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Multiple angiofibromas and collagenomas in a 45 year-old man with recurrent nephrolithiasis, fatigue, and vision loss

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CASE SUMMARY

History

A 45-year-old man was referred to the Dermatology Branch Consultation Service at the National Institutes of Health for evaluation of a 20 year history of multiple asymptomatic papules on the face and papulonodules on the trunk. The truncal lesions had been increasing in number and size over the past 5 years. Two lipomas located on the left anterior thigh and the right posterior thigh had been excised in his late teens.

Eighteen months prior to presentation, the patient was evaluated for recurrent nephrolithiasis, constipation, and fatigue. He was found to be hypercalcemic secondary to primary hyperparathyroidism and underwent right parathyroidectomy without complete normalization of his serum calcium values. Six months later he developed bilateral visual field deficits. A 5 cm pituitary mass was identified by magnetic resonance imaging and his serum prolactin level was elevated to 5380 mcg/L (reference range 3-29). A diagnosis of macroprolactinoma was made and medical therapy with cabergoline was instituted with complete recovery of his visual fields. Computed tomography of the abdomen demonstrated bilateral adrenal masses, and the patient was referred to the National Institutes of Health for further evaluation and treatment.

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This paper has not been presented previously.

Conflicts of Interest Disclosure: None declared

KEY TEACHING POINTS

- MEN1 is an autosomal dominant cancer syndrome that results from a mutation in the *MEN1* gene encoding menin. It is characterized by endocrine neoplasias of the parathyroid glands, enteropancreatic islet cells, and anterior pituitary.
- The presence of multiple angiofibromas and collagenomas should arouse suspicion of MEN1. Other cutaneous features include café au lait macules, lipomas, hypopigmented macules, and gingival papules.
- Early recognition of the cutaneous features of MEN1 could lead to early diagnosis and initiation of screening for endocrine disease.

Upon presentation, he complained of chronic headaches associated with nausea and vomiting without visual changes, myalgias, and bone pain. The patient also had a 20-year history of severe gastroesophageal reflux. He denied diarrhea and galactorrhea. There was no family history of endocrine disorder.

Physical Examination

On examination at the NIH, the patient weighed 144.2 kg and was 151 cm tall (BMI 63.2). Deep longitudinal furrows consistent with cutis verticis gyratum were noted on the parietal and occipital scalp. There was a prominent posterior neck fat pad. On the neck and axillae were approximately fifty, 3 to 10 mm soft, pedunculated papules suggestive of acrochordons (Fig 1, A). Larger lesions had mammillated surfaces. The skin in the neck and axillae was hyperpigmented with velvety hyperkeratosis, consistent with acanthosis nigricans (Fig 1, A). Approximately ten, 1 to 2 mm flat, skin-colored to pink papules, several with visible telangiectasia, were noted on the tip of the nose, the nares, and close to the vermilion border of the lips (Fig 1, B). Several small (<2 mm) erythematous papules were present on the attached gingiva over the maxillary incisors. The anterior abdominal wall was studded with greater than one hundred discrete, oval and round, soft to firm, nontender skin-colored papules ranging from 0.1 to 1 cm in diameter (Fig 1, C). There were two soft subcutaneous nodules on the ventral aspect of both upper extremities, suggestive of lipomas. Linear atrophic plaques consistent with striae were present on the lower abdomen and upper thighs.

Histopathology

Histopathologic examination of three anterior abdominal papules demonstrated large areas of coarse dermal collagen without adnexal structures (Fig 1, D, E). Verhoeff-Van Gieson elastin stains of these regions revealed markedly decreased elastic fibers compared with adjacent dermis, consistent with collagenomas (Fig 1, F). A biopsy specimen of a polypoid neck lesion demonstrated lobules of mature adipose tissue admixed with abundant fibrous tissue typical of fibrolipoma.

Other significant diagnostic studies

Laboratory investigations were significant for the following: parathyroid hormone, 128 pg/mL (reference range 16-87); venous ionized calcium, 1.56 mmol/L (1.12-1.32); prolactin, 705 mcg/L (3-29); 24 hour urine calcium excretion, 17.8 mmol/24h (1.25-7.50). A serum gastrin level of 98 pg/ml was at the upper limits of normal (<100). Other normal laboratory studies included plasma fractionated normetanephrine, 51 pg/ml (18-112); plasma fractionated metanephrine, 23 pg/ml (12-61); adrenocorticotrophic hormone, 24.8 pg/ml (0.0-46.0); serial serum cortisol levels (30 minutes apart) 7.5 mcg/dL and 5.3 mcg/dL (5.0-25); thyroid stimulating hormone, 1.00 micIU/ml (0.40-4.00); thyroxine, 7.9 mcg/dL (4.5-12.5), free thyroxine, 0.9 ng/dl (0.8-1.9); and triiodothyronine, 180ng/dL (90-215).

Indium In-111 octreotide scintigraphy demonstrated increased uptake in the pituitary region and magnetic resonance imaging revealed a 3 × 3 × 4 cm pituitary adenoma. Bilaterally enlarged adrenals, as well as pancreatic and duodenal masses were detected by magnetic resonance imaging and computed tomography of the abdomen. No hepatic masses were identified. Computed tomography scan revealed renal calculi and a possible parathyroid nodule. This was further characterized as a 1.3 cm parathyroid adenoma by ultrasound and nuclear medicine parathyroid scan. A 7 mm duodenal nodule was detected and biopsied by esophagogastroduodenoscopy. Histopathology revealed this to be a gastrinoma. A DEXA scan of the radius revealed markedly decreased bone density with a Z score of -4.6.

Follow-up

Subtotal pancreatectomy, splenectomy, and left adrenalectomy was performed. A pancreatic nodule was identified which was positive for synaptophysin, CD56, and chromogranin, and negative for S100 and calcitonin, consistent with a neuroendocrine tumor. The left adrenal specimen was consistent with adrenal hyperplasia.

DIAGNOSIS

Multiple endocrine neoplasia type 1 (MEN-1) with prolactinoma, primary hyperparathyroidism, bilateral adrenal hyperplasia, and gastrinoma, with cutaneous findings of multiple angiofibromas, collagenomas, fibrolipomas and gingival papules.

DISCUSSION

MEN1 is one of several subtypes of the multiple endocrine neoplasia syndromes, a group of hereditary cancer syndromes. These autosomal dominant MEN disorders are distinguished by the development of tumors within multiple specific endocrine and selected nonendocrine organs. MEN1 is caused by mutations in the *MEN1* gene and is characterized by tumors of the parathyroid glands, enteropancreatic islet cells, and pituitary, as well as benign cutaneous hamartomas, most frequently multiple angiofibromas and collagenomas. The penetrance of organ involvement is high, but tumor patterns are heterogeneous and, unlike MEN2, there are no recognized syndromic variants. MEN2 results from mutation of the transmembrane tyrosine kinase genes *RET* and presents as three clinical variants. MEN2A (Sipple's Syndrome) is characterized by medullary thyroid carcinoma (MTC), pheochromocytomas, and hyperparathyroidism; MEN2B consists of mucosal neuromas, pheochromocytomas, and MTC; and familial MTC causes the least aggressive MTC of the three MEN2 variants and is not associated with other endocrine disorders.¹

Hypercalcemia resulting from parathyroid tumor is the presenting manifestation in 90% of patients with MEN1. Primary hyperparathyroidism reaches nearly 100% penetrance by age 50, with typical onset around age 20. However, MEN1 accounts for only 2-4% of all cases of primary hyperparathyroidism.¹ Enteropancreatic tumors occur in 30-75% of patients with MEN1. The majority of the MEN1 enteropancreatic tumors are multifocal duodenal gastrinomas, often resulting in the Zollinger-Ellison syndrome of gastrin hypersecretion.^{1,2} Gastrinomas are the leading cause of morbidity and mortality in patients with MEN1, with most deaths currently attributed to hepatic metastases rather than to acid-related peptic ulcer disease.³ One third of patients with MEN1 have anterior pituitary adenomas, which tend to be larger and more aggressive than sporadic pituitary tumors.⁴ Adrenocortical lesions have been reported in up to 40% of patients and most frequently present as nonfunctional bilateral enlargement.⁵

In 1997, Darling et al.⁶ reported the cutaneous features of 32 consecutive patients with established diagnoses of MEN1 evaluated at the NIH. Collagenomas were detected in 72%, café au lait macules in 38%, lipomas in 34%, confetti-like hypopigmented macules in 6%, and multiple gingival papules in 6%. Multiple angiofibromas, previously regarded primarily as a diagnostic feature of tuberous sclerosis complex (TSC), were found in 88% of patients with MEN1. The angiofibromas were histologically identical to those found in TSC, but were generally smaller, fewer in number, and more likely to be concentrated on the vermilion border of the upper lip. Angiofibromas were also identified in 43% of a series of 28 Japanese patients with germline *MEN1* gene mutation.⁷ Asgharian et al.⁸ found that the occurrence of a collagenoma and more than three angiofibromas was 75% sensitive and 95% specific for MEN1 in patients with gastrinomas.

The *MEN1* gene consists of 10 exons with an 1830-bp coding region located on chromosome 11q13. Menin, the 610-amino acid protein gene product, is a predominantly nuclear protein that is involved in cell cycle regulation and proliferation. Protein-truncating mutations account for more than 70% of the 700 germline mutations so far identified. Tumors arise in various endocrine organs when there is loss of heterozygosity of the second allele of *MEN1*, consistent with the gene's proposed tumor suppressor function. Cutaneous tumors in patients with MEN 1 also show allelic deletion of the *MEN1* gene.⁹ There is no known correlation between specific *MEN1* mutations and clinical presentation or prognosis.^{10, 11} Germline *MEN1* mutations have been described in the allelic syndrome known as familial isolated hyperparathyroidism, and somatic mutations have been reported in sporadic parathyroid adenomas, gastrinomas, prolactinomas, foregut carcinomas, lipomas, and angiofibromas. About 10% of cases are new mutations.^{1, 2, 12}

Although biochemical and DNA screening may potentially limit morbidity associated with MEN1, definitive data on the value of screening are needed.¹³ A 2001 consensus statement detailed annual biochemical screening guidelines for patients with MEN1 beginning at 5 years of age.¹

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Abbreviations

MEN1, Multiple endocrine neoplasia; MTC, Medullary thyroid carcinoma; TSC, Tuberous sclerosis complex.

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A

B

c

D

E

F

Fig 1.

(A) Numerous pedunculated papules and velvety hyperpigmented hyperkeratosis on the posterior neck. (B) Multiple telangiectatic papules on the nose. (C) Periumbilical skin-colored papulonodules. (D, E) Skin biopsy from the abdomen demonstrates widened collagen bundles and loss of adnexae (hematoxylin-eosin stain; original magnifications: 2.5 $\times$, 5 $\times$). (F) Verhoeff-Van Gieson elastin stain of similar field shown as (E) demonstrates normal elastin staining at the periphery of the papule (left side) and decreased elastic fibers at the site of the collagenoma (original magnification: 5 $\times$).