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Combination of Multiple Skin Malignancies with Multiple Endocrine Neoplasia Type 1: Coincidental or Pathogenetically Related?

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Multiple endocrine neoplasia · Squamous cell carcinoma · Melanoma · Papillomatosis · Carcinogenesis

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited autosomal-dominant disease featuring combinations of over 20 different endocrine and nonendocrine tumors [1–6]. Most patients with MEN1 have germline mutations in the *MEN1* gene [1, 7], a tumor suppressor gene located at chromosome 11q13, which codes for a protein called menin [1, 7–9]. In patients with MEN1, various benign skin tumors – such as angiofibromas, collagenomas, and lipomas [1, 8, 10, 11] – as well as malignant melanoma [2, 7–9] have been found. We describe a patient with MEN1 who had confluent and reticulated papillomatosis, well-differentiated squamous cell carcinoma, superficial spreading malignant melanoma, and liver metastases from a pancreatic neuroendocrine tumor. This constellation of clinical findings appears to be unique in the literature. We investigated a possible pathogenic relationship between MEN1 and the skin tumors by studying loss of heterozygosity (LOH) of the *MEN1* gene in these lesions.

Case Report

A 70-year-old man presented with a 20-year history of a medically refractory nonpruritic scaly rash on the trunk. No other family member had similar skin changes or a history of other dermatological diseases. On physical examination, multiple, sharply circumscribed, pigmented papules with ichthyosiform scaling in the interscapular and intermammary regions were seen, which were confluent in the center and reticulated at the periphery (fig. 1a). Histological examination revealed orthohyperkeratosis, papillomatosis, acanthosis, mild hypermelanosis in the basal layer and perivascular lymphocytic infiltration in the upper dermis. Both periodic acid-Schiff and Congo red staining were negative, excluding fungal infection and amyloid deposits, respectively.

Upon further dermatological examination, the patient had an asymmetrically and darkly pigmented 0.8 × 0.6 cm macula behind his right ear which was excised and diagnosed as malignant melanoma Clark level III, invasion 0.9 mm (fig. 1b). Another skin biopsy taken parasternally demonstrated a well-differentiated squamous cell carcinoma. No other classical cutaneous manifestations of MEN1-like angiofibroma, collagenoma or lipomas were found, nor were they reported by the patient to have been present before.

In 1999, MEN1 had been diagnosed in the patient and his son. For several years, the patient had suffered from bilateral nephrolithiasis caused by hyperparathyroidism. In addition, he had an euthyroid goiter; as a result, he underwent parathyroidectomy and thyroidectomy. Following persistent abdominal pain in 1999, a pancreatic tumor was suspected. There was no evidence of acromegaly, a gastrinoma or insulinoma. On computerized tomography, a 3-cm pancreatic tumor was seen. Subsequently, the pancreas and spleen were surgically removed. Histologically, a neuroendocrine tumor of the pancreas was diagnosed, with liver metastases, in 2001, which were found by ultrasound, computerized tomography, scintigraphy with ^{111}In-labeled octreotide, and subsequent liver biopsy. Complete blood count, electrolytes (including calcium), liver function and renal function tests were normal. Serum gastrin, serotonin, prolactin, and insulin-like growth factor-1 were within the normal range. Because of the absence of clinical complaints and any evidence of hormonal activity, as well as the slow progression, the liver metastases of the pancreatic neuroendocrine tumor were not treated.

The coding region (exons 2–10) of the *MEN1* gene on chromosome 11 was analyzed for germline mutations. A heterozygotic deletion of 13 bp was found at the verge of intron 5 to exon 6 covering nucleotides 5,290–5,302.

Because of the multiple underlying diseases, no systemic therapy of papillomatosis confluens et reticularis was initiated, though it was the initial cause for presentation to the hospital. The melanoma and squamous cell carcinoma were excised with no apparent signs of metastasis.

Microdissection of tumor tissue (well-differentiated squamous cell carcinoma, melanoma) and normal skin tissue (sebaceous gland, lymphocytes, epidermis) was performed as previously described [12]. To search for loss of heterozygosity in the tumor tissue at the *MEN1* locus, microdissected tumor and normal DNA were amplified with the polymerase chain reaction using the polymorphic DNA markers/primers D11S480, D11S449 and PYGM which map to the *MEN1* gene locus at 11q13, as described by McKeeby et al. [3]. Primer sequences read for exon 5/6 forward: TCC CTG TTG GTT CTG ACC, and for exon 5/6 reverse: CGC CCG CCG CGC CCC GCG CCC GTC CCG CCG CCC CCG CCC GTG CCT CAG CCA CTG TTA GG.

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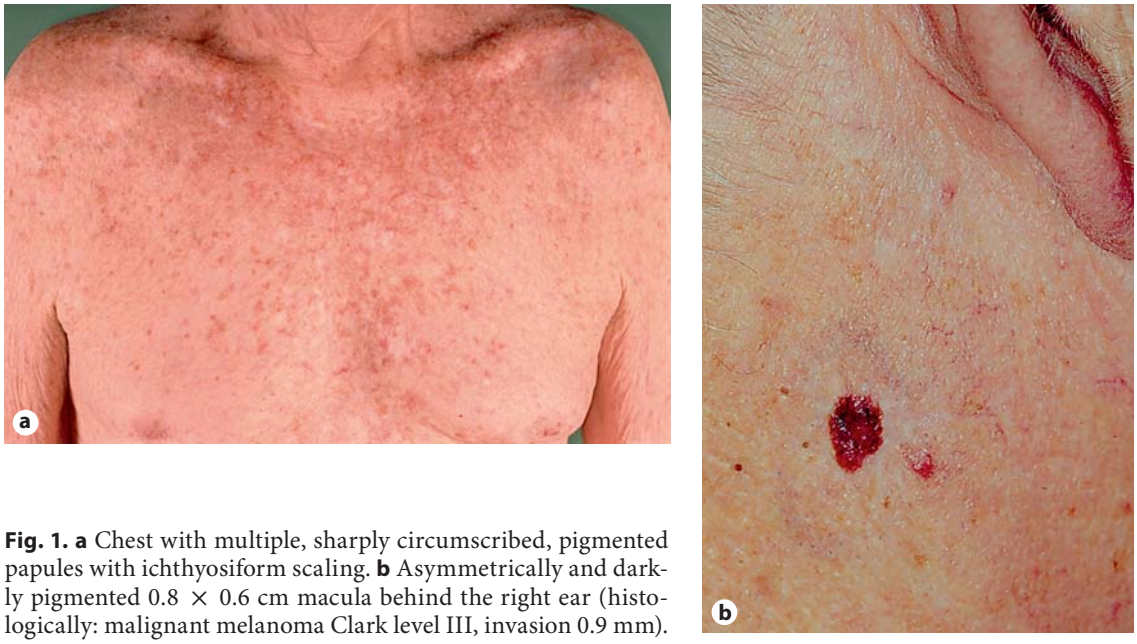

Fig. 1. a Chest with multiple, sharply circumscribed, pigmented papules with ichthyosiform scaling. **b** Asymmetrically and darkly pigmented 0.8 × 0.6 cm macula behind the right ear (histologically: malignant melanoma Clark level III, invasion 0.9 mm).

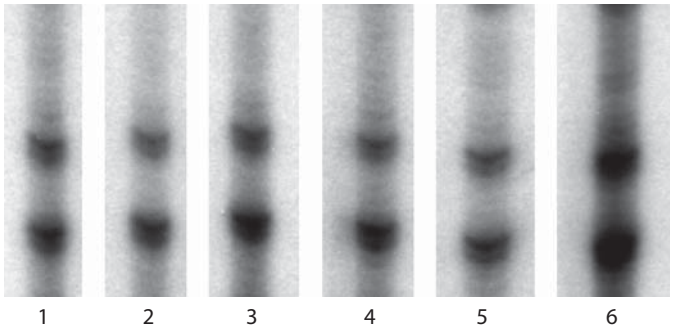

Fig. 2. Polymerase chain reaction of DNA dissected from SCC, melanoma and normal tissue. Amplification was performed with polymorphic DNA markers/primers D11S480, D11S449 and PYGM which map to the *MEN1* gene locus at 11q13. Lane 1: well-differentiated SCC; lane 2: sebaceous gland from normal skin; lane 3: lymphocytes from normal skin; lane 4: melanoma; lane 5: sebaceous gland from normal skin; lane 6: epidermis from normal skin.

Neither the well-differentiated squamous cell carcinoma nor the melanoma revealed LOH (fig. 2), with the only informative marker being PYGM which flanks to the *MEN1* gene locus.

Discussion

The patient reported here presented with 3 different skin neoplasias, of both benign and malignant origin, with the background of a hereditary endocrine disease and ensuing malignant internal disease. We have studied, and will now discuss, the possible pathogenic relation of these different entities. Confluent and reticulated papillomatosis is a rare benign skin disease of unknown etiology which affects teenagers and young adults, more commonly of female gender [13–16]. Though endocrine abnormalities, especially diabetes mellitus, obesity, thyroid disease, and hypopituitarism have been described [13–16], no association to MEN1 has been reported so far. Ultrastructural and immunohistochemical findings indicate an underlying abnormal keratinocyte differentiation or a genetically determined defect of keratinization [17, 18]. Alternatively, an abnormal host reaction to *Pityrosporum orbiculare* infection has been discussed [14, 15]. Other investigators have reported an association between confluent and reticulated papillomatosis and acanthosis nigricans [19, 20]. As the 2 disorders are identical under the microscope and sometimes overlap clinically, there is an ongoing debate as to whether or not they are one and the same disease. However, no association between confluent and reticulated papillomatosis and malignant skin tumors, such as malignant melanoma and squamous cell carcinoma, has been described so far.

MEN1 is a rare inherited autosomal-dominant disorder characterized by tumors of the parathyroid glands, pancreas, and anterior pituitary gland [1, 2]. In addition, mesenchymal tumors, such as leiomyomas and lipomas, as well as confetti-like hypopigmented macules, café-au-lait macules, multiple gingival papules, collagenomas, and multiple facial angiofibromas [1–4, 7, 8] are associated with MEN1. These tumors usually reveal LOH in patients with *MEN 1* germline mutation, following Knudson's two-hit hypothesis for tumor suppressor gene-linked hereditary syndromes [21–24]. Following mutation analysis of *MEN1* in malignant melanoma by Böni et al. [8], Nord et al. [9] studied the involvement of *MEN1* in malignant melanoma from MEN1 families as well as sporadic melanoma. They reported 7 cases of malignant melanoma occurring in MEN1 patients. Due to very small amounts of tumor cells, they were unable to screen for LOH in these cases. However, LOH in 11q13 could be detected in 6 spon-

taneous melanomas, and in 4 of these the pattern of LOH suggested the involvement of the MEN1 gene locus. Their results indicate that *MEN1* plays a role in the tumorigenesis of a small subgroup of melanoma.

To investigate whether *MEN1* gene alterations play a role in squamous cell carcinoma and melanoma in our case and whether the tumor spectrum of MEN1 is broader than described so far, we analyzed the skin tumors of our patient who had a known *MEN1* germline mutation for LOH at the MEN1 gene locus. Microdissection, which has been successfully applied previously [2, 12], ensured that only tumor cells were studied [3]. Accordingly, the absence of LOH at 11q13 with the informative polymorphic markers used can be interpreted as a true result rather than an obscuring effect of admixed non-neoplastic cells. Although there is no evidence for LOH using the polymorphic DNA markers D11S480, D11S449, and PYGM, we cannot exclude other mechanisms of somatic inactivation of the MEN1 gene such as smaller deletions, point mutations, and also promoter hypermethylation. These results suggest that squamous cell carcinoma and melanoma in our patient occurred coincidentally rather than being triggered by *MEN1* gene alterations.

Alternatively, as yet unknown growth factors or hormones that induce epidermal growth might be released in patients with MEN1. Since both benign and malignant epithelial proliferations as well as a malignant melanocytic tumor were present in our patient, a common denominator such as a single growth mediator appears unlikely. At the same time, the benign dermal and vascular tumors, which are the most common cutaneous manifestations of MEN1 [1, 2, 5], were absent in our patient. In summary, the combination of several skin neoplasias in our patient is conspicuous. The individual skin manifestations seem unrelated to each other as well as to MEN1, and coincidental rather than pathogenetically related. Still, patients with MEN1 should be monitored for skin manifestations regularly.

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