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Histopathological and Bacteriological Findings in Prurigo Nodularis

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Prurigo nodularis is a chronic disease with unknown aetiology. Biopsy specimens of 43 patients with prurigo nodularis were taken for histopathological and mycobacteriological analyses. By conventional histopathology, 25 (58 %) samples, and by immunostaining for S100 protein, 31 (72 %) samples had changes relevant to prurigo nodularis. Twelve (28 %) of the samples were positive for acid fast bacilli in tissue staining by Ziehl-Neelsen technique, including 4 of the 6 samples also positive for mycobacteria in cultivation. The results verified the usefulness of S100 staining in detection of neural hyperplasia in dermal nerves, a feature regarded as diagnostic for prurigo nodularis. They also indicated that atypical mycobacteria may be a contributing factor in prurigo nodularis. ***Key words: atypical mycobacteria; neural hyperplasia; skin manifestations.***

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Prurigo nodularis (PN) is a chronic disease characterized clinically by intensely itchy nodules, which are localized mainly to the limbs and in severe forms also affect the trunk (1).

The cause of PN is unknown, although atopic background, gluten enteropathy, emotional stress, anemia, hepatic and other metabolic dysfunctions and insect bites seem to be contributory factors (2–4). Histological changes regarded as characteristic for PN by ordinary histopathological stainings consist of epidermal hyperplasia associated with hyperkeratosis on the surface epithelium and downward proliferation of the epidermis (5). To the criteria of PN, some authors also add the detection of significant hyperplasia of dermal nerves (6).

The aim of this study was to make a comparative evaluation between clinical and histopathological criteria used to diagnose PN. For this purpose, we examined skin biopsy specimens of lesions of 43 patients with clinically defined PN, using both the basic histochemical and immunohistochemical techniques developed for the demonstration of neural fibers. Two immunohistochemical stainings were used: staining for S100, which is a protein typically present in neural (i.e. glial and Schwann cells) and in various non-nervous normal and neoplastic tissues, and staining for neurofilament (NF), which is a neural marker (7). We also evaluated a possible association of PN with nontuberculous mycobacteria, which may have a role in the aetiology of PN (8).

MATERIAL AND METHODS

This study was a part of a prospective project performed from October 1989 to March 1991 in Kuopio and Oulu University Hospitals. The initial study population consisted of 90 patients with chronic or subchronic skin manifestations of unknown origin. Among this group, 43 patients had the clinical diagnosis of PN. The group consisted of 24 women and 19 men. The age varied from 20 to 85 years (mean 57.8 years). PN had a mean duration of 12 years (range 6 to 40 years). None of the patients had ever had tuberculosis or other mycobacterial infections. Two parallel skin biopsy specimens, either from the same or identical lesions, were taken for histopathological and microbiological studies.

The histopathological specimens were stained with van Gieson, periodic acid-Schiff (PAS), haematoxylin and eosin (HE) techniques, as well as with Ziehl-Neelsen staining for acid fast bacteria (AFB). Representative sections were also stained for demonstration of neural fibers, using antibodies against S100 and neurofilament proteins (DAKO, Glostrup, Denmark) by the avidin-biotin-peroxidase complex method (9).

For microbiological examination the specimens were cultured in solid (10) and liquid (Bactec 12B, Becton Dickinson, Towson, Md) media for a 6-month incubation at +32 °C and +36 °C (8).

RESULTS

Histological changes regarded as characteristic for PN by ordinary histopathological stainings (PN sensu stricto) were only found in 25 cases (58 %). In the remaining 18 cases the histological diagnosis was either nonspecific or irrelevant to PN (Table I).

By the two immunostainings used, changes indicating dermal nervous hyperplasia could be detected in 16 (37%) samples by the NF staining and in 31 (72%) samples by the S100 staining. In the NF staining, the result was often weak and difficult to interpret in comparison with the S100 results. The samples staining positive for neural hyperplasia by S100 included 22 cases classified as PN sensu stricto by the basic techniques (Fig. 1), and in addition 5 of the 6 with ulcerative lesions (Table I). In 12 of the examined patients, no neural hyperplasia could be demonstrated by the immunostainings. Since all examined patients were regarded as true PN on clinical grounds, the sensitivity of S100 was higher than conventional histopathology (72% and 58%, respectively). The lowest sensitivity was obtained by NF staining (37%).

By the Ziehl-Neelsen staining of tissue sections, AFB were detected in low numbers in the upper epidermal layers of 12 (28 %) specimens (Fig. 2). Six of the specimens grew mycobacteria in culture; 3 grew *M. avium-intracellulare* complex, one *M. malmoense* and 2 mycobacterial species other than the presently known mycobacterial pathogens. These two species could be classified only to genus level. Granulomatous changes were not present in any of these samples. All 6 species were detectable after 1 to 6 months at +32 °C (Table I).

DISCUSSION

The clinical diagnosis of PN had a poor correlation with conventional histopathological criteria. Only 58 % of the clinically defined cases had changes regarded as typical of PN. Due to intense itching, a prominent feature in PN, skin lesions with nonspecific ulcerative changes may even be expected.

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Table I. *Conventional histopathology and immunostaining for detection of neural hyperplasia in 43 patients with prurigo nodularis*
AFB: acid fast bacteria

Conventional histopathology		Dermal neural hyperplasia present by immunostaining		AFB detected in tissue staining	Mycobacteria detected by culture
		S100	Neurofilament		
Prurigo nodularis	25	22	11	8	4
Nonspecific ulceration	6	5	1	2	0
Nonspecific dermatitis	9	2	3	1	2
Erythema fixum	1	1	1	0	0
Lichen planus	1	1	0	0	0
Panniculitis	1	0	0	1	0
Total number	43	31 (72 %)	16 (37 %)	12 (28 %)	6 (14 %)

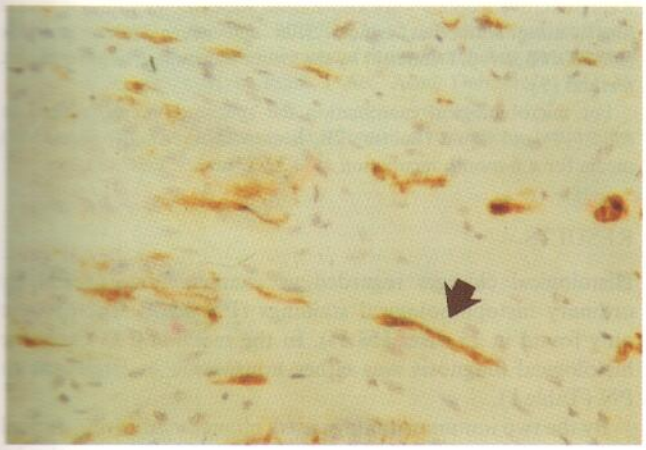

Fig. 1. Neural hyperplasia colouring as brown in prurigo nodularis (S100 × 43).

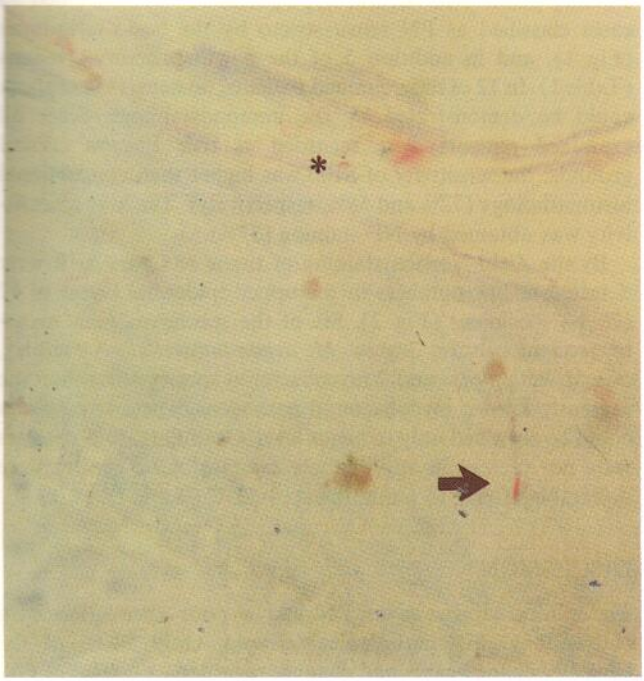

Fig. 2. Two acid fast bacilli can be seen on the epidermis, marked *arrow* or *star* (Ziehl-Neelsen × 60).

Regarding also ulcerative changes as acceptable for the diagnosis of PN, histopathological changes relevant to PN were detected in 31 samples (72%).

To enhance histopathological diagnosis of PN, demonstration of neural hyperplasia has been recommended (11,12), though it is regarded as neither an essential nor a common feature of the disorder (13). Among the 31 samples filling the conventional histopathological criteria of PN, dermal hyperplasia was detectable in 27 (87 %) by the S100 immunostaining. In contrast, the NF staining used was found less sensitive for detection of neural hyperplasia in PN. This difference is possibly due to the different target protein in the staining (7). Also the formalin fixation and paraffin embedding diminish the antigenicity of neurofilament proteins, so that most delicate nerve fibers are less beyond the detection by the NF method. In all, dermal neural hyperplasia was found to be quite common in examined specimens compared to earlier reports (13,6).

A high number of biopsies were positive for mycobacteria in culture (14 %) and an even higher number positive for AFB (28 %) in tissue sections. Contamination of specimens with AFB during the process of histopathological staining could have been one explanation for the high percentage of AFB detected (14). Evidence against the possibility of contamination is the good correlation between the positive microbiological culture result and the staining performed at the histopathological laboratory. Four of the 6 culture positive samples were also positive for AFB. The two techniques were employed on separate biopsy specimens in separate laboratories.

Among the specimens of the 47 patients other than PN in this project, 10 (21 %) had AFB detectable by staining (15). Out of these, 5 had bacteriologically verified tuberculosis (16), and 3 were positive for atypical mycobacteria. Thus unverified AFB, i.e. culture negative result, was only detected in 7 (15 %) of the non-PN patients.

PN is a chronic skin disorder of unknown aetiology, which is seldom cured spontaneously. The high prevalence of patients with specimens positive for AFB in histopathological staining (28%) indicates that atypical mycobacteria could be aetiological or contributing agents in PN. Recent observations have proven how some species of pathogenic mycobacteria may be very difficult or impossible to cultivate by present techniques. *M. leprae* is the best known of the uncultivable skin pathogenic species. Some recently found species are other examples of mycobacteria very difficult to detect (17, 18).

Many atypical mycobacteria seem to have skin as a predilection site. They cause a variety of manifestations varying from localized abscesses, appearing posttraumatically or postoperatively, to progressive superficial skin infections (19–22). Immunocompromized patients, e.g. those with HIV, renal dysfunction or malignancies, are prone to dissemination with poor outcome if untreated (23, 24). The lack of granuloma formation in all cases with detectable AFB in the present study may be due to an unspecified skin-associated defect in the cell-mediated immune response. A failure to express granuloma formation when exposed to agents like atypical mycobacteria may be a basic skin-associated defect of PN, as it is a systematic defect in infections such as HIV (24).

Our results indicate that more specific histopathological and bacteriological techniques help us to verify diagnostic criteria and that they may lead to the aetiology behind PN. We suggest that both demonstration of neural hyperplasia and cultivation of mycobacteria should be included in the diagnostic procedures of PN.

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