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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.
White Sponge Nevus

Ronald J. Jorgenson, DDS, PhD, L. Stefan Levin, DDS, MSD

White sponge nevus (WSN) is one of a number of white lesions of the oral mucosa. It is an autosomal dominant disorder of wide variability and high penetrance. White sponge nevus is characterized by white, spongy lesions of the oral mucosa, although extramucosal lesions may also be affected. Onset is early in life, and both sexes are affected equally. There are no extramucosal lesions associated with WSN. The plaques of WSN are benign and may undergo alternate periods of remission and exacerbation. In two of our cases from an affected family, penicillin precipitated remission of the plaques.

(From Dermatol 117:73-76, 1981)

White sponge nevus (WSN) is an autosomal dominant disorder characterized by benign, nonpainful, white, spongy plaques of the oral mucosa; the nasal, esophageal, laryngeal, vaginal, and anal mucosa may also be affected. The expression of WSN is variable. Any part of the oral mucosa may be affected, and it is not uncommon for a single individual to have plaques on the skin and mouth. The reason for changes in severity and extent of the disease is unknown. It has been reported that penicillin use is associated with remission, but there is no association between severity and age of the patient during the menstrual cycle, that the plaques become more pronounced with pregnancy, and that treatment with vitamins or antihistamines produces no benefit. The plaques of WSN are asymptomatic and are usually present in the mouth, nose, and other mucosal surfaces. Microscopically, the plaques consist of parakeratotic and acanthotic epithelium. The cells in all layers of the epithelium may be vacuolated, or the vacuolization may be patchy in distribution. Cell nuclei are pyknotic, and the subjacent connective tissue is normal.

The pathogenesis of WSN has been suggested to be an alteration in the distribution of tonofibrils in epithelial cells. In addition, there is considerable variation in the way in which fibrous protein is stored in the cytoplasm, which suggests an error in the maturation of epithelial cells. The epithelial cells do not desquamate normally, resulting in a thickened horny layer.

The purpose of this report is to describe a family with WSN and to review cases previously reported.

METHODS

Clinical evaluations were carried out on three members of the family of a 26-year-old man who was seen for evaluation of white plaques on his buccal mucosa. Biopsies were performed on the plaques in his mouth and on those in his mother's mouth, and on microscopic inspection the plaques were diagnosed as WSN.

The available literature was searched for cases of WSN. For each reported case, notation was made of the location of the intraoral plaques, the presence of plaques on other mucosal surfaces, the apparent age of the patient at onset of the plaques, and associated findings. Pedigrees were constructed from the description of familial cases or were reproduced from the original reports for a study of the segregation of WSN in families.

REPORT OF A CASE

A 26-year-old white man was seen for evaluation of white plaques of the buccal mucosa (Fig 1). The plaques were bilateral, had been present since birth, and were limited to the buccal mucosa. There had been periods of exacerbation and remission of the lesions throughout his childhood. During exacerbation, the buccal and labial mucosa and the mucosa of the soft palate and uvula were involved. For the past several years, the size and character of the plaques had not changed unless penicillin was taken; then, they became smaller and projected less from the surrounding mucosa. Occasionally, small portions of the plaques would desquamate spontaneously. The plaques had never been painful, and the mucosa under desquamated areas was said to be pink and nonhemorrhagic. Several modes of treatment, including vitamin therapy and mouth rinses, had been recommended, but none was successful.

On examination, the plaques were raised and had a slightly
SUMMARY OF REPORTED CASES

Seventy-six cases of WSN recorded in the literature were considered sufficiently well described for analysis of their clinical features.14-16,29 These 76 patients derived from 42 families, 28 of which had more than one affected family member. Other reported cases were not included in the analysis because they were inadequately reported.15,27,30-44 The family described here raises the number of well-validated cases to 80 in 43 families.

Race was specified or was apparent from clinical photographs in 69 of the 80 cases; 57 patients were white, two were black, and one was an East Indian. Thirty-nine patients were male and 41 were female, a 1:1.06 sex ratio. However, 60 male relatives and 53 female relatives of the described patients were reported to be affected, for an overall sex ratio of 1.05:1. The ages of the patients reported ranged from 2 to 67 years.

Table 1 lists the distribution of the plaques on the oral mucosa of isolated and familial cases. The buccal mucosa was involved in all but one case. The hard palate, soft palate, and palatine pillars were affected least often in isolated and familial cases. Among familial cases, the buccal mucosa was affected most frequently, followed by the labial mucosa, tongue, alveolar mucosa, and floor of the mouth. There were too few isolated cases to be certain of the relative frequency of involvement of affected sites. In general, the plaques were more extensive in isolated cases than in familial cases.

Other mucosal surfaces were said to be affected in 11 of the 80 reported cases and to be normal in 23. The mucous membrane or epithelial surfaces affected were those of the nose, esophagus, vagina, anus, and penis. No statements about other mucosal sites or diseases were consistently reported as associated with WSN; herpetic lesions were present in affected individuals of one family19 and mental retardation in another.27

The age at onset of the plaques was reported to be during infancy in seven cases, during childhood in seven, and as "always remembered" in four. Specific ages of first report were noted for 33 cases; the ages were at birth in eight cases, ages 2 to 10 years in nine cases, ages 11 to 20 years in 12 cases, and over 20 years in four cases. The most advanced age at first report was 42 years. In 29 cases, the age at onset or first report was not mentioned.

The pedigrees of 16 families described in the literature and of the family reported here (Fig. 3) were sufficiently complete to be included in a test of the hypothesis

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Fig 1.—White sponge nevus in proband of family.

Fig 2.—Photomicrograph of white sponge nevus from buccal mucosa of proband. Aggregates of vacuolated epithelial cells are present (hematoxylin-eosin, original magnification x 160).

Fig 3.—Pedigree of proband’s family. Arrow indicates proband.

shaggy surface. They were located on the buccal mucosa at the level of the plane of occlusion. There were no associated lesions of the eyes, skin, or other mucosal surfaces.

A biopsy specimen was submitted for light microscopic study. The specimen consisted of stratified squamous epithelium and fibrous connective tissue (Fig. 2). The surface epithelium was acanthotic and covered by a thick layer of parakeratotic cells. Scattered throughout the epithelium under the parakeratin layer were individual prematurely keratinized cells. Many islands of enlarged epithelial cells without cytoplasm were found, most of which were devoid of nuclei; the nuclei present were smaller than normal. The subjacent fibrous connective tissue was normal, and there were no signs of inflammation.

The patient reported that his mother, half-brother, and a maternal aunt were similarly affected (Fig 3). The mother’s lesions were noted on examination to be limited to the buccal mucosa and the floor of the mouth. However, they reportedly involved the labial mucosa during exacerbation. Flares were not related to a known environmental agent and did not occur at specific times of the month or year. Biopsy specimens from her buccal mucosa demonstrated changes similar to those of her son, although the epithelium was thinner and lacked the shaggy parakeratin surface. The aunt’s lesions involved the buccal mucosa and floor of the mouth at the time of examination; however, she did not feel that she was affected, and no further history or biopsy specimen could be obtained. The half-brother was not examined, but his lesions were reported to involve only the buccal mucosa.
Table 1.—Distribution of White Sponge Nevus on Oral Mucosa

<table>
<thead>
<tr>
<th></th>
<th>Labial Mucosa</th>
<th>Buccal Mucosa</th>
<th>Alveolar Mucosa</th>
<th>Floor of Mouth</th>
<th>Tongue</th>
<th>Hard Palate</th>
<th>Soft Palate</th>
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Table 2.—Test of Autosomal Dominant Mode of Inheritance of White Sponge Nevus

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<th>No. of Persons</th>
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<th>Affected</th>
<th>Observed (O)</th>
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COMMENT

Differential Diagnosis

White lesions of the oral cavity may occur alone or may be associated with other mucosal and nonmucosal defects. The oral lesions of leukoplakia, chemical burns, trauma, tobacco use, and syphilis may occur alone and are not known to be genetic in etiology. They are sufficiently different from the plaques of WSN in clinical and microscopic appearance to be easily differentiated, especially when a family history is absent and there is a positive history of environmental cause. In addition, these lesions lack the characteristic hyperparakeratosis, aggregates of vacuolated epithelial cells with pyknotic nuclei, and prematurely keratinized epithelial cells of WSN. The underlying fibrous connective tissue in WSN is normally not infiltrated by inflammatory cells unless the lesions are secondarily traumatized. White sponge nevus may be confused with candidiasis; however, biopsy specimens, culture of the organisms, and response to antifungal agents differentiate the two.

The lesions of pachyonichia congenita, hereditary benign intraepithelial dyskeratosis (HBID), Darier’s disease, dyskeratosis congenita, lichen planus, and lupus erythematosus (LE) may be similar to those of WSN. Except for lichen planus and, rarely, LE, which may be limited to the oral cavity, associated extranodal lesions distinguish these disorders from WSN. Patients with pachyonichia congenita have palmoplantar hyperkeratoses, hyperhidrosis, and abnormalities of the nails; individuals with HBID have foamy gelatinous plaques on the bulbar conjunctiva, and they lack white plaques on other mucosal surfaces. Vacuolated epithelial cells similar to those in WSN are not found on light microscopic examination of the mucosal lesions of Darier’s disease or dyskeratosis congenita. On light microscopy of the mucosal lesions of lichen planus, saw-tooth rete pegs, necrosis of the basal cell layer with replacement by an eosinophilic coagulum, and a lymphocytic infiltrate limited to the most superficial portion of the connective tissue are noted. The oral lesions of LE are characterized by hyperkeratosis, acanthosis, occasional pseudopitheliodomas hyperplasia and atrophy, necrosis of the basal cell layer, and an inflammatory cell infiltrate in the superficial and deep connective tissue. Neither lichen planus nor LE displays the typical hyperparakeratosis and epithelial cell vacuolization of WSN.

Clinical Features

According to our review of well-described cases, the buccal mucosa is the most common site for WSN, followed by the labial mucosa, the alveolar ridges, and the floor of the mouth. The mucosae of males and females are affected with equal frequency and to equal degrees, but nonfamilial cases are reported as more severely affected than familial cases. This difference in severity may be a result of ascertainment bias; the diagnosis may be made in mildly affected individuals when a relative is known to be affected. Also, in a nonfamilial case the patient may be labeled as having traumatic keratosis of the mucosa or clinical leukoplakia, unless the lesions are so widespread as to make these diagnoses unlikely.

White sponge nevus may be congenital or noted during the first few decades of life. In cases of apparent late onset, the time of origin cannot be precisely ascertained,

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*References 2, 12, 17, 19, 23, 24, 27, 29, 31, 33, 34, 37.

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since the plaques may have existed for years without being noticed.

**Genetics**

The segregation of WSN in families is compatible with that of an autosomal dominant trait. Thus, the risk that children of an affected individual will be affected is 50%.

The expression of WSN is variable, that is, the extent of involvement of the oral mucosa and other surfaces varies from case to case. Penetration for WSN is 71%; in well-described families, there have been 44 sibs in which one or the other parent was an obligate heterozygote and for which the status of the parents has been described. One parent was affected in 37 of these sibships. In four well-described families, recessive inheritance was possible, but the segregation ratio was not compatible with recessive inheritance. One reported family was not included in the segregation analysis, since an only child was affected and new mutation could not be discounted.

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**References**