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Cutaneous Lichen Amyloidosis Associated with Multiple Endocrine Neoplasia Type 2A

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We have previously described a kindred with hereditary medullary thyroid carcinoma and pheochromocytoma (multiple endocrine neoplasia type 2A [MEN 2A]) with localized pruritic cutaneous manifestations present only in affected members. Although the initial skin biopsies reported did not show amyloidosis, subsequent skin biopsy results reported here have demonstrated amyloid which stained for keratin but not for calcitonin and established that this family represents an association of a rare autosomal dominant form of lichen amyloidosis with MEN 2A. (Henry Ford Hosp Med J 1989;37:144-6)

Since no phenotypic characteristics have been described in multiple endocrine neoplasia type 2A (MEN 2A), the expected occurrence of thyroid tumors in this syndrome requires affected members to be identified by periodic evaluation of basal and stimulated calcitonin (CT) levels begun at an early age. However, we have reported a kindred with MEN 2A in which a cutaneous manifestation was noted only in affected adult members (1). The skin manifestations appeared early in life and may have preceded the biochemical presentation of thyroid tumor. Initial histologic study disclosed no characteristic abnormalities and the condition was considered to be hereditary localized pruritus. However, after becoming aware of another family in whom MEN 2A appeared to cosegregate with lichen amyloidosis (2,3), we performed further studies which also demonstrated amyloidosis of the skin in our family.

Patients and Methods
The pedigree of the M family was shown in our initial publication (1). After the propositus was diagnosed as having medullary thyroid carcinoma (MTC), 40 members in five generations were identified (1). Twenty-nine members were examined at our clinic, and data on three additional members were obtained from clinical records supplied by other hospitals. All the relatives examined had analyses as described in our earlier description of the family (1).

Clinical and Biochemical Data
A retrospective diagnosis of MEN 2A can be made for two relatives, both deceased, and a total of ten members were diagnosed as being affected on the basis of clinical and biochemical data. These ten members, five men and five women, were between 18 and 66 years old (mean age 36 years) at the time of diagnosis. MTC was surgically proven in each with histology showing the typical MTC pattern with amyloid in all cases. Generally, the cervical lymph nodes were involved in the older patients, and the main symptom was diarrhea in the presence of liver metastases. Flushing of the face and neck after even a moderate emotion was observed in two members. CT levels were very high in all but four patients who showed an excessive response only after pentagastrin stimulation (1). Carcinoembryonic antigen levels were very high in four patients (more than 50 µg/L) but did not correlate with CT levels. Three patients have died from MTC and one from an undiagnosed pheochromocytoma. The remaining six patients have had surgery, and all but two now have normal CT levels.

Pheochromocytomas were identified in three members. A 46-year-old man had a history of sustained hypertension during the three years prior to being hospitalized for a severe hypertensive attack. He died two days later; a right adrenal pheochromocytoma and an unsuspected MTC were found at autopsy. In two patients, computed tomography showed adrenal masses that were surgically proven to be typical pheochromocytomas. Those patients who had increased urinary vanillylmandelic acid excretion and epinephrine/norepinephrine ratios were found to be normotensive, and the youngest had a one-year history of orthostatic hypotension. Serum calcium and parathyroid hormone levels were normal in all patients, and parathyroid histology performed in seven cases did not show hyperplasia.

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Cutaneous Manifestations

All affected members examined showed cutaneous manifestations (1) consisting of intermittent itching in a roughly circular area, 5 to 10 cm in diameter, located on the back at the level of the first thoracic vertebrae extending from the midline to the right or left scapular region. This symptom generally began at age 4 or 5 years, and in adults hyperkeratosis was evident as a darkened, raised area. Family members reported that such manifestations were present in two ancestors in whom the diagnosis of MEN 2A has been formulated either by clinical records or retrospectively. None of the relatives who were unaffected and older than 30 years have this peculiarity of the skin. In generation IV, three children between ages 4 and 11 years have this cutaneous pruritus. They have been considered to be unaffected because of normal basal and stimulated CT levels. However, an abnormal CT response was recently demonstrated in one patient (peak 1.2 μg/L) by a combined pentagastrin plus calcium test (2 mg/kg body weight) (4).

Cutaneous biopsy performed on one affected member revealed deposition of an amorphous material at the interface between the dermis and epidermis which stained with hematoxylin-eosin and Congo red stain (Fig 1) as typical amyloid. For immunoperoxidase staining, paraffin sections were incubated with two monoclonal antibodies which recognize 57-66 and 48, 51, 52, and 54 kilodalton forms of keratin (DAKO Corporation, Santa Barbara, CA) as previously described (5). The immunohistochemical stains for CT were performed utilizing a polyclonal rabbit antiserum against human CT (DAKO Corporation, Santa Barbara, CA). Immunohistochemical stains of the amyloid for keratin were positive particularly for low molecular weight keratins (Fig 2) but were negative for CT. MTCs from all affected members stained positive for CT.

Discussion

The only cutaneous abnormalities described in the MEN 2 syndromes are masses of myelinated and nonmyelinated nerves observed in the dermis of clinically normal skin of patients with MEN 2B who otherwise do not complain of itching (6). Skin histology of our patient has shown cutaneous lichen amyloidosis, a rare skin manifestation occurring in both sporadic and hereditary forms. The hereditary form of this disease is transmitted as an autosomal dominant trait, and 65 cases have been reported since 1960 (7-17). The skin lesions usually appear as pruritic papular and pigmented lesions located either on the back as in our family (8,10,17) or on the extensor surfaces of the thighs, legs, or arms (7,8,11,13,14,18). Amyloid deposition is noted in the skin, as in our family, with no amyloid elsewhere in the body. The chemical nature of the amyloid (19,20) has not been definitely characterized, but it is believed to be derived from keratin.

In the previous study (1) we described two affected members of the same MEN 2A kindred who complained of intermittent itching but had no evident hyperkeratosis. Cutaneous biopsy performed on both had failed to demonstrate amyloid (1). Such negative results could have come from sampling error, or, alternatively, perhaps dermal amyloid can be demonstrated only after long-term scratching when the skin appears clearly hyperkeratotic and pigmented. If so, dermal amyloid may occur only secondary to the chronic scratching trauma.

After becoming aware of another unrelated family in whom MEN 2A and cutaneous lichen amyloidosis appear to cosegregate (2,3), we performed the additional skin biopsy which showed amyloidosis even though previous biopsy on that individual and another affected member had failed to demonstrate amyloidosis (1). Gagel et al (2) and Donovan et al (3) described three members having the same typical skin lesions and MEN 2A and two additional members with MEN 2A but no observable skin changes. Those who were positive for both diseases had noted local itching since age 18. The age of onset of pruritus in their family was different from that in the kindred in which the localized itching appeared before the age of 10.

The cosegregation of MEN 2A and cutaneous lichen amyloidosis in two unrelated families is unlikely to have oc-
curred by chance alone. It is highly probable that the cutaneous lichen amyloidosis/MEN 2A syndrome represents an overlapping of contiguous gene syndromes in which a microdeletion or mutation has caused both diseases (21,22). In these families cutaneous lichen amyloidosis may be considered as a phenotypic marker for screening in future generations. In patients with hereditary cutaneous lichen amyloidosis, we suggest an appropriate screening for MEN 2A tumors to determine the prevalence of this newly described syndrome.

References