Familial Case of White Sponge Nevus – Diagnosis and Therapeutical Challenges

White sponge nevus (WSN) is a rare autosomal dominant disorder with variable penetrance (1). It was first described by Hyde in 1909 (2); in 1935 Cannon named it white sponge nevus (3). Several other names have been applied to this condition: Hyde-Cannon's disease, familial white folded dysplasia, congenital leukokeratosis mucose oris, hereditary leukokeratosis, and white folded gingivostomatosis.

The lesions of WSN involve non-cornified stratified epithelia, especially of the oral mucosa. The suspected mechanism is a keratinization defect (1), mutations of keratin genes 4 and 13 being likely. These mutations lead to the disruption of the intracellular filament network (4-6).

WSN is characterized by the presence of white-greyish, folded, spongy, and thickened plaques on the oral mucosa that are usually asymptomatic. Occasionally, extraoral sites are involved. WSN of the vaginal, rectal, nasal, and esophageal mucosa have been described (7). The lesions are most often present at birth or develop in early childhood, but due to the lack of associated symptoms they are discovered only incidentally and are frequently misdiagnosed as candidiasis (8).

Diagnosis requires a high index of suspicion. A biopsy is generally needed for differential diagnosis. Apart from hyperkeratosis and acanthosis of the affected epithelium, histopathological examination reveals the characteristic eosinophilic perinuclear condensation representing aggregation of cytokeratin filaments (9,10). We report a case of WSN in an otherwise healthy white male with a familial history of similar lesions in 6 other family members from three generations.

An 18-year-old non-smoker male patient was referred to our Department for a 13-year history of white verrucous bilateral plaques on the oral mucosa. Presumed to be oral candidiasis, this condition had been recurrently treated with systemic or topical antifungal therapies and with local antiseptics, without clinical benefit. Even though the lesions were asymptomatic, the patient was extremely concerned about their nature, as well as their unaesthetic aspect.

Clinical examination revealed a rough, folded surface of the oral mucosa, presenting thick white plaques, involving the soft and hard palate, the jugal mucosa, the gingiva, the ventral tongue, the floor of the mouth, and the labial mucosa (Figure 2, 3). Although the large plaques were firmly attached to the underlying tissue, small fragments peeled away revealing a pale, thin mucosa. We also noticed good oral hygienic status, healthy teeth, and the absence of cervical adenopathies. No extraoral sites were involved.

Blood tests results were within normal ranges, including immunogram, human immunodeficiency virus (HIV), and lupus erythematosus serology. Oral bacterial and fungal infections were excluded based on negative cultures.

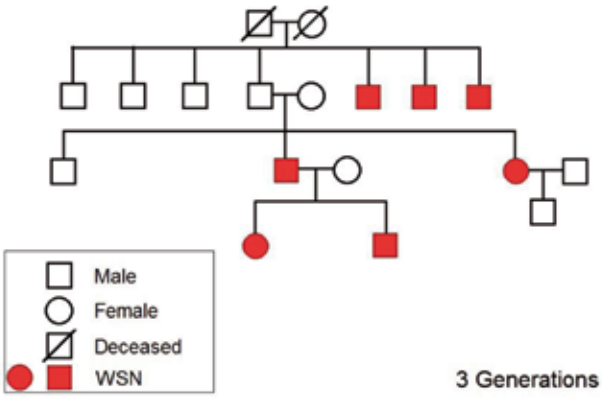

Figure 1. Family history of family affected by white sponge nevus (WSN).

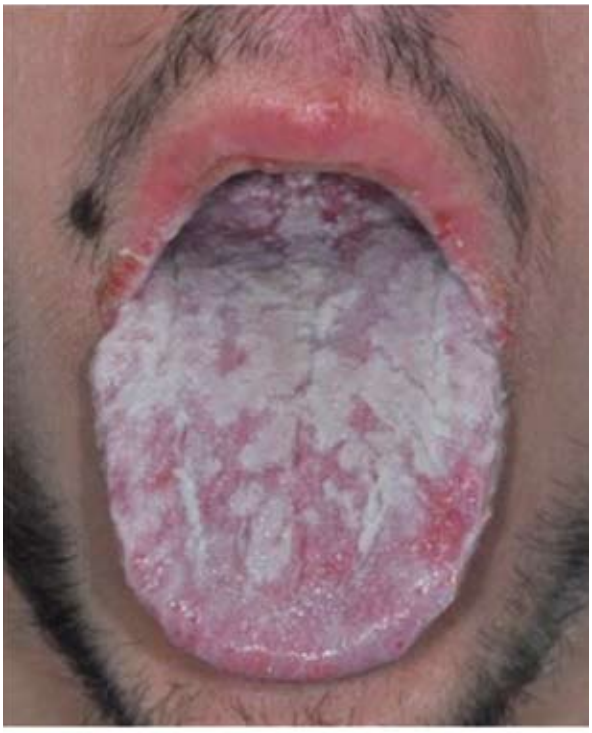

Figure 2. Thick white plaques involving the ventral tongue.

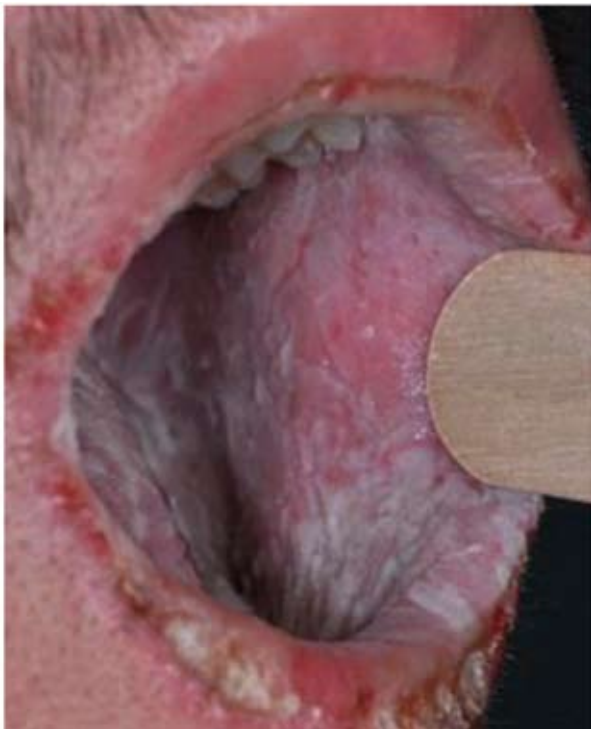

Figure 3. Rough, folded surface of the oral mucosa and thick white plaques.

In order to rule out oral dysplasia and chronic inflammatory disorders, an incisional biopsy was performed. The histopathological exam revealed hyperproliferative epidermis with focal parakeratosis, moderate orthokeratosis, slight hypergranulosis with large keratohyalin granules in the superficial epithelial layers, and a discrete verruciform pattern. Significant acanthosis, spongiosis, and a minimal perilesional chronic inflammatory infiltrate were also noted (Figure 4). These findings were suggestive of WSN.

Considering the heritability of the disease, we examined the patient's family members and found similar oral mucosa lesions in both his father and sister. A thorough patient interview led to the identification of 4 other predecessors who suffered from white plaques of the oral mucosa.

For personal reasons, the patient and his family refused genetic testing.

Based on the clinical picture, family history, and histopathological data, we established the diagnosis of WSN.

The patient and his family were assured of the benign nature of the disease. They were instructed how to keep good dental hygiene and were recommended mouth rinsing with clorhexidine 0.12% twice daily.

Nevertheless, at follow-up visits, the patient complained of multiple episodes of worsening of the oral lesions despite strict adherence to oral hygiene recommendations. Such episodes had no obvious trigger and manifested as a diffuse thickening of the oral plaques with moderate pain and intolerance to

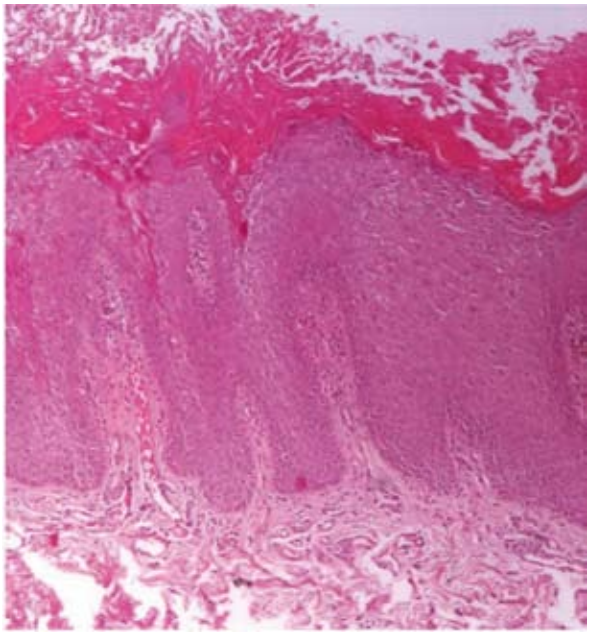

Figure 4. Histopathological aspect of white sponge nevus (hematoxylin and eosin (H&E), ×20).

extreme temperatures. Repeated fungal and bacterial cultures from oral samples taken during these episodes yielded negative results. Moreover, the unaesthetic aspect of the lesions that involved not only the oral mucosa, but also the lips, had a profoundly distressing effect on the patient.

Therefore, we decided to initiate low dose therapy with acitretin (10 mg/day) after obtaining the patient's written informed consent. The patient was monitored monthly for 3 months. He presented with no exacerbation during this interval, but the oral lesions only modestly improved. As a consequence, acitretin treatment was ceased after 3 months.

To our knowledge, this is the first case report of the evolution of WSN under systemic retinoid treatment.

WSN is a very rare clinical entity. A PubMed database search identified 98 reports of WSN published between 1956 and 2014.

The clinical appearance of WSN is suggestive but not pathognomonic, so biopsy is usually recommended in order to differentiate it from other conditions, some with potentially severe repercussions. Oral candidiasis with a pseudomembranous appearance might suggest HIV infection and acquired immunodeficiency syndrome. Oral florid papillomatosis, similar in appearance, is also associated with HIV infection. Although other genodermatoses such as pachyonychia congenita and benign intraepithelial dyskeratosis might present similar mucous involvement, they can be excluded by the lack of concomitant lesions in other sites, such as hyperkeratotic nails and palmo-plantar skin and ocular plaques, respectively. Mechanical factors, such as cheek biting, or biochemical factors, such as smoking, might cause similar complaints but are easily eliminated by a thorough history. In leukoedema, the grey, pale lesion does not persist at the eversion of the buccal mucosa, differentiating it from WSN. It can also be confused with oral lichen planus, although the reticular pattern, the presence of Wickham striae, and the rare onset during childhood in the later should aid the differential diagnosis. Honeycomb plaques of oral lupus erythematosus or the verrucous oral manifestation of the same disease should be discarded by histopathological examination. Biopsy is mandatory in cases in which oral dysplasia is suspected. With WSN, clinicians are faced not only with diagnostic but also with therapeutic challenges. Currently there is no specific treatment for this pathology, and therapeutic data derive exclusively from isolated case reports.

Several studies revealed the importance of the prevention and immediate treatment of septic complications, particularly suprainfection with *Staphylococcus aureus* (11) or *Candida albicans* (12). Topical treatment with antibiotics such as tetracycline 0.25% or 1% (13-16) or antiseptics such as clorhexidine 0.12% (11,17) can lead to partial or even complete clearance of the lesions, with good symptomatic relief and also a sustained long-term prevention of recurrences. Several centers reported favorable immediate results with administration of systemic beta-lactam (13,15,18,19), macrolide (20), or tetracycline antibiotics (13,18). However, in the long term, recurrences were frequent and the individual and epidemiological impact of antibiotherapy outweighed the need for symptomatic control of WSN. Invasive therapies such as CO2 and Nd:YAG (neodymium-doped yttrium aluminium garnet; Nd:Y3Al5O12) laser vaporization have also been attempted with disappointing results (20,21). Surgical resection was also performed on limited oral lesions and was reported to be efficient (21).

Although a benign and generally asymptomatic disease, WSN can be associated with significant distress and impaired quality of life in affected individuals. This justifies the search for new therapies that could provide long-term benefits.

In view of the high efficiency of oral retinoids in the treatment of severe inherited keratinization disorders in children, such as lamellar ichthyosis or bullous ichthyosiform erythroderma (22), and the reported partial improvement of WSN under topical retinoid therapy (21,23), we believe the effect of oral retinoids on WSN should be the subject of further study. In our opinion, they represent attractive therapeutic agents, given their potential to regulate accelerated epidermopoiesis and epidermal cell differentiation.

Considering that response to oral acitretin is dose dependent, the low dose administered in our patient might explain the limited benefit observed in this case. Nevertheless, acitretin treatment is usually started at very low doses in keratinization disorders (ichtyosis, palmo-plantar keratoderma, Darier's disease) in order to prevent initial exacerbation and to avoid potential side effects that are also dose dependent (24). The optimal dose regimens and treatment duration in patients with WSN remain to be discovered.

WSN should be kept in mind in the differential diagnosis of white oral lesions. Although clinical

appearance is suggestive for the diagnosis, biopsy is usually recommended in order to differentiate it from other conditions.

In the absence of a specific treatment, prevention and immediate treatment of bacterial or fungal infections are essential in these patients. Oral retinoids should not be discarded as a potential beneficial treatment for this disorder.

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