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Literature Review

White sponge nevus as a hereditary disease: A brief narrative review

Fatma Yasmin Mahdani[1,2], Karlina Puspasari[1], Ida Bagus Pramana Putra Manuaba[1], Salsabila Fitriana Putri[3], Naqiya Ayunnisa[3], Diah Savitri Ernawati[2], Hening Tuti Hendarti[2]
[1]Oral Medicine Specialist Study Program, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Bachelor Dental Science Program, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

ABSTRACT

Background: White sponge nevus (WSN) is an autosomal dominant hereditary genetic disorder characterized by thickened keratin in the oral mucosa that appears folded, wavy, spongy, thick, and rough. WSN do not have the potential to become malignant, but an accurate diagnosis is still needed to prevent unnecessary treatment and reduce potential remissions and exacerbations due to infection. **Purpose:** to provide a detailed description of white sponge nevus as a hereditary disease by means of narrative review. **Review:** A literature search using ScienceDirect and PubMed yielded results between 2012 and 2024. The keywords of the search strategy were "hereditary disease" and "white sponge nevus" or "Cannon's disease" or "white folded gingivostomatitis" or "leukokeratosis.". White sponge nevus (WSN) was first discovered by Hyde in 1909 and usually occurs in children and people under 20 years old. The main etiology of WSN is an autosomal dominant hereditary genetic disorder; KRT4 and KRT13 are specific keratin encoders that cause WSN, and there are predisposing factors such as bacterial infection, smoking, and alcohol consumption. **Conclusion:** In determining the diagnosis of WSN, it is necessary to carry out blood tests, subjective examinations, objective examinations, and supporting examinations in the form of exfoliative cytology and biopsies. As well as the need for comprehensive treatment, even though the prognosis of this disorder is good.

Keywords: white sponge nevus; hereditary disease; oral mucosa; quality adjusted life year; medicine.

Correspondence: Fatma Yasmin Mahdani. Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjend Prof. Dr. Moestopo 47 Surabaya, 60132 Indonesia. Email: fatmayasminmahdani@fkg.unair.ac.id

INTRODUCTION

One of the genetic diseases that can be found in the oral mucosa is white sponge nevus (WSN). WSN is an autosomal dominant hereditary genetic condition characterized by the presence of thickened keratin on the mucosa, which appears folded, wavy, spongy, thick, and rough. WSN can be found in the oral cavity, including the labial mucosa, buccal mucosa, floor of the mouth, soft palate, and tongue. However, it can also be found in extra-oral regions, namely the nasal, laryngeal, esophageal, and anogenital mucosa.[1–3]

WSN does not have the potential to become malignant, but an accurate diagnosis of this disorder is necessary to prevent unnecessary treatment and reduce potential remissions and exacerbations due to infection.[4,5] There are several differential diagnoses from WSN, including leukoedema, leukoplakia, and plaque-type lichen planus, as well as chronic hyperplastic candidiasis. The similarities that can be found between these lesions and WSN are these lesions are classified as white plaque lesions on the oral mucosa, which also generally affect non-keratinized mucosa and are bilaterally symmetrical, except for leukoplakia and chronic hyperplastic candidiasis.[1,6,7] Furthermore, the objective of this review is to describe the current explanation of white sponge nevus as a hereditary disease.

REVIEW

White sponge nevus (WSN) was first discovered by Hyde in 1909. Then in 1935, Cannon succeeded in describing and naming the lesion as a white sponge nevus or naevus spongiosus albus mucosae so that it is also known as the diagnosis of Cannon's disease.[8] WSN prevalence is estimated at 1:200,000 individuals worldwide. It usually occurs in children and people under 20 years old, as a population study of 181.338 men aged 18-20 years old found 2 cases of WSN.[2] It is known that males and females have equal opportunities of suffering from this disorder.[5]

The clinical manifestations are gray and white corrugated folds or furrows, in the shape of grass or wrinkled paper, in a special pearlescent color or bright pink. The

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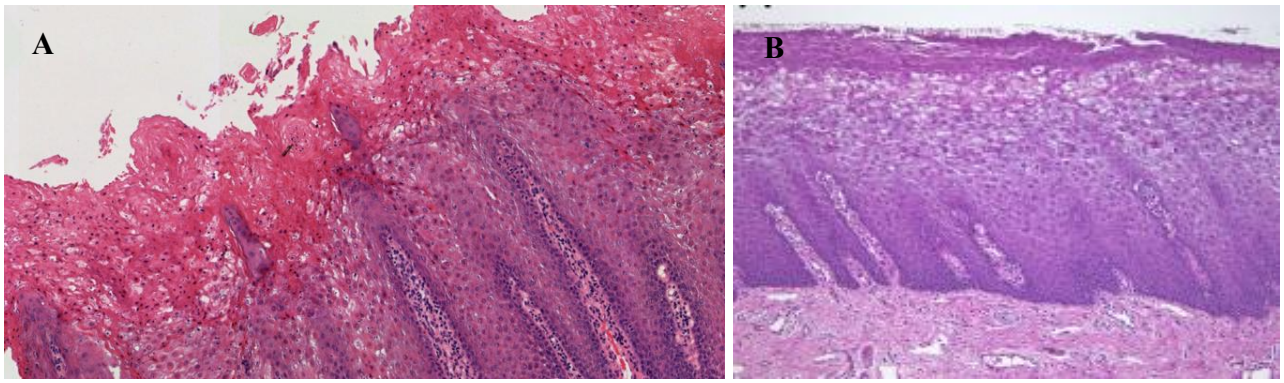

Figure 1. Histopathological analysis of both cases of WSN revealed a consistent pattern, characterized by acanthosis and parakeratosis in the squamous epithelium. This finding was observed in both cases, indicating a similar histological presentation of the condition.[8,12]

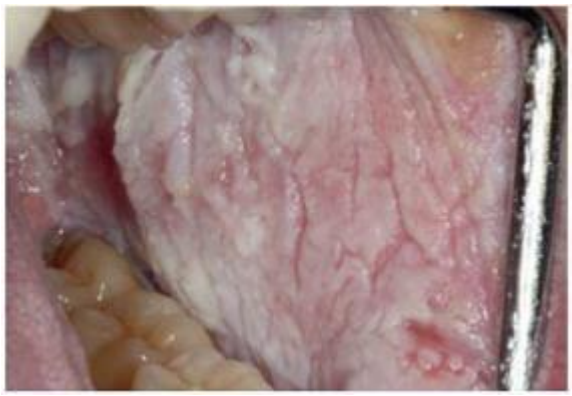

Figure 2. White sponge nevus on the buccal mucosa.[2]

uneven surface may be present as small follicles with a soft texture. The mucous membrane can be removed with no pain or bleeding after swabbing.[9] There are usually no obvious symptoms, but the change in mucosal texture and appearance may have a psychological impact on the patient. In addition, a few people may feel a roughness, a burning pain, or a loss of taste.[10] Although WSN patients had no significant physical pain, they often complained of an altered texture of the mucosa or the bad-looking lesions.[11] This condition might appear as diffuse white plaques, which are a common symptom of a variety of oral diseases. Lichen planus, leukoedema, leukoplakia, oral candidiasis, frictional leukokeratosis, and even squamous cell cancer should be considered in the differential diagnosis.[12,13]

The primary histological observations of WSN are acanthosis with intercellular edema and vacuolization, along with parakeratotic or orthokeratotic hyperkeratosis in the superficial layers.[14] Prada-García *et al.* in their report described the histological finding of WSN in the buccal mucosa of a 61-year-old patient. The finding included acanthosis with regular elongation of crests and intracellular edema, alongside foci of parakeratosis and some dyskeratotic cells exhibiting paranuclear eosinophilic condensations, affecting only the upper layers. A slight, nonspecific perivascular chronic infiltration and a few dilated capillaries were seen in the underlying chorion. No fungi were found using the Periodic Acid-Schiff (PAS) technique (Figure 1A).[12] In another case report by Ishikawa *et al.,* the histological analysis also showed vacuolated cytoplasm in the spinous layer without any evidence of epithelial dysplasia. Furthermore, the spinous layer cells exhibited nuclear condensation and perinuclear acidification (Figure 1B).[8]

In this study, large areas of painless spongy white plaques appeared on both sides of the buccal mucosa of the proband and his father and on both sides of the buccal mucosa and upper lips of the twin sisters. The monozygotic twins had extremely similar symptoms, characterized by the same plaque position and thicker folds compared with the proband and father. It may be attributed to the similarities of twin genes, dietary structure, and living habits.[10]

An autosomal dominant hereditary genetic disorder is the main etiology of WSN, in which mutations occur in the gene responsible for coding and producing keratin, namely keratin (KRT) type 4 or 13. These gene mutations cause defects in epithelial maturation and disruption of epithelial desquamation. This condition is only found in the mucosa, not in the skin, because keratin type 4 and keratin 13 are only found in mucosal epithelial cells.[3,4,7] It is known that there are several predisposing factors for WSN, such as bacterial infections, smoking habits, and alcohol consumption, but the mechanism is unknown.[8,15] However, the presence of a wavy and rough texture of WSN is known due to the overgrowth of bacteria and results in infection; therefore, the role of maintaining oral hygiene plays an important role.[4] A literature search using ScienceDirect and PubMed yielded results between 2012 and 2024. The keywords of the search strategy were “hereditary disease” and “white sponge nevus” or “Cannon’s disease” or “white folded gingivostomatitis” or “leukokeratosis.”

DISCUSSION

Abnormalities of the gene coding for KRT cause the WSN, which is the largest subgroup of intermediate filament

proteins found in the skin and mucosa and plays a role in the cellular cytoskeleton. KRT4 and KRT13 are specific KRTs that have a major role in regulating the differentiation of the mucosa and epithelium of the buccal, nasal, esophageal, vaginal, and anogenital mucosa. The distribution of the WSN sites suggests that mutations in KRT4 and/or KRT13 are the main hypotheses for the etiology of this disorder.[4,16] Deletion of 3 bp KRT4 results in the loss of asparagine (Asn), and the point mutation of KRT13 causes the substitution of leucine (Leu) to proline (Pro), which is the first mutation condition reported, with the main target being exon 1A KRT.[3]

Blood tests from patients with WSN were analyzed for KRT4 and KRT13 sequences using Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and Western blot methods, and the results showed KRT4 and KRT13 had low expression. 16 Another study was conducted with a KRT13 knock-out design in mice by modifying the Cas9 or Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 pathway in exon 1A KRT13. It was proven that low expression of KRT13 caused a loss of epithelial proliferation and differentiation homeostasis, and clinically, white and wrinkled lesions were found on the tongue of the modified mice in the day 20 since the birth of the mice when compared to normal wild-type mice.[3]

Several tests are needed to ensure the presence of a WSN. The subjective examination is carried out through anamnesis in patients who generally have no complaints of pain but often complain of discomfort with the texture of the mucosa and esthetics of the oral cavity.[5–7] Since the disorder is part of a hereditary disease, it is necessary to obtain information on the same condition in other family members. Although in some cases the same condition is not found in the family history.[4,17] Assessing whether the lesions are associated with systemic conditions affecting the oral cavity or are confined to the oral mucosa is crucial for differentiating WSN from other white lesion disorders, such as chronic hyperplastic candidiasis and oral lichen planus.[14]

The objective examination was carried out by looking directly at the patient's oral cavity, which found white plaque lesions, bilateral or symmetrical, thick, folded, wavy, wrinkled, spongy or rubbery texture, varying in size following mucosal involvement, clear boundaries, rough surface, cannot be scraped, no pain, and the color of the surrounding area is normal.[1,7,16] It is also necessary to carry out supporting examinations such as exfoliative cytological examination with Papanicolaou staining and obtain a picture of epithelial cells with eosinophilic perinuclear condensation. Biopsy examination can also be performed and shows epithelial hyperplasia accompanied by hyperkeratosis and acanthosis, as well as vacuolization and eosinophilic perinuclear condensation in the stratum spinosum. There were no signs of epithelial dysplasia or lymphocytic infiltration.[4]

It is necessary to carry out comprehensive treatment for the WSN condition. Penicillin, tetracycline, and macrolide antibiotics can be given to WSN patients with complaints of pain, but not all therapies provide optimal results.[3] In addition, doxycycline 100 mg per day for 6 weeks can be given to patients with aesthetic complaints, and satisfactory results are obtained; hyperkeratosis is reduced and stable for 6 months. Doxycycline is a secondary class of tetracycline and has anti-inflammatory effects and keratin-modulating effects. This also shows that microorganisms can have a role in the expression of genetically predisposed diseases.[18] Generally, the prognosis of WSN is good; this condition generally lasts a lifetime but is benign and causes no complaints. No special treatment is required for the disorder.[19,20] This review requires further development due to the limited research exploring the relationship between family history and the inheritance of gene mutations in WSN. Understanding the suspect for these mutations to be inherited across generations is essential for improving early detection of WSN, particularly during prenatal or childhood stages.

In conclusion, as a hereditary disease, WSN is strongly associated with mutations in the genes that encode keratin. Although it is generally considered to have no malignant potential and has a favorable prognosis, WSN still requires careful management and comprehensive treatment. Accurate diagnosis is crucial, which can be achieved through a combination of subjective and objective assessments, along with supporting tests such as exfoliative cytology and biopsies. Future studies should address this gap to enhance diagnostic accuracy and prevent any overtreatment, ultimately contributing to better management of the condition.

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