Familial Cutaneous Lichen Amyloidosis in Association with Multiple Endocrine Neoplasia Type 2A: A New Variant

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Multiple endocrine neoplasia type 2A (MEN 2A) is a rare hereditary disease transmitted in families as an autosomal dominant trait. We have identified a family in which the expression of a rare autosomal dominant form of cutaneous lichen amyloidosis appears to cosegregate with MEN 2A. In this family the skin lesion presented as multiple infiltrated papules overlying well demarcated plaques over the scapular area (right or left). Immunohistochemical studies demonstrated amyloid which stained for keratin but not calcitonin. A total of 19 members were screened. Three members of the family have the characteristic skin lesion and MEN 2A; two additional members have MEN 2A but have not manifested observable skin changes of lichen amyloidosis. Another unrelated Italian family with a similar type of pruritic skin rash and MEN 2A has been reported recently. Although the initial skin biopsies were negative for amyloidosis, subsequent biopsy established the association of MEN 2A with amyloidosis in this family also. When these kindreds are combined, several conclusions can be drawn. First, the syndrome of cutaneous amyloidosis and MEN 2A appears to be a clearly defined autosomal dominant hereditary syndrome. Whether this syndrome can be linked to chromosome 10 is not yet known. Second, the dermal amyloid appears to be caused by deposition of keratin-like peptides rather than calcitonin-like peptides. Third, we believe that patients with the hereditary form of cutaneous amyloid should be screened for medullary thyroid carcinoma to determine the true frequency of this syndrome.

Multiple endocrine neoplasia type 2A (MEN 2A) is a rare clinical syndrome of malignant tumors that is transmitted in an autosomally dominant pattern (1). It results in medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia. Since its initial description as a clinical entity and its characterization as a genetic syndrome, MEN 2A has undergone intensive scientific investigation because it is a well-delineated example of hereditary malignancy (2-4). Early investigative efforts focused on delineation of the clinical characteristics of the syndrome and led to the discovery of calcitonin (CT) as a tumor marker (5-8). The second evolutionary phase of the disease has been the introduction and widespread employment of prospective family screening to improve treatment of the disease (9,10). The third phase has been the application of modern molecular biologic techniques to search for the genetic defect responsible for the syndrome. Investigation in recent years has resulted in mapping of the gene of MEN 2A to chromosome 10 (11-13).

Hereditary lichen amyloidosis is a rare skin disease transmitted as an autosomally dominant trait that presents as a scaly, papular lesion associated with intense pruritus. It may occur on the back or extensor surfaces of the extremities. During routine screening of a recently discovered family with MEN 2A, a cutaneous skin lesion was noted on the upper backs of three of the family members affected with MTC (14). Further evaluation of the skin lesions demonstrated them to be consistent with cutaneous lichen amyloidosis. This finding prompted further investigation into the possible association of familial cutaneous lichen amyloidosis in MEN 2A (Fig 1).

Materials and Methods

In 1981, a new family with MEN 2A was discovered following the presentation of the propositus with bilateral pheochromocytoma and MTC. Screening was offered to other family members who declined any investigation until 1987. At that time the propositus and several family members agreed to further screening (Fig 1). During routine physical examination, a scaly, papular skin lesion on the upper back over the right scapula was discovered in the propositus and biopsied. Two additional affected family members in whom similar skin lesions were found underwent a punch biopsy of the affected skin (Fig 2).
Fig 1—Pedigree of A-kindred demonstrating members affected with medullary thyroid carcinoma and cutaneous amyloidosis.

The screening procedures for MEN 2A in this family and the biopsy procedures are detailed in the original publication regarding this family (14).

Results

Following treatment of the propositus (III-12), other family members agreed to routine screening in 1987. Screening revealed five family members to be gene carriers for MEN 2A. Four had documented MTC found in surgically resected specimens. The fifth patient has bilateral thyroid nodules and markedly elevated pentagastrin-stimulated CT levels but has refused any surgical treatment. Three of the five patients with MTC were noted to have skin lesions on the upper back. The lesion in the propositus is a large, scaly, papular skin lesion overlying the left scapula of the upper back that does not extend across the midline. It was first noted by the patient at the age of 18. The mother of the propositus (II-6) had a similar, somewhat larger lesion over the left scapular region that was first noted when she was a young adult (Fig 2). The third patient (II-5) possessed a similar, slightly more erythematous lesion over the right scapular region. All the patients described the lesions to be associated with periods of intense pruritus. Two additional patients (aged 26 and 32, daughters of patient II-5), both with known MTC, have not manifested any skin lesions to date.

Punch biopsies of the skin lesions were performed. The microscopic findings of amyloid deposition in the region of the basal layer at the interface of dermis and epidermis are consistent with cutaneous lichen amyloidosis (Fig 3). These observations have been confirmed by positive stains with Congo red and Crystal violet. Immunohistochemical stains of the amyloid were positive for keratin and negative for CT. The amyloid from a focus of MTC of one of the family members has stained positive for CT utilizing the same histochemical techniques employed on the skin lesions. One of the two patients (III-9), who has documented MTC but who has not manifested the characteristic skin lesions, underwent a random biopsy in the region of the back where her mother’s lesion is located. The biopsy results were consistent with normal skin without evidence of amyloid deposition. Further investigation of the families failed to reveal any evidence of peripheral neuropathy, cardiomyopathy, or renal disease usually found in the systemic forms of amyloidosis. Chromosomal analysis in the propositus and her mother also has been been unremarkable (14).

Discussion

Cutaneous lichen amyloidosis is a rare skin abnormality that usually presents as a scaly, thickened, papular, pigmented area on the lateral extensor surfaces of the legs and arms or on the upper back. It is associated with intermittent periods of intense pruritus. Histologically, it is characterized by the intradermal deposition of amyloid in the papillary dermis. The amyloid is believed to be derived from keratin, but definitive confirmation of this has not been made. Cutaneous lichen amyloidosis has been reported to occur both in hereditary and sporadic forms. The familial form is transmitted in an autosomal dominant pattern. Less than 75 cases have been reported in the literature (15-25). Histologic description in the hereditary cases is identical to the skin lesions found in our patients. None of the previous reports has found amyloidosis in other organ systems, and no evidence of systemic involvement was found in our patients. There is no mention of other malignancies such as MTC in the families described to date.

MEN 2A is an uncommon syndrome of malignant tumors that follows an autosomal dominant pattern of transmission. The association of MTC with pheochromocytoma and parathyroid hyperplasia is well documented (2,4). The well described variant
MEN 2B is associated with a Marfanoid habitus and mucosal and gastrointestinal ganglioneuromatosis (26-28). Our patients do not have any features of the MEN 2B syndrome.

The findings of familial cutaneous lichen amyloidosis occurring in a family with MEN 2A, however, prompted us to query whether there is a link between the two syndromes. A recent report by Nunziata et al (29) describing a family with MEN 2A who had an almost identical skin lesion to one we report has supported our initial impression. These authors describe a family in which several members with MTC also manifested a pigmented, raised lesion on the upper back. The affected members experienced periods of intense localized pruritus. Affected patients initially developed severe pruritic lesions on the upper back during childhood at the age of 4 or 5; the lesions have persisted into adulthood with a residual 5 to 10 cm lesion on the upper back that does not cross the midline. In this Italian kindred, all adults with the skin lesion developed MEN 2A. In addition, they have recently demonstrated the presence of amyloid at the interface of the dermis and epidermis (30). Three children of parents with MTC have developed a skin lesion on the upper back. Initially, they all had normal CT levels. One of these children has since had elevation of pentagastrin-stimulated CT, and C-cell hyperplasia was confirmed following thyroidectomy. In our patients, there have been no cases of the skin lesion occurring in the absence of MTC. While two patients with MTC have not yet manifested the skin lesion, they are still both young and may do so in the future.

With the exception of the development of the skin lesion at an earlier age, striking similarities can be noted between our family and the kindred reported by Nunziata et al (29,30). Both families have MEN 2A. Members of each family have developed a hereditary pruritic skin lesion of the upper back that clinically and histologically is consistent with familial cutaneous lichen amyloidosis. In adult family members, the lesion has always occurred in conjunction with MTC.

Current understanding of the presence and nature of the amyloid found in these syndromes is incomplete. In familial cutaneous lichen amyloidosis, evidence suggests that the amyloid is derived from a keratin-like peptide in the skin. This concept is supported by positive immunohistochemical staining for keratin in our patients (14) and in the Italian family (30). However, the known genes related to keratin production are located on chromosomes 12 and 17 (31-35). The amyloid present in MTC appears to be related to the presence of an incomplete or abnormal CT gene product. The failure to document the presence of CT in skin lesions of our patients by immunohistochemical methods suggests that the amyloid is probably not a CT gene-related product (36).

Evidence is not available to explain completely the association of hereditary cutaneous lichen amyloidosis and MEN 2A. The evidence thus far is very suggestive of a contiguous gene syndrome (37) which is a disorder caused by the individual or additive effects of a deletion or mutation of contiguous genes on a single chromosome. While the association of two autosomally dominant hereditary diseases may have occurred by chance alone, or alternatively by a series of interrelated biochemical events regulated by genes on two or more chromosomes, the evidence and rules of probability do not support this theory.

Fig 3—Histologic appearance of characteristic features of lichen amyloidosis demonstrating the amyloid deposition (arrows) at the epidermal and dermal interface (hematoxylin-eosin stain, X200).

Conclusions

The association of familial cutaneous lichen amyloidosis in MEN 2A is a newly defined entity. The rarity of the two syndromes occurring together suggests that it should be categorized as a variant of MEN 2A and not as a separate syndrome. The syndrome does not appear to be related to any detectable chromosomal abnormalities. There is a definite but distinct abnormality of protein production resulting in deposition of a different form of amyloid in the thyroid than in the dermis of the skin. The association of cutaneous lichen amyloidosis in MEN 2A may be explained by a contiguous gene syndrome phenomenon. We recommend that all patients with MEN 2A should be examined for the presence of cutaneous lichen amyloidosis and all patients with hereditary cutaneous lichen amyloidosis should be screened for MEN 2A. Further investigation into the genetic relationship of the two syndromes is currently under way.

Addendum

Basal serum CT values in four patients from one family (16) with hereditary cutaneous lichen amyloidosis and normal thyroid examinations were measured and found to be normal (highest value 22 pg/mL).

References


