Cutaneous Lesion Associated with Multiple Endocrine Neoplasia Type 2A: Lichen Amyloidosis or Notalgia Paresthetica?

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Three patients of a French family demonstrated an association of multiple endocrine neoplasia type 2A (MEN 2A) with a pruritic scapular skin lesion. The lesions are similar to those described as familial cutaneous lichen amyloidosis in unrelated MEN 2A and medullary thyroid carcinoma families, but histological, immunohistochemical, and ultrastructural analysis of skin biopsies from each patient in the French family did not show amyloid deposition. The topography of the lesion follows dermatomes C8-D3. The patients report not only pruritus but also paresthesia and hyperalgesia, and one showed touch hypoesthesia and pain hyperesthesia in the area of the lesion. Such an association of cutaneous and neurological features suggests notalgia paresthetica (NP), a neuropathy of the posterior dorsal rami nerves. We thus suggest that the cutaneous lesions associated with MEN 2A might be secondary to pathology in the neural crest-derived dorsal sensory nerves. The amyloid, when present, would be secondary to scratching. We propose that patients presenting with familial NP be suspect for MEN 2A.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A (MEN 2A) IS A GENETIC DISEASE CONSISTING OF MEDULLARY THYROID CARCINOMA (MTC), PHEOCHROMOCYTOMA, AND PARATHYROID HYPERPLASIA. ITS GENE HAS BEEN RECENTLY ASSIGNED TO THE PERICENTROMERIC REGION OF CHROMOSOME 10 (1-3), AS HAVE THE GENES FOR THE RELATED MEN 2B AND FAMILIAL MTC SYNDROMES (3,4). SINCE 1989, A NEW CLINICAL MANIFESTATION HAS BEEN DESCRIBED IN THREE FAMILIES, TWO WITH MEN 2A (5,6) AND ONE WITH MTC ONLY (7). THE MANIFESTATION CONSISTS OF PRURITUS IN THE SCAPULAR AREA, WITH OR WITHOUT AN ASSOCIATED SKIN LESION. THE FINDING OF AMYLOID DEPOSITS IN THE PAPILLARY DERMIS IN SOME OF THESE LESIONS (6-9) LED TO A DIAGNOSIS OF CUTANEOUS LICHEN AMYLOIDOSIS (CLA), A RARE DERMATOLOGICAL DISEASE WHICH EXISTS BOTH IN SPORADIC AND FAMILIAL (FCLA) FORMS.

The genetic linkage of this variety of FCLA to the MEN 2 locus has recently been demonstrated (10). We report a French MEN 2A family in which three patients present with the same type of pruritic scapular skin lesions, but also mention paresthesia and hyperalgesia in the same area. Despite extensive analysis of three skin biopsies per patient, no amyloid deposits were found. We discuss a new hypothesis on the pathogenesis of this cutaneous manifestation associated with MEN 2A.
though the MEN 2A gene was probably transmitted by the mother of the propositus, no evidence of MEN 2A could be found in either the maternal or paternal relatives.

Dermatopathologic study
All subjects were questioned about the presence of dorsal pruritus. Subjects in group 1 also underwent physical examination. Three punch biopsies were performed in each patient with scapular skin lesions. One biopsy was fixed in Bouin solution, embedded in paraffin, and stained with hematoxylin eosin, Congo red, or thioflavin T. The second biopsy was fixed first in 2.5% glutaraldehyde, then in 1% osmium tetroxide and embedded in Epon for ultrastructural study. The third biopsy was processed for immunohistochemical studies on frozen sections. Antibodies were selected to study the following components: immunoglobulin deposits, complement and fibrinogen, colloid bodies, keratins, amyloid deposits, and immunologic phenotypes of lymphocytic infiltrates.

Neurological investigations
Patient IV-2 had a thorough neurological examination, an electromyographic study of dorsal roots C8 to D3, and a magnetic resonance imaging (MRI) study of the cervicothoracic spine.

Results

Clinical cutaneous and neurological manifestations
None of the subjects without MEN 2A had scapular pruritus or skin lesions. None of the deceased subjects was known to have complained of pruritus. Two male patients (III-10, 49 years old; III-11, 43 years old) and one female patient (IV-2, 20 years old) presented with chronic pruritic manifestation in the same specific area (Fig 2). This area was located in the upper back, at the level of the 1st to the 4th thoracic vertebra, along the midline and extending to the left (III-10) or the right (III-11, IV-2) scapular region. The symptomatology appeared at 11 years of age (patient IV-2) or about 16 years (patients III-10 and III-11) and preceded the lesion. In all three patients pruritus was described as paroxysmal and was associated with hyperalgesia, burning, and sometimes tingling. The symptomatology was much more intense for patient IV-2 than for patients III-10 and III-11. The lesions were restricted to the pruritic zone and showed in all patients a brown patch of macules. However, lesion characteristics were variable: the lesion of patient IV-2 (Fig 2B) showed lichenified papules in addition to the macules, whereas in patient III-10 (Fig 2A) hyperpigmentation of the epidermis and the hair was prominent. The lesion of patient III-11 (not shown) was discrete.

The neurological examination of patient IV-2 showed hyposthesia for light touch and hyperesthesia for pinprick in an area restricted to the skin lesion and its periphery. No other sensory or motor abnormality could be elicited, and the electromyogram and MRI were considered normal.

Histology
The morphological features were similar in all three patients, although more prominent in patient IV-2. The epidermis showed moderate acanthosis, focal hyperpigmentation, and hyperplasia of the basal layer, but no immunoreactivity for 56 kd keratins. No colloid bodies were seen. The dermo-epidermal junction showed segmentary thickenings facing acellular areas of the papillary dermis. The dermis showed a pigmentary incontinence and a perivascular lymphohistocytic infiltrate with a predominantly T8 phenotype. The ultrastructural study confirmed the alterations of the dermo-epidermal junction: reticular aspect of the lamina densa with destruction of the hemi-desmosomes. Immunohistochemical study showed no deposit of IgG but a deposit of C3 at the dermo-epidermal junction.

No amyloid deposit could be shown by either the special stainings or by ultrastructural or immunohistochemical study.
Discussion

The clinical cutaneous features of the three French patients reported here are similar to those reported earlier in two MEN 2A and one familial MTC families (5-7). The remarkable topography of the pruritus is identical: upper back at the level of the first thoracic vertebrae extending unilaterally to the right or left scapular regions. This pruritus preceded the appearance of a similar hyperpigmented skin lesion, also lichenified in patient IV-2 who had the most intense scratching. These similarities strongly suggest that the patients of all four families have the same skin pathology. As in the other families, all three French patients presenting with this skin pathology also have MEN 2A, consistent with the recent demonstration that it is genetically linked to the MEN 2 locus (10). As in two other families (6,7), some French patients do have MEN 2A but no scapular pruritus, suggesting that this skin manifestation provides a highly specific but not very sensitive marker of MEN 2A or MTC within families.

Despite these clinical similarities, our histological findings were different: we failed to detect amyloid deposition despite extensive analysis of biopsies in each patient, and we were at first reluctant to consider the diagnosis of FCLA in our patients. However, several interpretations can be found for this discrepancy. First, analysis of the data of the other families (5,6,7,9) showed that amyloid deposits have so far been found only in adult women; similarly, an epidemiological study on CLA (13) has reported a prevalence < 7% below 24 years old and a female: male ratio of 3:1. Thus sex and age factors in skin amyloidogenesis could explain our negative findings in two men (III-10, III-11) and one young woman (IV-2). Another explanation can be provided by a current theory on skin amyloidogenesis: it is believed that scratching may play an important role in amyloidogenesis by causing epidermal cell damage which leads to filamentous degeneration of keratinocytes, subsequent apoptosis, and conversion of filamentous masses into amyloid material (14-16). Unlike some “friction amyloidosis” cases in which scratching and hyperpigmentation were reported to precede pruritus (17), the pruritus in the MEN 2A/familial MTC cases seemed to be the first manifestation. The lack of amyloid in the French patients could possibly be explained by the pruritus occurring first followed by scratching, which was not intense (III-10, III-11) or of long enough duration (IV-2) to initiate significant amyloidogenesis.

However, three characteristics of the pruritic lesion associated with MEN 2A remain disturbing regarding the diagnosis of FCLA. First, its topography is unusual: the main localizations of lesions in other forms of CLA are legs, forearms, and back (18), with the back lesions being rarely isolated. Of the three reports of FCLA with exclusive back localizations (19-21) reviewed by Gagel et al (6), only one (20) was isolated and unilateral. In that report the skin lesions were clearly different than in MEN 2A patients since they were already present at birth and not pruritic. It should be stressed that the topography of the pruritus and skin lesion associated with MEN 2A follows dermatomes C8-D3 in the French patients (Fig 1) and apparently also in the other FCLA/MEN 2A families (5-7). Second, in the French patients at least, the pruritus is associated with hyperalgesia and paresthesia. In an epidemiological study on primary cutaneous amyloidosis, symptoms other than pruritus (burning sensations) were reported only in 0.78% of patients (13). Third, the MEN 2A-associated pruritus is paroxysmal, suggesting a neurological origin (22).

These three characteristics suggested a neurological cause for the pruritus associated with MEN 2A. Based on this hypothesis we reviewed the literature of localized pruritus of neurological origin and identified an entity called notalgia paresthetica (NP). NP refers to a neuropathy involving the dorsal primary divisions of spinal nerves. It was first described in 1934 (23) and recently reviewed by Weber and Poulos (24), who extended the term to several entities previously described as “localized pruritus” (25), “puzzling posterior pigmented patches” (26), and “peculiar spotty pigmentation” (27). Most cases are sporadic, but one family has been described (25). The main symptom of NP is pruritus, sometimes associated with hyperalgesia, burning, or ting-
gluing sensations, all localized unilaterally in the upper back at the level of the first thoracic vertebra. In this area the neurologi-
cal examination can reveal hypoesthesia to touch, hyperesthesia
to pinprick, and a reduced response to provoked sweating (24).
Electromyogram has in some cases showed signs of denervation
(28). In the same area the patients also present with a skin lesion
consisting of a brown patch of macules and sometimes lichen-
ified. Skin biopsies of the lesion show scattered keratinocytic
necrosis, moderate acanthosis (when lichenification is present),
and pigmentary incontinence. CLA is in the differential diagno-
sis of NP, but in NP there are no amyloid deposits in the papillar
dermis (27). Based on this description, we recalled our pa-
patients for neurological investigations and found only one patient
(IV-2) who had hypoesthesia and pinprick hyperesthesia in the
area of the lesion, consistent with the diagnosis of NP.

We propose that the FCLA associated with MEN 2A could be
due to a hypothetic neurologic lesion of the thoracic sensory
nerves (similar to NP) which is responsible for pruritus, scratch-
ing, and eventually friction amyloidosis. This hypothesis bears
both theoretical and practical interests. Like the thyroid C-cells
and the adrenal medullary chromaffin cells, the sensory thoracic
nerves are derived from the neural crest (29). FCLA could then
be included with MTC and pheochromocytoma as a common
neurocristopathy resulting from the expression of a gene(s) lo-
cated in the chromosome 10 pericentromeric region. From a
practical point of view, the recent report that local treatment
with capsaicin is effective in NP (30) suggests that a trial of cap-
saicin would be of interest in the symptomatic treatment of
FCLA associated with MEN 2A.

In order to test our hypothesis, we propose that the patients
presenting with FCLA associated with MEN 2A or MTC un-
dergo a neurological examination possibly with electromyog-
ographic studies to search for sensory defects. In addition, we
propose that patients presenting with familial NP be screened
for MEN 2A.

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