hyperparathyroidism and parathyroid hyperplasia led to a search for evidence of MEN 2A.

Evidence Acquisition—From medical records and discussion with family members, longitudinal follow-up of the patient and her descendants was obtained. Molecular diagnostics were integrated in the care of subsequent generations. The literature on hyperparathyroidism and MEN 2A was reviewed.

Results—Children of the proband exhibited all components of MEN 2A and the RET mutation of 634 TGC>zCGC. The pedigree was typical for this mutation. Papers on anthropologic studies demonstrate skeletal evidence of hyperparathyroidism in humans centuries ago.

Conclusions—The initial report of the proband preceded the publications defining both MTC and MEN 2A. The values of in-depth family histories and genetic analyses are exemplified.

Keywords

Hyperparathyroidism; parathyroid hyperplasia; Multiple Endocrine Neoplasia 2A; historical report

Perceptions of disease may be expanded by examining the first description of a disorder. Neumann *et al.* discovered, after historical and genetic analyses, that the first reported pheochromocytoma was in a patient with MEN 2A [1]. Hyperparathyroidism, another recognized component of MEN 2A, usually presents less dramatically and less frequently than either MTC or pheochromocytoma. Yet, the parathyroid abnormalities in the syndrome also warrant a historical purview. The excision of a parathyroid tumor from an 18 year old woman with osteitis fibrosa cystica in 1936 [2] was the basis for what appears to be the first portrayal of hyperparathyroidism in MEN 2A. Over time, recognition of probable MTC in this patient and the manifestations of MTC, pheochromocytomas and parathyroid hyperplasia in her children confirmed the syndromic diagnosis. The depiction of the proband was published in 1939 [2] and preceded the characterizations of MTC in 1959 [3] and the component tumors of

Address reprint requests to James C. Sisson, M.D. at Department of Radiology, Division of Nuclear Medicine; UH B1 G505D; University of Michigan Health System; Ann Arbor, MI 48109-0028 or at E-mail: jsisson@umich.edu..

No potential conflicts of interest relevant to this article were reported.

MEN 2A in 1961 [4]. The historical picture of hyperparathyroidism may lead to additional discoveries of a disease that is likely to be centuries old.

METHODS

REVIEW OF RECORDS

Initial clinical events were reported by Barker and Brines [2]. The existence of the publication was related by the children of the proband. She was 18 years old in 1936 when abdominal pain led to a laparotomy and removal of a normal appendix; apparently no abdominal abnormality was found. Also described in physical examination: "Just below and to the right of the cricoid cartilage there was a spherical tumor 2.5 cm. in diameter, which appeared to be rather deeply seated in the neck but freely moveable . . ." This observation led to a limited surgical exploration of the patient's neck. "A submaxillary lymph node measuring 15 mm. in diameter was removed. The larger tumor was situated beneath the platysma muscle, lying on the lower portion of the right lobe of the thyroid gland at its lateral border. . . the specimen consisted of an ovoid encapsulated mass measuring 23 mm. in maximum diameter. . . The pathologic diagnosis was hyperfunctioning adenoma of a parathyroid gland." Photomicrographs of the parathyroid tissue were printed. Not in the publication [2], but in the original pathology report was the description of the excised submaxillary lymph node: "Metastatic, highly malignant adenocarcinoma, strongly suggestive of renal origin." The primary site of the malignant neoplasm was not pursued.

No symptoms occurred in the postoperative period, and the patient became well. At 2.5 months after the operation, her serum calcium was "10.5 Gm. per hundred cubic centimeters [probably 10.5 mg/dL]". Two and one-half months after the operation, roentgenograms of skull, hands, shoulders, knees and spine were interpreted: "There was a fine granular mottling throughout all the bones with marked irregularity and thinning of trabeculae. The skull had a moth-eaten appearance, with small areas of increased density. There was a cyst in the distal extremity of the fifth metacarpal bone of the right hand, one at the upper end of the left humerus on the medial side just below the epiphyseal line, one in the lower end of the right femur above the medial condyle and one at the upper end of the left tibia on the medial side. The roentgen diagnosis was osteitis fibrosa cystica." Roentgen examination 22 months after her operation "revealed almost complete filling in of the cysts . . ."

Additional information was obtained from brief communications sent by community hospitals and reports of interviews with the patient. In 1947, an operation removed tissue from each thyroid lobe and included a "firm white nodule . . . composed of neoplastic epithelial cells which are spindle-shaped . . . there are numerous mitotic figures." In 1964, excised residual thyroid tissue was diagnosed as lymphocytic thyroiditis. During this operation a neck dissection removed lymph nodes containing "papillary thyroid carcinoma". Described in the dissected tissues was: ". . . a parathyroid gland is included and shows hyperplasia." Post-operative treatments with vitamin D and calcium were discontinued a year later.

Between 1964 and 1971, the patient was seen several times in the University of Michigan Health System; tissue from the last operation was reviewed, and the diagnosis of papillary carcinoma in lymph nodes was confirmed. Serum calcium concentrations varied between upper normal and elevated, 2.4 and 2.8 mmol/L; parathormone was not measured. In 1968, her chest roentgenogram was described as normal.

Between 1965 and 1968, her blood pressures were as high as 160/100 and 140/110. She died in 1978 at age 70 years of what was described by her children as "progressive cancer". Tissues from the proband have been destroyed.

The pedigree is depicted in Fig. 1A. At 27 years of age, the proband's daughter had, at another hospital, a total thyroidectomy that removed MTC; bilateral pheochromocytomas and a parathyroid gland (the size of which is unknown) were excised at 40 and 46 years of age, respectively (Table 1). Recurrences of MTC were resected from her neck and liver; her subsequent serum calcitonin levels have been >20,000 pg/mL. At age 63, her serum calcium level was 2.75 mmol/L (2.1-2.5) and intact parathormone (iPTH) 158 pg/mL (10-65). A hyperplastic parathyroid gland was then extirpated (Fig. 1B,C). Postoperative serum calcium concentrations were normal to borderline elevated, but her parathormone level was 10 pg/mL. In 2007, at 64 years of age she developed pain in her right hip. CT-guided bone biopsy displayed MTC, and radiation was directed at the metastasis.

The son of the proband had an abnormal serum calcitonin response to a pentagastrin stimulus at 30 years of age. A total thyroidectomy excised bilateral MTC that exhibited no extrathyroidal invasion (Table 1). Post-operative levels of serum calcitonin did not rise following stimulation. His pre-operative serum calcium and parathormone levels were normal, but a 12 × 9 × 4 mm hypercellular parathyroid gland was excised during the thyroidectomy (Fig. 1D). At age 50, a pheochromocytoma and adrenal medullary hyperplasia were removed in bilateral adrenalectomies. At 59 years, his serum values were: calcium (corrected for binding) 2.35 mmol/L (2.04-2.47), iPTH 98 ng/L (10-75), calcitonin 2 ng/L (<18 with normal thyroid gland), and carcino-embryonic antigen 1.0 ng/mL (<5).

Neither of the children had evidence of cutaneous lichen amyloidosis.

GENETIC MUTATION OF MEN 2A

For direct mutation analysis of the RET proto-oncogene in the proband's daughter (III:1) and great grandson (V:1) (Table 1), DNA was extracted from peripheral blood lymphocytes using a Puregene kit from Gentra Systems. To confirm clinical genetic testing results, the RET gene containing the known familial mutation was amplified from genomic DNA using the following primers: F: CAGAGCATACGCAGCCTGTA and R: TTGTGGGCAAACCTTGTGGTA. PCR amplification was performed by denaturing samples for 3 minutes at 95°C and were passed through 40 cycles of amplification, which consisted of 1 minute of denaturation at 95°C, 1 minute of primer annealing at 55°C, and 1 min of elongation at 72°C. PCR products were sequenced on an ABI 3730, and chromatograms were visually inspected by two reviewers and interpreted by Mutation Surveyor Software (Softgenetics, Inc., State College, Pennsylvania, USA).

RESULTS

Genetic testing identified a missense mutation in exon 11 of the RET protooncogene, codon 634 TGC>CGC that is exemplified in family member V1 of the pedigree (Table 1 and Fig. 1E). The chronologic patterns of the neoplasias varied over the generations as depicted in the pedigree seen in Table 1 and Fig. 1A. Although hyperparathyroidism was found in the proband (II:1) at age 18 years, the disorder was first treated in III:1 and III:2 at 46 and 30 years of age, respectively. Parathyroid disease has not been reported in additional members. Typical of abnormalities seen in MEN 2A, enlarged parathyroid glands consisting of diffuse and nodular hyperplasia of chief cells were present in III:1 and III:2. Hyperplastic nodules containing clear and oxyphilic cells were present in a gland from III:1 (Fig. 1B), a pattern recognized in the syndrome [5].

In III:1, III:2, and IV:1, MTC was discovered between ages 27 and 37 years. In subsequent generations, genetic testing elsewhere led to thyroidectomies that uncovered C-cell hyperplasia in 2 family members. Pheochromocytomas have been removed from III:1, III:2 and IV:1 at ages 41, 50 and 37 years, respectively.

DISCUSSION

There was no histologic interpretation of MTC in the proband. However, the description of malignancy in the lymph node resected at her first operation is consistent with MTC as is the microscopic appearance of the thyroid nodule removed at her second operation. It seems likely that she developed a second thyroid malignancy, papillary carcinoma, that was discovered in cervical lymph nodes during the third operation. The specific cause of death is unknown. Papillary carcinoma was also found in IV-4 who did not have the MEN 2A mutation; a familial form of this thyroid carcinoma may have also been present in this pedigree. Nevertheless, the presence of MEN 2A, is clearly established in the proband by the presence of the triad of features in her two children, and, in multiple descendants, a mutation common in the syndrome.

The proband also demonstrates the difficulty in comprehending the nature of diseases and syndromes until they have been fully described. Since MTC appears early in almost all cases of MEN 2A, hyperparathyroidism as the sole manifestation of the syndrome must now be rare. Hyperparathyroidism often presents with subtle manifestations. At the outset in our proband, her abdominal pain may have arisen from hypercalcemia, but she had no bone symptoms. However, there was roentgenographic evidence of osteitis fibrosa cystica, and the absence of tetany following the resection of the hyperplastic parathyroid gland predicted continuing hyperparathyroidism.

In patients with MEN 2A, hyperparathyroidism was suggested by the finding of a parathyroid adenoma at autopsy of a patient in Sipple's original description in 1961 [4]. In 1962, a parathyroid adenoma was reported to have been discovered in a 1949 autopsy of a patient, who, from data obtained on her descendants, had MEN 2A [6]. The first surgical treatment of hyperparathyroidism as a known component of MEN 2A was reported 1963 [7]. Occurring in 12-30% of patients [8,9], parathyroid hyperplasia/hyperparathyroidism [5] is the least common component of MEN 2A. Of those harboring a MEN 2A mutation, about half will manifest pheochromocytomas and nearly all will express MTC [8,9].

Most patients with hyperparathyroidism will have mutations in codon 634 [10], and, in families with mutations in this codon, hyperparathyroidism is more highly penetrant in some families than others. This multiple gland disorder arises from a germ-line mutation affecting parathyroid cells and not from an extra-glandular stimulus. Each parathyroid gland is prone to hyperplasia and recurrences of hyperparathyroidism have been reported in 11-40% of those afflicted [8, 11] and persistence in 11% [11]; but persistence was present in only 3-6% following more extensive operations [12]. The age of onset of parathyroid hyperfunction has been seen in patients as young as 9 [13] and as old as 70 [10], but most commonly in individuals between 17 and 49 years of age [8]. The mutation, 634 TGC>CGC, is a missense that substitutes arginine for the normal cysteine. Our family reflects a typical course for those inheriting this mutation.¹⁰

Bone disease was first associated with a parathyroid tumor in 1903 [14]. The first excision of a hyperparathyroid tumor was by Mandl in 1925 [15]. The patient exhibited osteitis fibrosa cystica; post-operatively his symptoms improved, but recurrent hyperparathyroidism was apparent within 6 years [16]. From a patient with osteitis fibrosa cystica in 1928, Olch was the first in the United States to remove a parathyroid adenoma; post-operative tetany did not occur [17]. Bone disease appears after marked and prolonged hyperparathyroidism, a state in which function of normal parathyroid gland(s) becomes suppressed while bones manifest a "hunger" for calcium, and, upon excision of all overactive glands, a period of tetany is expected. Thus, in the patients of Mandl and Olch, presumably more than one parathyroid gland exhibited abnormal function; whether either had MEN 2A is unknown. Other causes of multiple gland

contribution to hyperparathyroidism include MEN 1 [18] and familial isolated hyperparathyroidism that may or may not be associated with jaw tumors [19].

Siblings, aged 16 and 23 years, presented with osteitis fibrosa cystica in 1934, and had parathyroid adenomas, weighing 11.8 and 6.5 g respectively, removed [20]. Post-operative tetany followed the parathyroidectomy in the younger sister. The brother, who had a pathological fracture of his jaw related to a giant cell tumor, experienced no period of hypocalcemia. Intra-operative inspections of the thyroid glands revealed no abnormality except for a thyroid adenoma that was excised. The absence of gross MTC in each patient and the presence of the jaw tumor in one make the syndrome of MEN 2A unlikely.

Mutations of MEN 2A date from at least the 1890s [1] and are now geographically widespread [21,22]. How far into antiquity MEN 2A extends is unknown. However, anthropologic specimens suggest that osteitis fibrosa cystica was present during the time of the Roman Empire [23] and in early Neolithic skeletal remains 7000 years ago [24]. As science delves into the past, we will learn more about how and when diseases of today arose.

ACKNOWLEDGEMENTS

The authors are indebted to family members who generously gave their time and information. Dr. Leon Raskin, research fellow at the University of Michigan, provided technical assistance in genotyping. Dr. Gary Talpos, endocrine surgeon at Henry Ford Hospital in Detroit, MI, generously shared information about the family. The historical reviews of hyperparathyroidism by Dr. Norman Thompson, *Acta Chir Scand* 1990;156(1):5-21 and Dr. Claude H. Organ, Jr. *J Am Coll Surg* 2000;191(3):284-299 enabled perspective and insight into the disorder.

The Institutional Review Board of the University of Michigan approved this investigation (UMCC 2-79).

REFERENCES

1. Neumann HPH, Vortmeyer A, Schmidt D, et al. Evidence of MEN-2 in the original description of classic pheochromocytoma. *New Eng J Med* 2007;357:1311–1315. [PubMed: 17898100]
2. Barker VL, Brines OA. Hyperfunctioning adenoma of an ectopic parathyroid gland. *Arch Surg* 1939;39:205–213.
3. Hazard JB, Hawk WA, Crile G Jr. Medullary (solid) carcinoma of the thyroid -a clinicopathologic entity. *J Clin Endocrinol Metab* 1959;19:152–161. [PubMed: 13620740]
4. Sipple JH. The association of pheochromocytoma with carcinoma of the thyroid gland. *Am J Med* 1961;31:163–166.
5. World Health Organization Classification of Tumours. Pathology genetics of tumours of endocrine organs. DeLellis, RA.; Lloyd, RV.; Heitz, PU.; Eng, C., editors. IARC Press; Lyon, France: 2004. p. 215
6. Cushman P Jr. Familial endocrine tumors. Report of two unrelated kindred affected with pheochromocytomas, one also with multiple thyroid carcinomas. *Am J Med* 1962;32:352–360. [PubMed: 13882784]
7. Manning PC Jr, Molnar GD, Black BM, et al. Pheochromocytoma, hyperparathyroidism and thyroid carcinoma occurring coincidentally. Report of a case. *New Eng J Med* 1963;268:68–72.
8. Yip L, Cote GJ, Shapiro SE, et al. Multiple endocrine neoplasia type 2. Evaluation of the genotype-phenotype relationship. *Arch Surg* 2003;138:409–416. [PubMed: 12686527]
9. Modigliani E, Cohen R, Campos J-M, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. *Clin Endocrinol* 1998;48:265–273.
10. Schuffenecker I, Virally-Monad M, Brohet R, et al. Risk and penetrance of primary hyperparathyroidism in multiple endocrine neoplasia type 2A families with mutations at codon 634 of the RET proto-oncogene. *J Clin Endocrinol Metab* 1998;83:487–491. [PubMed: 9467562]
11. Kraimps J-L, Denizot A, Carnaille B, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type IIa: retrospective French multicentric study. *World J Surg* 1996;20:808–813. [PubMed: 8678955]

12. Raue F, Kraimps JL, Dralle H, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. *J Intern Med* 1995;238:369–373. [PubMed: 7595174]
13. Jackson MB, Guttentag M, Hedrick H, Moshang T Jr. Multiple endocrine neoplasia type 2A in a kindred with C634Y mutation. *Pediatrics* 2005;116:e468–471. [PubMed: 16099853]
14. Askanazy, M. Ueber ostitis deformans ohne osteoides gewebe. In: von Baumgarten, P., editor. *Arbeiten Pathologischen Anatomie und Bacteriologie*. Verlag von S. Hirzel; Leipzig, Germany: 1904. p. 398–422.
15. Mandl F. Therapeutischer versuch bei osteitis fibrosa generalisata mittels extirpation eines epithelkorperchentumors. *Wien Klin Wchenschr* 1925;38:1343–1344.
16. Mandl F. Hyperparathyroidism. *Surgery* 1947;21:394–440.
17. Barr DP, Bulger HA, Dixon HH. Hyperparathyroidism. *JAMA* 1929;92:951–952.
18. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658–5671. [PubMed: 11739416]
19. Mizusawa N, Uchino S, Iwata T, et al. Genetic analyses in patients with familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumour syndrome. *Clin Endocrinol* 2006;65:9–16.
20. Goldman L, Smyth FS. Hyperparathyroidism in siblings. *Ann Surg* 1936;104:971–981. [PubMed: 17856894]
21. Shirahama S, Ogura K, Takami H, et al. Mutational analysis of the RET proto-oncogene in 71 Japanese patients with medullary thyroid carcinoma. *J Hum Genet* 1998;43:101–106. [PubMed: 9621513]
22. Zhou Y, Zhao Y, Cui B, et al. RET proto-oncogene mutations are restricted to codons 634 and 918 in mainland Chinese families with MEN2A and MEN2B. *Clin Endocrinol* 2007;67:570–576.
23. Cook M, Molto EL, Anderson C. Possible case of hyperparathyroidism in a Roman period skeleton from the Dakhleh Oasis, Egypt, diagnosed using bone histomorphometry. *Am J Phys Anthropol* 1988;75:23–30. [PubMed: 3277446]
24. Zink AR, Panzer S, Fesq-Martin M, et al. Evidence for a 7000-year-old case of primary hyperparathyroidism. [Research Letter] *JAMA* 2005;293:40–42.

Table 1
Clinical features in a historic family with hyperplasia/hyperparathyroidism in MEN2A

Individual Pedigree ID	Relationship	Genotype	Cancer Phenotype (age)	Parathyroid (age)	Pheo (age)
I:2	Mother	N/A	Thyroid - unspecified	N/A	N/A
II:1	Proband	N/A	Nodal metastasis ? MTC (18); papillary carcinoma (46)	Hyperplasia/Hyperparathyroid (18)	N/A
II:2	Sibling	N/A	Thyroid - unspecified	N/A	+
II:4	Sibling	N/A	Thyroid - unspecified	N/A	N/A
II:5	Sibling	N/A	Pancreas - unspecified	N/A	N/A
III:1	Child	+	MTC (27)	Hyperplasia/Hyperparathyroid (47)	+ (41)
III:2	Child	+	MTC (30)	Hyperplasia (30)	+ (50)
IV:1	Grandchild	+	MTC (37)	-	+ (37)
IV:2	Grandchild	+	-		
IV:3	Grandchild	-	-	-	-
IV:4	Grandchild	-	Papillary thyroid	-	-
V:1	G. Grandchild	+	CCH	-	-
V:2	G. Grandchild	-	-	-	-
V:3	G. Grandchild	+	CCH	-	-
V:4	G. Grandchild	+	N/A	N/A	N/A
V:5	G. Grandchild	+	N/A	N/A	N/A

* Abbreviations: MTC is medullary thyroid cancer, CCH is C-cell hyperplasia. N/A: not available.