Porokeratosis with Large Skin Lesions

Histologic, Cytologic and Cytogenetic Study of Three Cases

FUJIO OTSUKA,1 RYOJI WATANABE,1 MAKOTO KAWASHIMA,1 YASUSHI TOMITA,2 KUNIAKI OHARA1 and YASUMASA ISHIBASHI2

Departments of Dermatology, 1Tokyo University Branch Hospital, 2Tokyo University Hospital, 3Tokyo Women’s Medical College, 4Toranomon Hospital, Tokyo, 5Tohoku University Hospital, Sendai, Japan

Three porokeratosis patients with large skin lesion(s) are reported. The histopathology of the large lesions revealed that the epidermis 1) frequently presented slight or marked acanthosis and/or elongation of the rete ridge, and 2) contained abnormal cells, e.g. hyperchromatic, large, multinucleated, and/or irregular shaped nuclei. The DAPI-DNA microfluorometric study revealed DNA ploidy and/or an increased population of epidermal cells with hyperdiploid and/or tetraploid DNA content. These results indicate the proliferating potential of the epidermis and the existence of a neoplastic clone or clones therein. This finding may explain the enlargement of skin lesions and possibly the development of malignancy, as sometimes occurs in large skin lesions. Furthermore, cultured skin fibroblasts from a patient’s skin lesion or its surrounding skin revealed various kinds of chromosomal structural abnormalities, which may serve as a basis for the development of abnormal neoplastic clones in the porokeratotic epidermis. Key words: DNA ploidy; Chromosomal abnormality; Large porokeratosis skin lesion.

(Accepted July 10, 1990.)

F. Otsuka, Department of Dermatology, Tokyo University Branch Hospital, 3-28-6, Mejirodai, Bunkyo-ku, Tokyo 112, Japan.

Porokeratosis (PK) is a rare cancer-prone genodermatosis with one, several, or even hundreds of skin lesions varying from a few millimetres to several centimetres in diameter. A large PK skin lesion (or lesions) sometimes develops. When such a lesion is quite large it can be called a giant PK (1). Although large PK lesions have been characterized clinically, their biological characteristics have not yet been detailed.

We recently examined 3 PK patients with a large skin lesion or lesions. We performed histopathologic, DAPI-DNA microfluorometric analyses of the epidermis of the patients’ skin lesions and a chromosome analysis of cultured dermal fibroblasts from one patient. The clinical and histologic features of the 3 cases and the cytologic and cytogenetic results are described.

CASE REPORTS

Case 1
A 58-year-old man noticed four small skin lesions on his knees and legs, 6 years ago. They enlarged to the size of around 7 cm in diameter, in which keratotic papules were scattered. He recently developed small PK lesions on his right arm (Fig. 1).

Case 2
A 66-year-old woman noticed a small skin lesion on her left elbow 20 years ago. It gradually enlarged to measure 13 × 9.5 cm². The lesion was a well demarcated, scaly, slightly atrophic erythema, in which slightly elevated keratotic areas are scattered.

Fig. 1. A large PK skin lesion on the shin (case 1).

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Case 3
A 62-year-old man noticed a small exanthema of the size of a grain of rice on his right buttock when he was around 20 years old. It gradually increased to 3.3 x 4.1 cm² during the ensuing 40 years. The skin lesion featured slightly elevated, keratotic, erythematosus and pigmented plaque with a small satellite lesion.

Histopathology
Ten specimens (two from case 1, five from case 2, and three from case 3) were taken from a large skin lesion on each of the patients. The five were from the periphery which included marginal keratotic wall, and the other five were from the non-peripheral intrallesional part. All the skin lesions featured cornoid lamelles at their border. In cases 1 and 2, the lesional epidermis was slightly atrophic in some specimens and slightly or markedly acanthotic with or without elongation of the epidermal rete ridge in others (Fig. 2). In case 3, the three specimens showed marked acanthosis with rete ridge elongation. The feature was fundamentally compatible with the clinical appearance of the skin specimen taken. Apparent dysplasia was not seen in any specimens but existed a small or large number of cells with hyperchromatic, large, or irregular shaped nuclei (Fig. 2). Atrophic lesional epidermis sometimes had such abnormally nucleated cells, while acanthotic epidermis often contained a number of such cells.

Microfluorimetric analysis of cellular ploidies in terms of DNA content
Ten porokeratosis skin lesion specimens and 11 normal appearing skin specimens from 4 healthy individuals and 4 patients with localized benign skin tumours were used for the study. The procedural details have been described elsewhere (2, 3). Briefly, however, paraffin-embedded 50-µm specimens were deparaffinized. The epidermis was trimmed and loosened, then sonified to produce a cell suspension. The cells were stained by 4,6-diamidino-2-phenylindole (DAPI). The fluorescence intensity produced by coupling DAPI to the adenine-thymine bond of DNA was measured by microfluorimetry. Stromal lymphocytes

Fig. 2. Histologic features of a large PK lesion (case 2) show acanthosis of the epidermis containing hyperchromatic nucleated cells.

Fig. 3. Distribution histogram of DNA content per cell. Abscissa: DNA content; ordinate: percentage of total nuclei measured. A: Small number of polyplid cells and an increased cell population in the hyperdiploid and tetraploid DNA content area (specimen from case 3). B: Diploid pattern with increased proportion of cells containing DNA content around hyperdiploid or tetraploid (specimen from case 3). C: A representative diploid pattern in 11 normal skin specimens from control donors.
Table I. Summary of chromosomal abnormalities of cultured cells derived from the patient in case 3.

<table>
<thead>
<tr>
<th>Specimen site</th>
<th>Abnormal karyotype</th>
</tr>
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<tbody>
<tr>
<td>Central part of lesion</td>
<td>46, XY, t(1p--; Cq+)</td>
</tr>
<tr>
<td></td>
<td>46, XY, t(Dq--; Dq+)</td>
</tr>
<tr>
<td></td>
<td>46, XY, Cq-</td>
</tr>
<tr>
<td></td>
<td>47, XY, +C</td>
</tr>
<tr>
<td>Periphery of lesion</td>
<td>46, XY, t(Fq--; Gp+)</td>
</tr>
<tr>
<td></td>
<td>46, XY, -E+F</td>
</tr>
<tr>
<td>Normal appearing skin</td>
<td>46, XY, t(C)</td>
</tr>
<tr>
<td>adjacent to lesion</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

PK sometimes features a solitary large skin lesion, or a few large lesions with or without small ones. Large PK lesions usually take many years to develop, from 6 to 40 years in our 3 cases and more than 20 years in cases in our Japanese literature survey (4). Although our 3 cases have not yet developed malignant skin tumours, large PK lesions have been reported to be a frequent precursor of malignant changes (4, 5).

The histopathology revealed that some part of the patients' large PK lesional epidermis was slightly or markedly acanthotic, with or without the elongation of the rete ridge, which is different from the usual atrophic feature of small typical PK skin lesions. Cells having hyperchromatic, large, or irregular shaped nuclei lay in the epidermis, which can be regarded as slightly dysplastic cells, or which give the impression of abnormal clonal cells. Cellular DNA ploidy abnormalities, such as polyploid cells and an increased proportion of cells having hyperdiploid and/or tetraploid DNA content, also suggest that an abnormal clone or clones, which has been presumed to exist (6) and has recently been demonstrated in our previous study (2), is present in the epidermis of the large skin lesions in the present study. Since these DNA ploidy abnormalities suggest the existence of abnormal neoplastic cells responsible for mitotic irregularities, and/or an increase in proliferating cells in the S or G2/M phase range of the cell cycle, greater abnormalities of DNA ploidy, which were reflected in the increased DNA index values of anacanthotic epidermis suggest a greater number of abnormal cells and/or proliferative activity. Although the greater DNA index values were not at the margin but in the large skin lesion, such proliferating potential may contribute to the enlargement of skin lesions. Furthermore, it is possibly a reflection of an early malignant condition, since great DNA ploidy abnormalities are usually a characteristic of malignant tumours rather than a benign condition. This view may support the literature evidence that malignancy often develops in the non-peripheral area of large PK lesions (5).

PK is known to be inherited in an autosomal dominant fashion, although sporadic cases are often encountered, the latter of which have been presumed to result from somatic mutation (7). Neoplastic and potentially malignant clones may derive from the genetically determined predisposition. Chromosomal instability has been reported in cultured dermal...
fibroblasts derived mainly from PK skin lesions, which suggests a relationship to malignant tumour development (8, 9). Although we examined chromosomal abnormalities in cells from various sites in the lesion and the normal-appearing skin of case 3, no clonal proliferation of such abnormal cells could be detected, nor could the specific site of such abnormalities be identified. However, various kinds of structural abnormalities were found in fibroblasts of this patient’s skin. These abnormal cells may explain the development of abnormal clones in the epidermis of the PK skin lesion, even though the mechanism or process has not been clarified.

Our present study suggests that large PK skin lesions contain proliferating clones in the epidermis, which are probably responsible for the formation of large skin lesions.

REFERENCES

Superficial Actinic Porokeratosis and Cystic Fibrosis

L. Klapholz, M. Goldenhersh, Y. Sherman and V. Leibovici

Departments of Dermatology and Pathology, Hadassah University Hospital, Jerusalem, Israel

A 24-year-old woman, presenting with cystic fibrosis, developed superficial actinic porokeratosis. Immunosuppression due to cystic fibrosis may be either the cause of or the exacerbating factor in superficial actinic porokeratosis in our patient.

(Accepted December 17, 1990.)


V. Leibovici, Post Office Box 12018, Hadassah University Hospital, Jerusalem 91120, Israel.

Porokeratosis is a distinctive skin eruption characterized by hyperkeratotic plaques with elevated borders and atrophic centres. In addition to the original plaque type described by Mibelli, several other varieties have been reported, including a superficial disseminated form, disseminated superficial actinic porokeratosis (DSAP), punctate porokeratosis of the palms and soles, and a linear type. Although each form represents a distinct clinical entity, they share similar histological changes, i.e. a characteristic column of parakeratotic cells (cornoid lamella).

Recently several authors reported the association of porokeratosis with immunosuppression. To the best of our knowledge, this is the first case report of superficial actinic porokeratosis occurring in a patient with cystic fibrosis.

CASE REPORT

A 24-year-old woman suffering from multiple hyperkeratotic lesions on both legs, was referred to the Department of Dermatology at Hadassah Medical Center. The lesions, with a diameter of 0.5-1.0 cm, had an elevated border and were asymptomatic (Fig. 1). There was no family history of porokeratosis of Mibelli. Cystic fibrosis, which was diagnosed in her infancy, was complicated by liver cirrhosis at the age of 10 years. In 1975 an urgent porto-caval shunt was performed following acute hemorrhage of varice veins in the esophagus. Since 1981 she has been treated with glibenclamide for diabetes mellitus. During the past 2 years she had twelve episodes of pulmonary infections, most of them...