An ultrastructural study of familial type and non-familial type of white sponge nevus

Toshio Demitsu¹, Yoshinori Jinbu², Mayumi Komine⁴, Naoka Umemoto¹, Maki Kakurai¹, Kozo Yoneda³, Aki Yamamoto², Hidetoshi Tsuda⁴, Mamitaro Ohtsuki⁴, Yoshiyuki Mori²

1. Dermatology, Jichi Medical University Saitama Medical Center, Saitama City, Saitama, Japan. 2. Dentistry, Oral and Maxillofacial Surgery, Jichi Medical University , Shimotsuke, Japan. 3. Clinical Pharmacology, School of Pharmacy, Osaka Ohtani University, Tondabayashi, Japan. 4. Dermatology, Jichi Medical University , Shimotsuke, Japan.

Abstract

- White sponge nevus (WSN) is a rare autosomal dominant disorder characterized by a widespread white, soft, thick plaques with a spongy texture, and it predominantly affects on the oral mucosa. The diagnosis of WSN is performed by clinical findings and histologic features. Recent reports have identified point mutations in the keratin 4 and keratin 13 genes in familial cases. Non-familial or sporadic cases have been also known. In the previous study, tonofilament aggregation has been reported to be a characteristic ultrastructural finding in WSN. Most of the reports are a single case study.
- To clarify the pathogenetic mechanisms of familial and non-familial WSN, we analyzed 10 patients with WSN (including two familial and eight non-familial cases) by electron microscopic study.
- Ultrastructurally, one familial case showed aggregation of the tonofilaments at the perinuclear areas and the other familial case of WSN demonstrated numerous tonofilament-related keratohyaline granules in the vacuolated keratinocytes. In non-familial cases, one showed also increased electron density due to aggregation of the tonofilaments in the cytoplasm but other seven cases demonstrated no tonofilament aggregation. The previous studies suggested that a dense aggregation of tonofilaments was a cardinal feature in WSN. However, only two cases showed dense aggregation of tonofilaments and other patients with familial and non-familial WSN demonstrated the sparse distribution of tonofilaments with few tonofilament bundles in the vacuolated cells. We suggest that impaired tonofilament bundle formation with sparse tonofilament distribution is a common significant finding in both types of WSN. Accordingly, dense tonofilaments aggregation described in the previous literature is not necessarily for the diagnosis of WSN. WSN might be caused by heterogeneous pathogenetic factors. The comparative study of ultrastructure and keratin mutation is needed to clarify the pathogenetic mechanisms of WSN

Introduction

- White sponge nevus (WSN) is characterized by widespread white, soft, thick plaques on the oral mucosa, and is considered to be a rare autosomal dominant disorder [1,Cannon]. WSN predominantly affects on the oral mucosa. Extraoral sites such as esophagus, anal, and vaginal mucosa are also involved. Histopathologically acanthosis and pale, clear epithelial cells are characteristic. Recent reports have identified point mutations in the keratin 4 (K4) and keratin 13 (K13) genes which were specifically expressed in the spinous cell layer of the oral mucosa in familial cases [2,3Rugg/Richard].
- To date several hundred cases have been reported. Most of the studies are a single report or keratin mutation reports. The cases without family history have been also known (4 Cai W). It has been also suggested that smoking, viral infection or mechanical irritation might be involved in the pathogenesis. It has been reported that topical or systemic antibiotics therapy improved the oral symptoms of WSN (5,6,7 Alinovi/Lim/Jinbu). The exact pathogenesis of both familial and non-familial WSN is unknown. To clarify the pathogenesis of WSN, we have analyzed two cases of familial type and eight cases of non-familial type of WSN using transmission electron microscopy.

Patients and Methods

Patients

- Biopsy specimens from 10 Japanese patients with WSN including two familial and eight non-familial cases who had been diagnosed by clinical and histologic features such as characteristic white spongy plaques and vacuolated epithelial cells of the oral mucosa. The patients' profile was listed in Table 1.

Methods EM study

- Biopsy samples taken from the oral lesion were fixed using 2.5% glutaraldehyde in 0.1 mol/L cacodylate buffer (pH 7.4) at 4°C for 2 h, washed four times with 0.1 mol/L cacodylate buffer (pH 7.4), fixed in 1% OsO₄ in 0.1 mol/L cacodylate buffer (pH 7.4) at 4°C for 90 min, dehydrated in ethanol series and embedded in epoxy resin (Quetol 812; Nissin EM, Tokyo, Japan).
- Sections were prepared and stained using 2% uranyl acetate and Reynolds solution for 5 min, then examined using an H-7600 electron microscope (Hitachi, Tokyo, Japan).

Table 1 The patients' profile in the study

No	age	sex	type	sites	systemic treatment	course
1	35	female	familial	buccal mucosa	CFDN	no effect
2	38	female	familial	buccal mucosa, lower lip	AZM	slightly improved
3	20	male	non-familial	buccal mucosa	AZM/CAM	slightly improved
4	36	female	non-familial	buccal mucosa	CFDN/CEZ	cleared up
5	24	female	non-familial	buccal mucosa, lower lip	AZM	slightly improved
6	30	male	non-familial	buccal mucosa, lower lip	AZM	cleared up
7	26	male	non-familial	buccal mucosa	AZM	markedly improved
8	35	female	non-familial	buccal mucosa, tongue	AZM	improved
9	19	female	non-familial	lower lip, tongue	AZM	markedly improved
10	50	female	non-familial	upper/lower lip, tongue	AZM	cleared up

AZM: Azithromycin CAM: Clarithromycin
CFDN: Cefdinir CEZ: Cefazolin

Figure 1 Clinical view of familial cases

Figure 2 Histopathology of the two family cases

Figure 3a Clinical view of non-familial cases

White plaques with a spongy texture of several months' to several years' duration. No family history of the same lesion.

Figure 4 Histopathology of 8 non-familial cases

Figure 5a Familial WSN-1 (Case 1)

Figure 5b Familial WSN-1 (Case 1)

Figure 6 Familial WSN-2 (Case 2)

Figure 7 Non-familial WSN (Case 8) aggregation of tonofilaments(*) and keratohyaline granules (arrow)

Figure 8 Non-familial WSN (Case 8) No tonofilament bundles even in dense aggregation of tonofilaments.

Figure 9 Non-familial WSN (Case 7)

Figure 10 Non-familial Case 10

Results

- (1) One familial case of WSN clearly demonstrated the perinuclear high density areas of tonofilament aggregation in the vacuolated cells (Figure 5). This finding is known as a characteristic feature in the previous literature (8,9,10 Whitten/McGininis/Morris). The other familial case of WSN revealed no remarkable aggregation of tonofilaments but various number of tonofilament-related keratohyaline granules in the vacuolated cells (Figure 6).
- (2) One of 9 patients with non-familial WSN demonstrated the aggregation of tonofilaments in the epithelial cells similar to one of familial WSN (Figure 7, 8).
- (3) Both familial and non-familial WSN demonstrated few tonofilaments bundle formation with sparse density of tonofilaments. Numerous abundant intracytoplasmic granules were observed. These were the common important findings in familial and non-familial cases of WSN (Figure 9,10).
- (4) The desmosomes were morphologically altered and the radiating pattern consisting of tonofilaments was unclear in some degenerated keratinocytes (Figure 9,10). However, the desmosomes of the intercellular spaces of the epithelial cells were morphologically preserved mid-and lower epithelium

Summary

- The previous studies suggested that a dense aggregation of tonofilaments was a cardinal feature in WSN. However, only two cases showed dense aggregation of tonofilaments and other patients with familial and non-familial WSN demonstrated the sparse distribution of tonofilaments with few tonofilament bundles in the vacuolated cells. Thus, there is no difference of ultrastructural findings between the two types of WSN.
- We suggest that impaired tonofilament bundle formation with sparse tonofilament distribution is a common significant finding in both types of WSN. Accordingly, dense tonofilaments aggregation described in the previous literature is not necessarily for the diagnosis of WSN. WSN might be caused by heterogeneous pathogenetic factors. The comparative study of ultrastructure and keratin mutation is needed to clarify the pathogenetic mechanisms of WSN.

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