The spectrum of dermatological symptoms of pachydermoperiostosis (primary hypertrophic osteoarthropathy): a genetic, cytogenetic and ultrastructural study


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ABSTRACT. Pachydermoperiostosis (PDP) is characterized by finger clubbing, periostosis and peculiar skin involvement (pachydermia, seborrhea and folliculitis). The aim of our work was to determine the occurrence of dermatological symptoms in patients with PDP and their relatives, and to study ultrastructural skin changes in the complete and incomplete forms of the disease. A genetic and cytogenetic study was performed in order to identify the mechanism of transmission, to discover possible links to other genetic and non-genetic diseases and to determine the chromosomal complement and eventual chromosomal anomalies.

Pachydermia was the most frequent skin alteration together with seborrhea; folliculitis was present in five patients. In the relatives mild pachydermia was detected in 2 out of 26, while seborrhea was present in 6 subjects. Light microscopic observation showed acanthotic epidermis and endothelial hyperplasia in the dermis with partial occlusion of the lumen, lymphohistiocytic infiltrate, and thickening and packing of collagen fibers. Electron microscopy showed fibroblast activation with increased fibrillogenic activity as shown by hypertrophic Golgi complexes and rough endoplasmatic reticulum with cisternae filled with microfilaments. Endothelial cells partially or completely occluded the capillary lumen and presented an increased amount of Weibel Palade bodies.

These data show that skin involvement in PDP is a prominent feature, that sometimes these symptoms may also be present in their relatives, and that endothelial and fibroblast activation is present in the skin. Unfortunately the cytogenetic study did not provide any information about possible karyotype abnormalities.

Key words: pachydermoperiostosis, endothelial cells, fibroblasts, ultrastructure.

Introduction

Hypertrophic osteoarthropathy is a well defined entity characterized by finger clubbing, periostosis and arthritis (1). It is distinguished by two forms: the primary (2, 3) and the secondary to several diseases (4). The primary form, also called pachydermoperiostosis (PDP), presents the symptomatological triad (finger clubbing, periostosis and arthritis) but exhibits skin involvement as a prominent and striking feature. It may be characterised by different degrees of pachydermia, seborrhea, folliculitis, and cutis verticis gyrata. Touraine, Solente and Golé in 1935 first described three clinical forms of PDP: the complete (periostosis, pachydermia), the incomplete (periostosis without pachydermia) and the frustra (pachydermia with minimal signs of periostal changes) (5), and reported that PDP never develops before puberty. Recently we proposed a new
classification based upon the differentiation of the three forms through the differing occurrence of signs and symptoms (2).

The disorder seems to be inherited as an autosomal recessive trait (6, 7, 8) and shows a predilection for males. It may affect several members of the same family (3) and it has been presumed to be heterogenous with a Mendelian mechanism of transmission which is either autosomal dominant or recessive (8). The aim of our study was to determine the real occurrence of the dermatological symptoms in patients with PDP and their relatives, and to study the ultrastructural skin changes taking place in patients with PDP (both the complete and incomplete forms). A genetic and cytogenetic study was also performed in the attempt to: i) identify the mechanism of transmission; ii) discover possible links with other forms of genetic and non-genetic diseases; and iii) determine the chromosomal complement and the presence of numerical and/or morphological chromosomal anomalies in the patients.

Materials and methods

In the study 13 Caucasian families belonging to different ethnic groups were involved; 12 families were residing in Yugoslavia and 1 in Italy. The 13 index subjects were all males aged between 30 and 54 years. The total number of patients with PDP in the 13 families studied was 26 (22 males and 4 females). All patients stated that the disease had developed after 18 years of age.

The criteria for including the patients in the study were the presence of digital clubbing and periostosis (2).

After consent was obtained, in three patients affected with the complete form and in a single patient affected with the incomplete form, a biopsy of the periungual tissue was taken, processed and studied by light and electron microscopy.

Cytogenetic investigation of the blood lymphocytes was carried out on the 13 index patients. Lymphocytes were cultured from peripheral blood using Moorhead’s basic technique (7). Three cultures were prepared for each patient. The following banding techniques were applied: RHG for the R banding, ASG for the G bands, and QFO for the Q bands. High resolution banding was performed in 3 cases only.

Results

Clinical symptoms

All patients showed the presence of periostosis and finger clubbing. The most frequent skin alteration was pachydermia (100%). All the patients complained of modifications in their aesthetic appearance by deep facial furrowing (Fig. 1), skin thickening and oiliness. In 8 cases the skin hypertrophy was so marked as to induce ptosis of the eyelids. Seborrhea and folliculitis were present in all and in five patients, respectively. Moreover, the skin showed sebaceous hyperplasia with wide open sebaceous pores filled with plugs of sebum. Cutis verticis gyrata was never observed. The skin of the hands and feet appeared thickened, in particular on the dorsum, while the palms and soles showed continuous sweating. This latter symptom seems to be correlated to the involvement of the autonomic nervous system concomitantly with the flushing and the blanching which were present in 11 out of 13 subjects. In all the patients oedema was evident on the lower part of the legs with the consequent column-like aspect.

Mild pachydermia was present in 2 of the 26 relatives investigated while seborrhea was more frequent (6 subjects). No cutis verticis gyrata, folliculitis, or sweating was observed. Seven subjects (2 female, 5 male) had finger clubbing but no periostosis was found. All the patients and their relatives showed normal laboratory readings for the following tests: ESR, WBC, RBC, protein electrophoresis, and CRP.

Ultrastructural data

Light microscopy examination of the specimens showed similar data in the four cases. The epidermis was acanthotic with a normal granular layer and in the dermis diffuse endothelial hyperplasia (more evident in the capillaries) was present with partial occlusion at the vascular lumen, variable degrees of pericapillary lymphohistiocytic infiltrate, and thickening and packing of collagen fibers (more evident in the complete form).

Electron microscopy revealed in all four cases fibroblast activation with increased fibrillogenic activity as
shown by hypertrophic Golgi complexes and rough endoplasmatic reticulum with cisternees filled with microfibrils. The latter were also present in abundance in the extracellular matrix.

Endothelial cells partially or completely occluded the lumen and showed hypertrophic Golgi complexes, abundant microfilaments, numerous Weibel-Palade bodies (Fig. 1) and vesicles of microphagocytosis. The complete form showed a thickened microvascular basement membrane which appeared to be multi-layered (Fig. 1) and filled with cytoplasmatic fragments, presumably of fibroblastic origin (Fig. 2), in different stages of degeneration (mitochondria and other cytoplasmatic organelles and ill-defined cisternees with a mixed granular and microfibrillar content). These data were not observed in the incomplete form which showed only a mild apposition of connective fibers to the basement membrane of the microvessels (Fig. 3).

Discussion

Our data show that cutaneous involvement is a prominent feature of PDP patients and that sometimes these symptoms may also be present in their relatives. The cytogenetic investigation did not show any correlation between the genetic pattern and the observed clinical signs and symptoms.

In 1965 Rimoin (10) pointed out the importance of genetic transmission and a year later Tzaneva-Maneva (10) described a 47 XXY karyotype in a male patient. This finding was not confirmed later by Susmano's cytogenetic study (12). To our knowledge no cytogenetic investigation has been performed on patients affected with PDP.

Other authors reported that PDP has a high family recurrence (11, 12, 13). The literature suggests two different mechanisms of transmission: autosomal recessive or autosomal dominant (6, 10, 13). Our data seem to confirm a Mendelian inheritance and strengthen the hypothesis of an autosomal dominant mechanism of transmission, at least in 7 of the 13 families in the study. In these families the symptoms of the disease were observed in subsequent generations, with both males and females affected. No evidence of the disease skipping a generation was found.

It should be stressed that two out of the four women investigated in these families had a less serious clinical phenotype (only mild finger clubbing), while the disease appeared more pronounced in males, who usually showed severe finger clubbing (5), seborrhea (6 cases), periostosis and pachydermia (2 cases).

In the other six families our genetic and cytogenetic study did not provide any information regarding the pattern of genetic transmission.

The absence of cases of consanguinity does not support the hypothesis of a possible autosomal recessive mechanism of transmission, as was first suggested by Brugsch (13). Moreover, we were unable to find any elements which might confirm the existence of a sex-linked transmission.

Our study offers interesting data because the patients, although living in the same geographical area, come from different ethnic groups (Turks, Albanians, Italians, Bulgarians, Hungarians and Rumanians).

The histological observation using light microscopy showed no noticeable differences between the periungual tissue of the subjects with the complete and incomplete forms. The ultrastructural study showed marked differences in the constitution of the basement membrane of micro-

Fig. 2. Pachydermoperiostosis in its complete form. Several fragments of cytoplasm derived from fibroblasts are visible among the connective fibres (P/G1 - OsO4; Ur + Pb, x 2300).

Fig. 3. Pachydermoperiostosis in its incomplete form. Thickening of the basal membrane of the vessels is evident. It seems in part due to the apposition of the connective fibres (P/G1 - OsO4; Ur + Pb, x 3900).
vessels which might permit one to distinguish the two forms. In fact the basement membrane, which appears multilayered in the complete form, is generally provided with a single basal lamina in the incomplete form with milder cutaneous involvement. From this observation we can speculate that the incomplete form might represent the disease in an early phase that has not yet reached a complete development.

The fibroblasts seem to be involved in the process and to be in an active state of fibrillogenesis, thus producing an increased amount of collagen fibers. This demonstrates that fibroblasts participate actively in the connective tissue modifications (14), but it still remains to be defined exactly which stimuli induce their metabolic changes.

It should be stressed that both light and electron microscopy confirmed endothelial hyperplasia and activation, as previously described by us in a single case of PDP (15). This evidence clearly indicates that the endothelium may be involved in the pathogenesis of PDP.

Further studies are warranted to clarify the pathogenetic phases of the disease and the relationship between endotheliocytes and fibroblasts.

References