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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Four Hereditary Mucosal Syndromes

Comparative Histology and Exfoliative Cytology of Darier-White’s Disease, Hereditary Benign Intraepithelial Dyskeratosis, White Sponge Neum, and Pachyonychia Congenita

Introduction

White lesions of the oral mucosa, clinically resembling leukoplakia, have been encountered in a variety of conditions. Among these diseases are 4 rare hereditary dyskeratoses: Darier-White’s disease,$^1$ $^2$ hereditary benign intraepithelial dyskeratosis,$^3$ white sponge neum of Cannon,$^4$ and pachyonychia congenita of Jadassohn and Lewandowsky.$^5$ In contrast to leukoplakia, which is characterized by premalignant dyskeratosis, these latter conditions run a chronic but benign course. Leukoplakia is usually localized to one site, while all 4 of the hereditary diseases may show involvement of other structures. A comparative study of tissue sections and exfoliative cytology of the oral lesions of these conditions was undertaken to investigate the cellular abnormalities revealed by this technique. To our knowledge only the exfoliative cytology pattern of hereditary benign intraepithelial dyskeratosis has been reported previously.$^6$

Methods and Materials

Patient material was obtained from families studied by the Genetics Section of the National Institute of Dental Research and the School of Dentistry, University of Minnesota. Exfoliative smear were made of oral lesions after the method of Wilkop$^7$ and stained by the Papanicolaou technique. Biopsy specimens were taken of oral lesions, fixed in 10% formalin, embedded in paraffin, and sectioned in the usual manner.
HEIBERDITERNAL MUCOSAL SYNDROTTIES

Sections and smears were stained with hematoxy-
lin and eosin, Papanicolaou's stain, Giemsa, and
special stains, such as PAS, Elvehjem's acridine
orange, periodic acid-Schiff, and periodic acid-salci-
hyde-orcein-Hematoxylin stains. The exfoliated smear
was compared to normal controls in each in-
stance. Comparisons were made of the staining,
and morphological characteristics of the cellular
inclusions observed in the exfoliative smears
with those of the tissue sections.

Darier-White's Disease

This condition usually begins in child-
hood and is characterized by numerous dis-
crete flesh-colored keratotic papules, which
by confluence may form numerous crusted
areas on the skin. The head, neck, trunk,
and extremities are symmetrically af-
fected. The back of the hands and feet
are spared. Lesions may be covered by minute lesions which
may be revealed by palm printing. Ulcer-
ation and secondary infection may occur, producing an offensive odor. The oral mu-
cosa and occasionally the uvula, pharynx, and
larynx may be involved, showing a rough,
ecky surface or exuive verrucose white
plaque.

According to Pels and Goodman 8 and
Brünner, 8 this disease was first described by White 8 in 1889, under the term follicul-
lar keratosis. Shortly thereafter, Darier 11 independently described the condition as
prurigo parapharingeal viaggiante and stated that it was characterized by the
beginning of the disease around the neck and face. Fabry 6 in 1894, states
that the first to mention the clinical ap-
ppearance of the oral lesions affecting the
mouth and throat. An early report by
Hillebrand 41 described lesions of the lips
and posterior buccal mucosa as small groups
of papules and white plaques. Ele-
man 12 stated that the oral mucosa may
be the first and only site affected. Brünner, 8 and recently, Gordin and Chaudhry 13 de-
scribed the histologic picture of the disease
as it appears on the oral mucosa. Histo-
logically there is acanthosis, suprabasilar
keratosis lined by small epithelial cells, and
a benign dyskeratosis characterized by corps
and grains. The disease appears to be
inherited as an irregular autosomal dom-
inant trait, although reports of isolated
cases are common. Careful examination of
the entire kindred is frequently necessary
to detect affected individuals because some
cases may be relatively mild and may show
oral lesions only.

Results

Sections from lesions of the hard palate
showed a peculiar papillomatous configur-
ation. Acanthosis was marked, but hyper-
keratosis was less than that seen in the
dermal leuka. The lacunar formation and
benign dyskeratosis were virtually identical
to that observed in the skin lesions (Fig. 1). The
benign dyskeratosis is characterized by
numerous cells—corps and grains, the
former occurring mainly in the stratum
spinsum, the latter in the stratum corneum.
Corpus and grains are larger than normal apo-
somes cells and are characterized by horve-
cous round basophilic nuclei and dark
Fig. 1—Darier-White's disease. Section of skin
showing interfollicular edema, hyperkeratosis,
and dyskeratosis. Cross section of small papules
and corpora (X 240).

Materials

Tissues from families of the National
Institute of Mental Health, and the School of
Medicine, Northwestern University, after the
method of the Papanicolaou 6 were taken of the
5

Wiley—Gordin
eosinophilic cytoplasm. The grains are small, frequently elongated parakeratinized cells, seen also in the keratose which existed directly above the basal layer.

Exfoliative cytology smears taken from the posterior one-third of the hard palate were stained by the same methods used for the tissue sections. The normal exfoliative pattern from the hard palate shows, with the Papanicolaou stain, the following ratio of cells: prekeratinized 4, cornified 9, and superficial keratinized 36. The hard palate is normally a highly keratinized surface, and some layer squamous cells are rarely seen. Of 7 sites in the normal oral mucosa studied by Witzkop's only smears from the uvula showed parakeratin cells, and these were uncommon.

The exfoliative smears from lesions of Darier-White's disease differed markedly from the normal patterns. There was a ratio of about 25 blue, 50 red, 16 orange, and 25 yellow cells. Many of the blue staining cells were small parakeratotic cells with large nuclei, some showing normal mitotic figures (Fig. 2). Parakeratin cells with active looking hyperchromic nuclei were frequent (Fig. 3). These parakeratotic-type cells show morphological and staining characteristics similar to the small cells lining the buccal mucosa described above. Among the parakeratotic-type cells were numerous examples showing a nuclear and perinuclear eosinophilic degeneration. Some of these degenerated cells resembled Russell-Fuchs bodies (Fig. 4). Small eosinophilic cells, and slightly larger orange staining cells with elongated nuclei, represent the grains seen in tissue sections (Fig. 4). The nuclear cytoplasmic ratio of these cells varied from 1:1 to 1:2. The orange staining grains resemble the parakeratotic rigid waxy "en-bloc" cells seen in hereditary benign intraepithelial dyskeratosis. Large round bodies, some containing several nuclei (Fig. 5), and resembling minute epithelial pearls, were seen. These bodies were composed of an orange staining large central cell surrounded by a more normal appearing inner or outer layer squamous cell. The nuclei of the latter was often pushed to one side and was sickle shaped (Fig. 4). These bodies resembled the corpus rods seen in tissue section.

Hereditary Benign Intraepithelial Dyskeratosis

This condition is a congenital disease affecting oral mucosa and bulbar conjunctivae. The oral lesions are asymptomatic, consisting of soft white spongy folds and plaques of thickened mucosa. Lesions have been observed on the mucosal surface of commissures of the mouth, the buccal and labial mucosa, the floor of the mouth, the...
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neural and lateral surfaces of the tongue, the gingiva, fauces, and palate. The eye lesion is a foamy gelatinous plaque on the conjunctiva. It occurs in a perilesional fashion both nasally and temporally. Marked photophobia may be a symptom, especially in children. The dermatoic process may involve the cornea and may shed spontaneously. Permanent blindness may result after vascularization of the cornea. The condition is transmitted as an autosomal dominant trait with a high degree of penetrance.

Witkop et al. described the clinical and histological appearance of the lesions and gave evidence for the genetic transmission. Von Salomon and Pataro presented a detailed description of the eye lesions. The histological findings in the sebaceous and conjunctival lesions were similar, consisting of hyperplasia of the epithelium, acanthosis, vacuolation of the prickle cells, and intracellular dyskeratosis characterized by eosinophilic cells and a "cell within cell" pattern. Witkop et al. state that the inner 2 findings were especially pronounced in buccal and conjunctival smears stained with the Papanicolaou technique and were diagnostic of the disease.

Results

Sections from the buccal mucosal lesions showed an increase in the thickness of the epithelium. The submucosa was unremarkable. The epithelium was acanthotic, the basement membrane was intact, and there was no invasion of the lamina propria by epithelial cells. No lacunae were present. The hyperplastic middle and upper prickle-cell layers contained many large vacuolated cells. Throughout these layers, and continuing to the surface, were numerous oxyphilic cells, the nuclei of which could best be seen in the Papanicolaou and Giemsa stained sections. The eosinophilic cells were elongated, wheat shaped, and somewhat smaller than surrounding normal appearing prickle cells. The eosinophilic bodies resembled minute

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Fig. 6. Hereditary benign intraepithelial dyskeratosis. Small orange staining dyskeratotic cells and round body stained by sebacate hexasulphide are distributed throughout a squamous epithelium; lacunae are absent; buccal mucosa (Hanna stain; reduced about 20% from mag. 50 X 100).

Epithelial pearls composed of a central dyskeratotic cell surrounded by one to several more normal appearing epithelial cells. These cells and bodies stained a dark orange color with the Papanicolaou stain. Special stains failed to reveal any specific substance in these acidophilic cells. They failed to give the reaction typical of keratin. Azurine-orange stains, viewed by ultraviolet light to determine DNA and RNA, failed to show any unusual distribution of these substances. There were no inclusion bodies of the type usually attributed to a virus.

Buccal mucosal smears from normal persons stained with Papanicolaou's stain contain blue and red staining cells in the proportion of 2 to 3 with an occasional yellow staining superficial keratinized cell. The blue cells are mostly inner layer squamous cells, the red are outer layer squamous cells, which roughly correspond to the prioniform and cornified cells of the vaginal mucosa.
In contrast to the usual patterns, the scrapings from the buccal lesions revealed an increase in the thickness of the epithelium. The submucosa was unremarkable.

**Results**

Sections from the buccal lesions showed an increase in the thickness of the epithelium. The submucosa was unremarkable. The epithelium was acanthotic. The basement membrane was intact, and there was no inflammatory infiltrate.

![White sponge nevus of Cannon](image_url)

**White Sponge Nevus of Cannon**

Cannon first described the clinical and histological aspects of this disease, which he found in 3 generations of a family. According to Zegarelli, a total of 23 cases have been reported in the English literature, and the inheritance patterns were compatible with that of an autosomal dominant trait. Lesions have been described affecting the oral, pharyngeal, vaginal, and anal mucosa.
included in this study, nasal mucosa covering the nose in addition to oral mucosa affected the cheeks, hard and soft palate, and the mouth. The thickness of the mucosa presented a "". These lesions are often seen in the nose. To increase in severity, the most frequent histologic changes were keratinization, thickening of hyperplasia and ulceration of the lamina propria, neovascularization, and reactive inclusions were noted. No invasion of the lamina propria by epithelial cells. No lacunae were present. Starting with the prickle cell layer and continuing to the surface there were large spongy cells showing intracellular eosin. The surface epithelium showed little cornification. The Papanicolaou and Gram stains demonstrated dyskeratotic cells having a rigid eosinophilic cytoplasm throughout three layers (Fig. 9). These cells were smaller than the vacuolated prickle cells. In contrast to a normal exfoliative pattern from the bocall mucosa, smears of the bocall lesions of white sponge nemaus, stained with Papanicolaou's stain, had a ratio of 3 blue, 92 red, and 5 yellow cells. Numerous cells showed an acidophilic or orange staining, characteristic condensed nuclei of the squamous layer of the nemaus. Special stains failed to further define the type of material contained in the acidophilic condensations. Fig. 10—Papbetocia conglutina. Uniform intraepithelial accumulation is seen throughout the section of nasal mucosa. No dyskeratotic cells are seen (Papanicolaou's stain; reduced about 40% from mag. x 66).

**Papbetocia Conglutina of Jadassohn and Lewandowsky**

Since the condition was described by Jadassohn and Lewandowsky in 1906, only a few cases have appeared in the literature. The oral lesions accompanying **papbetocia conglutina** are clinically and histopathologically similar to white sponge nemaus. The report of Grad and Chudry indicated that the condition is benign. Accompanying the oral disorder are dystrophic changes in the nails, hyperkeratosis of the palms and soles, follicular keratosis, especially of the knee and elbow, and hyperhidrosis of the hands and feet. Occasionally dystrophic changes are also observed in the hair and cornea. Plantar bursae are not uncommon. Jackson and Lander believed that a single dominant gene is the responsible factor. Isolated cases have also been reported. A similar complex known as the Cob-Ramschek-Toomey syndrome is probably inherited as a recessive trait. This condition shows dyskeratosis conglobata with pigmentation, dystrophic ungues, and leukokeratosis oris. The oral lesions have been reported as a true leukoplakia which preceded oral squamous cell carcinoma in these patients. A recent article links this condition with the hyperkeratosis of the Pennone-Herlitz syndrome.

**Results**

The epithelium from bocall mucosa and tongue was acanthotic with a uniform intraepithelial vacuolization (Fig. 11). The intercellular bridges in the prickle-cell layer were missing. Marked parakeratinosis existed in the absence of the stratum granulosum. A Schiff stain revealed no Schiff-positive material within the epithelium. Exfoliative smears from the bocall mucosa had a ratio of 19 blue, 71 red, and 10 yellow cells. The epithelial cells appeared...
to be large, wrinkled, many showing intra-
cytoplasmic vacuoles and relatively small
nuclei reminiscent of follicular phase vagi-
nal smears. An occasional cell contained a
small round osteophilic staining body that
appeared similar to the cytoplasmic con-
densations seen in white sponge nevus. The
entire smear was quite nonspecific without
any particular characteristics to distinguish
it from smears taken from some normal
individuals (Fig. 12).

Comment

These hereditary mucous syndromes have
certain historical and exfoliative cytology
features in common. Pachyonychia con-
genita, white sponge nevus, and hereditary
benign intraepithelial dyskeratosis all have
the features of hyperplasia and intracellular
edema of the prickle cell layers, and acan-
thosis. White sponge nevus, hereditary
benign intraepithelial dyskeratosis, and
Darier-White's disease all exhibit intracel-
lular dyskeratosis. The cytoplasmic con-
densations in white sponge nevus are simi-
lar to cytoplasmic condensations seen
rarely in normal slides or in slides from
individuals who have pachyonychia orals.
However, large numbers of these cells in
any slide should make one highly suspicious
of this disease. The dyskeratotic cells seen
in hereditary benign dyskeratosis and in
Darier-White's disease have certain fea-
tures in common. The grains of Darier-
White's disease very closely resemble the
so-called "tobacco cells" of hereditary be-
ign dyskeratosis, and the "cell-within-cell"
body closely resembles the corps ronds seen
in Darier's disease. In one experience the
cell-within-cell bodies of hereditary benign
dyskeratosis were much more numerous in
smears than the corps ronds from Darier-
White's disease. This feature and the lack
of the small blue parabasal cells easily
differentiated smears from hereditary be-
ign intraepithelial dyskeratosis from the
smears of Darier-White's disease.

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Summary

The co-operative histological and exfo-
liative cytology slides of 4 hereditary mucous
syndromes have been presented. Both the
histological and cytological characteristics
of these diseases indicate that they are
benign. Darier-White's disease, hereditary
benign intraepithelial dyskeratosis and
white sponge nevus of Cawson have distinc-
tive cytological features which can aid in
the diagnosis of these conditions. Smears
from pachyonychia congenita of Jakobske
and Levaradovska did not show specific
changes by this method.

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