Preceding Cutaneous Manifestation as an Early Identification of Multiple Endocrine Neoplasia Type 1 Syndrome: A Case Report

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ABSTRACT:

Background: Multiple Endocrine Neoplasia type 1 (MEN1) syndrome is a rare genetic disorder associated with the development of tumors in various endocrine glands. Cutaneous manifestations, such as angiofibromas and collagenomas, can be early indicators of the syndrome.

Case Report: A female patient with a history of progressive headache, rhinorrhea, secondary amenorrhea, and spontaneous galactorrhea was diagnosed with invasive pituitary adenoma. Over the past 10 years, she developed multiple skin-colored and brownish nodules, similar to those seen in her relatives, which were histologically consistent with collagenomas. Additional investigations revealed primary hyperparathyroidism. These combined clinical features led to the diagnosis of MEN1 syndrome. Notably, her mother had collagenomas more than 20 years prior and was subsequently diagnosed with a thyroid mass and invasive prolactinoma. Pathogenic variants of the MEN1 gene were identified in the patient, her mother, and her sister. Genetic counseling, as well as biochemical and radiological surveillance, was recommended for the patient and her affected family members.

Conclusion: Collagenoma is a crucial clue for early diagnosis of MEN1 syndrome. Detection of multiple collagenomas should prompt investigations for MEN1-related endocrine and non-endocrine tumors

Key words: Multiple Endocrine Neoplasia Type 1, Collagenoma, Neuroendocrine Tumor, Pituitary Neoplasm, Primary Hyperparathyroidism

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Case presentation

A 29-year-old woman experienced transient spontaneous galactorrhea and secondary amenorrhea about ten years ago. Over the past decade, she developed multiple skin-colored and brownish nodules on her abdomen and axillae, which grew 1-2 mm per year. No other cutaneous findings were observed. (Figure 1)

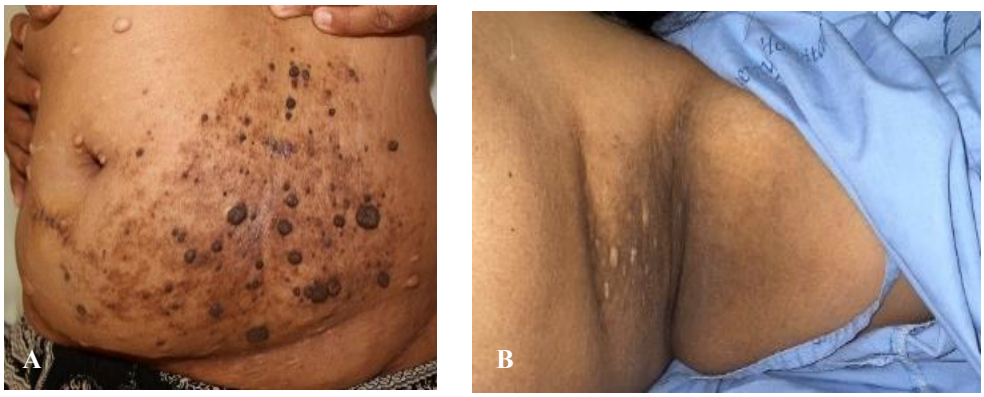

Figure 1 Multiple skin-colored and brownish nodules were present on the lower abdomen (A), and multiple skin-colored nodules on the left axilla (B)

Similar cutaneous lesions were observed in her family members. Her mother had two collagenomas on her right wrist and her sister had lesions on the coccyx and right thigh. Her late grandmother had similar lesions on her right arm and trunk, while her aunt had a solitary lesion on her trunk. The latter three family members had similar lesions, though not biopsy-proven. (Figure 2)

Eight years later, she developed intermittent throbbing headaches, worsened by

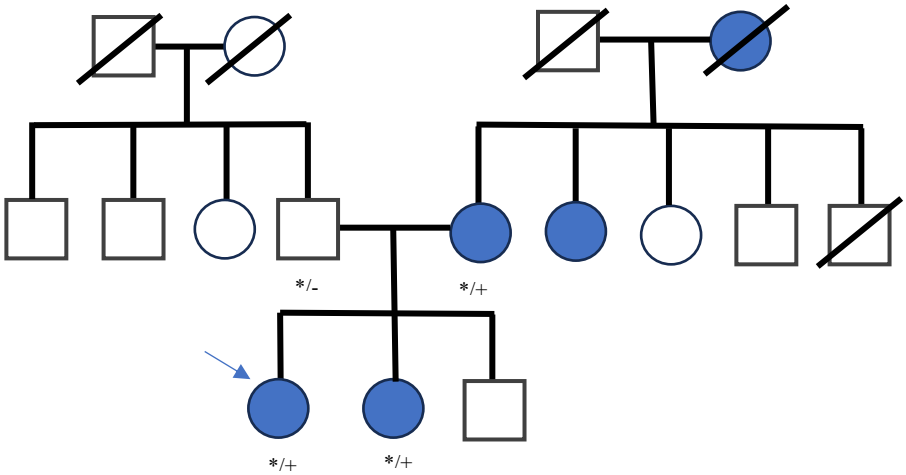

Figure 2 The pedigree displays family members with multiple skin-colored nodules (solid symbols). * denotes MEN1 testing, + indicates a positive mutation result, and – indicates a negative mutation result

coughing and sneezing, along with rhinorrhea lasting five days. Magnetic Resonance Imaging (MRI) of the brain revealed a 4.7 x 5.5 x 3 cm intrasellar mass extending into the sphenoid bones and involving the left internal carotid artery. (Figure 3).

She underwent surgery at Thammasat University Hospital via an Endoscopic Endonasal Approach. Histopathology revealed a large cell neoplasm positive for synaptophysin, chromogranin-A, and prolactin, with sparse CAM5.2 positivity and a Ki67 index of 2-3%. The diagnosis was invasive pituitary adenoma associated with hyperprolactinemia.

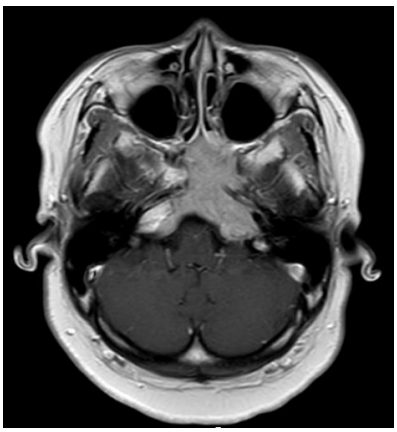

Figure 3 MRI of the brain revealed a 4.7 x 5.5 x 3 cm intrasellar mass extending into the sphenoid bones and affecting the left internal carotid artery

Workup for her history of secondary amenorrhea showed low luteinizing hormone and estradiol levels, indicating hypogonadotropic hypogonadism. Additional tests, including thyroid function, morning cortisol, ACTH levels, the 1 mg dexamethasone suppression test, the 1 mcg ACTH stimulation test, and insulin-like growth factor, were normal. Biopsies of the skin-colored and brownish nodules on the lower abdomen revealed acanthosis, basal hyperpigmentation, and perpendicular collagen bundles, consistent with collagenoma. (Figure 4)

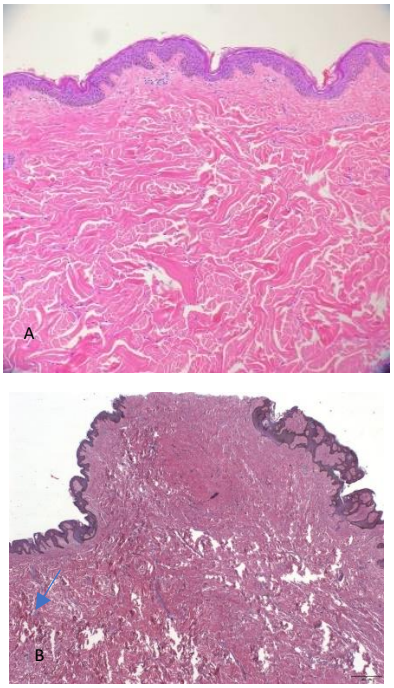

Figure 4 Histopathological examination of the skin-colored nodule (A) and the brownish nodule (B) from the lower abdomen revealed regular acanthosis, basal hyperpigmentation, thickened collagen and perpendicular alignment in the dermis, consistent with collagenoma. The findings were observed at magnifications of 100x and 40x respectively

Further endocrine investigations identified PTH-related hypercalcemia. Laboratory tests indicated high serum calcium and parathyroid hormone, with normal albumin and phosphorus, and low vitamin D. Ultrasonography and parathyroid scans were unremarkable. Additional tests, including serum gastrin, C-peptide levels, and Computed tomography scans of the chest and abdomen were normal.

The combination of pituitary tumor, primary hyperparathyroidism, and collagenomas confirmed Multiple Endocrine Neoplasia Type 1 syndrome. Genetic testing revealed a

heterozygous duplication of nucleotides 196 to 200 (c.196_200dup), resulting in a frameshift mutation and a prematurely truncated protein (p.Asp70Profs*51). This variant is classified as pathogenic[1]. Sanger sequencing confirmed this mutation in the patient, her mother, and her sister, but not in her father. All sequencing chromatograms are provided. (Figure 5).

Bromocriptine was initiated to manage hyperprolactinemia. Genetic counseling was provided, and regular biochemical and radiological surveillance was recommended for the patient and her affected family members. Because of the benign tumor, collagenomas do not require any treatment, and the patient denied any cosmetic concern.

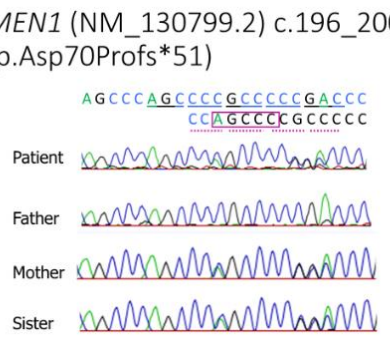

Figure 5 The DNA sequencing chromatogram shows the heterozygous c.196_200dup mutation in the MEN1 gene for our patient, her mother, and her sister, resulting in a frameshift mutation. In contrast, the wild-type sequence is observed in her father. The box highlights the duplicated AGCCC nucleotides, the underline denotes the reference codon, and the dotted line indicates the variant codon

Details regarding the evaluation of family members were limited. According to the available medical records and information, her mother was diagnosed with progressive end-stage renal disease from uncontrolled diabetes, a thyroid mass pending surgery, and invasive prolactinoma, with unknown endocrinological workup, suggesting that collagenomas may have preceded multiple endocrine disorders. Her sister was advised to undergo MEN1 syndrome evaluation but has been unable to pursue this recommendation due to a busy schedule.

Discussion

MEN1 syndrome is an autosomal dominant condition resulting from mutations in the MEN1 gene. It typically involves tumors or hyperplasia in the parathyroid, pancreas, and pituitary and may include non-endocrine tumors and cutaneous lesions[2].

Cutaneous manifestations such as facial angiofibromas and collagenomas are common and often early features of MEN1 syndrome, with a prevalence of 11-88% and 40-72%, respectively[3]. These lesions have high sensitivity (50–65%) and specificity (92–100%) for MEN1 diagnosis, especially in patients with gastrinoma[4]. Other cutaneous findings include gingival papules and confetti-like macules[3-4].

Collagenomas are benign connective tissue tumors that appear as firm, dome-shaped nodules or papules, usually skin-colored. They commonly manifest symmetrically on the upper trunk, neck, and shoulders and may present either alongside other skin tumors or as isolated lesions[3]. They can also be associated with conditions such as familial cutaneous collagenomas, tuberous sclerosis, Buschke-Ollendorf syndrome, Birt-Hogg-Dubé syndrome, Cowden syndrome, and Down syndrome[5].

In MEN1 syndrome, collagenomas generally vary in size from 2 to 10 mm. The smaller lesions (under 3 mm) are numerous, while the larger lesions (over 3 mm) are less frequent[6]. These lesions often appear early and progress slowly, sometimes up to 20 years before internal tumors are found. They may also increase rapidly in number and size over 5 years before diagnosis. Rapid growth has been observed following vasoactive intestinal peptide-secreting tumors (VIPomas) surgery[5].

Similar to angiofibromas, the number of collagenomas often correlates with age.

In our patient, the gradual increase in the number of collagenomas, including both large and small lesions, along with spontaneous galactorrhea, occurred a decade before the MEN1 diagnosis. Similarly, her mother's collagenomas were noted almost 20 years prior to the onset of multiple endocrine disorders. These findings suggest that collagenomas can aid in the early detection of MEN1 syndrome.

Angiofibromas, collagenomas, and lipomas in MEN1 syndrome are linked to mutation in the MEN1 gene, which encodes menin. The loss of menin function affects cutaneous tumor development by disrupting cellular proliferation, cell division, cell differentiation, and genetic stability[7]. Bi-allelic mutations of the MEN1 gene are not observed in other cutaneous tumors like melanocytic nevi and acrochordons, suggesting these are incidental rather than directly related to MEN1.

Specific genetic mutations identified in MEN1 patients with collagenomas include 713delG, W436R, a C>A substitution in exon 4, and c.265delC[3]. These mutations differ from those found in our patient.

Frameshift and truncated mutations are present in 75% of MEN1 patients. The c.196_200dup mutation has been reported in several MEN1 cases. However, the clinical presentation in our patient differs from previous reports, indicating no clear genotype-phenotype correlation. (Table 1)

Table 1 Characteristic of patients with heterozygous c.196_200dupAGCCC mutation leading to frameshift MEN1 mutation FH, family history; F, female; M, Male; -, negative; +, positive; NFPA, Non-functioning pituitary adenoma; PTC, papillary thyroid carcinoma

Case number	Sex/ Age	FH	Pituitary adenoma	Parathyroid disorder	Pancreatic tumor	Additional findings	Citation
1	M/50	+	-	-	Nonfunctioning	-	[8]
2	F/27	+	Prolactinoma	Adenoma	Nonfunctioning	Adrenal tumor	[8]
3	M/48	+	-	Hyperparathyroidism	Nonfunctioning	Adrenal tumor	[8]
4	F/46	-	NFPA	Nonfunctioning	Calcitonin	- PTC - Breast Cancer -Thymic neuroendocrine tumor - Adrenal tumor	[9]
5	F/45	-	Prolactinoma	Adenoma	Calcitonin	-Invasive ductal carcinoma -PTC -Adrenal adenoma -Thymic neuroendocrine tumor -Lung hamartoma	[10]
6 Our case	F/29	+	Prolactinoma	Hyperparathyroidism	-	-	-

Given the high risk of developing multiple tumors that can impact morbidity and mortality, the Endocrine Society recommends regular surveillance for MEN1 starting at age 5 for affected individuals and asymptomatic carriers.

Prognosis varies based on the type and extent of organ involvement.

Conclusion

Multiple skin-colored nodules consistent with collagenomas can provide important clues for the early diagnosis of MEN1 syndrome. Additionally, tumor and hyperplasia in both neuroendocrine and non-neuroendocrine systems should be investigated to confirm the diagnosis. Early diagnosis facilitates genetic counseling, appropriate workup, and improved patient outcomes.

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