ACTAS Dermo-Sifiliográficas 112 (2021) 463–483

ACTAS
Dermo-Sifiliográficas

Full English text available at
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CASE AND RESEARCH LETTERS

Successful Treatment of White Sponge Nevus with Oral Doxycycline: A Case Report and Review of the Literature☆

Tratamiento del nevus blanco esponjoso. Aportación de un caso con respuesta a doxiciclina oral y revisión de la literatura

To the Editor:

White sponge nevus (WSN) is a rare and benign disease that usually affects the oral mucosa and manifests as white spongy plaques. Because it is usually clinically asymptomatic, treatment of WSN is focused on improving the aesthetics and texture of the mucosa.[1] Given the low prevalence of this condition, description of the available therapeutic options is limited to isolated clinical case reports and short cases series.

A 46-year-old male non-smoker with no relevant personal history was seen for oral lesions that had been present since childhood. Clinical examination revealed bilateral, whitish, soft plaques that were located on the buccal mucosa and the lateral aspects of the tongue and remained adhered after scraping (Fig. 1A and B). The patient had no similar lesions in other locations and reported no relevant family history. Although the lesions were asymptomatic, they had a significant aesthetic impact on the patient. A biopsy of

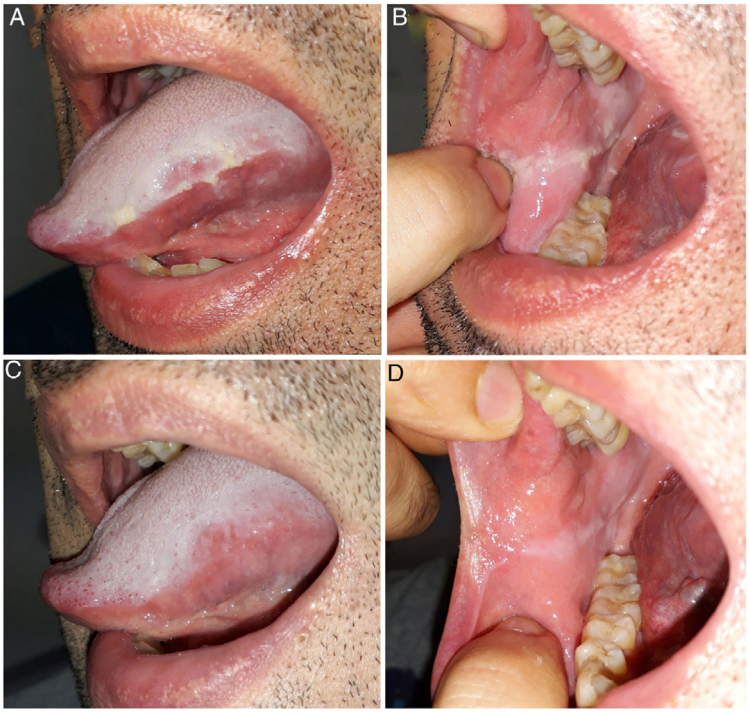

Figure 1 Wrinkled, whitish lesions on the sides of the tongue (A) and on the buccal mucosa (B). Clinical improvement of the lesions on the side of the tongue (C) and on the buccal mucosa (D) after treatment with oral doxycycline.

☆ Please cite this article as: Amores-Martín E, Melé-Ninot G, Del Alcázar Viladomiu E, Fernández-Figueras MT. Tratamiento del nevus blanco esponjoso. Aportación de un caso con respuesta a doxiciclina oral y revisión de la literatura. Actas Dermosifiliogr. 2021;112:463–466.

Table 1 Published Cases of White Sponge Nevus: Therapeutic Guidelines, Clinical Responses, and Recurrences

Authors	Sex	Age	Family History	Treatment	Response	Recurrence/ Maintenance Therapy
Otobe et al.[3]	F	23	Yes	Tetracycline rinses (0.25%, 5 mL for 1 min) 2 times per day for 12 weeks	Partial	No
	F	27	Yes	Tetracycline rinses (0.25%, 5 mL for 1 min) 2 times per day for 12 weeks	Partial	No
	F	46	No	Tetracycline rinses (0.25%, 5 mL for 1 min) 2 times per day for 12 weeks	Complete	No
	M	24	No	Tetracycline rinses (0.25%, 5 mL for 1 min) 2 times per day for 12 weeks	Complete	5 months
Lamey et al.[6]	M	1.5	Yes	Tetracycline 250 mg once per day for 4 weeks Penicillin 250 mg once per day for 2 weeks	No No	-
	M	24	Yes	Tetracycline 250 mg 4 times per day for 4 weeks Tetracycline 250 mg once per day for 30 weeks	Partial Partial	8 weeks/Tetracycline 250 mg/wk
	M	52	No	Amoxicillin 250 mg 3 times per day for 4 weeks Minocycline 50 mg 2 times per day for 6 weeks	Partial No	8 weeks/Amoxicillin 250 mg/wk
	F	11	No	Penicillin 250 mg 4 times per day for 4 weeks Penicillin 250 mg once per day for 20 weeks	Partial Partial	Yes/Penicillin 250 mg/wk
	M	32	Yes	Tetracycline 250 mg 4 times per day for 4 weeks Amoxicillin 250 mg 3 times per day for 4 weeks	Partial Partial	10 weeks/No
	F	6	Yes	Amoxicillin 125 mg 3 times per day for 4 weeks	No	-
Otobe et al.[4]	M	10	No	Tetracycline rinses (0.25%) 2 times per day for 12 weeks	Complete	4 months
Lim et al.[7]	F	36	No	Penicillin G procaine 1.2 MU IM once per day for 3 days Tetracycline rinse (0.25%), single dose	No Partial	-
Contreras-Steyls et al.[5]	M	26	Yes	Doxycycline 200 mg once per day and tetracycline rinses (0.25%) 2 times per day for 12 weeks	Complete	-
Satriano et al.[8]	M	15	Yes	Chlorhexidine rinse (0.12%, 5 mL for 45 seconds) 2 times per day for 8 days	Partial	Chlorhexidine rinses 1 wk per month
	F	50	Yes	Chlorhexidine rinse (0.12%, 5 mL for 45 seconds) 2 times per day for 8 days	Partial	Chlorhexidine rinses 1 wk per month
Piqué et al.[2]	M	46	No	Amoxicillin 500 mg 3 times per day for 10 days Retinoic acid (0.01% aqueous solution) for 4 weeks	No Complete	- Intermittent regimen of topical retinoids
Becker et al.[9]	F	12	No	Tetracycline rinses (0.25%, 2 times per day) for 12 weeks	Partial	Tetracycline rinses ad libitum
Amores-Martín et al.*	M	46	No	Oral adhesive excipient containing 0.1% triamcinolone acetonide and 0.1% retinoic acid once per day for 8 weeks Doxycycline 100 mg once per day for 6 weeks	No Partial	- No

Abbreviations: F, female; IM, intramuscular; MU, million units; M, male.
* Present case.

one of the lesions on the buccal mucosa revealed epithelial hyperplasia, edema, and discrete cytoplasmic clearance in squamous cells. Taken together with the clinical context, these findings were compatible with WSN.

Treatment for 2 months with topical triamcinolone acetonide (0.1%) and retinoic acid (0.1%) in oral adhesive excipient resulted in no clinical improvement, and it was decided to begin treatment with oral doxycycline (100 mg/d) for 6 weeks. The extension and texture of the lesions improved by the end of the treatment cycle, providing an acceptable aesthetic result, and the patient remained stable for the next 6 months (Fig. 1C and D).

WSN is a rare, autosomal dominant disease with incomplete penetrance, despite isolated reports of cases with no family history.[1,2] It was first described by Hyde in 1909.[1] Clinically, it is characterized by bilateral, well-defined, villous white plaques with a spongy texture, usually located on the oral mucosa, often with involvement of the bite line and the anterior third of the buccal mucosa.[1,3] It usually manifests during childhood or adolescence, with no sexual predisposition, and the lesions tend to remain stable throughout life. Histology shows acanthosis with intercellular edema and vacuolization, as well as parakeratotic or orthokeratotic hyperkeratosis in the superficial layers.[4,5] Diagnosis is based on clinical–pathological correlation and, where possible, analysis of mutations in keratin 4 (*KRT4*) and keratin 13 (*KRT13*), genes responsible for epithelial keratinization.[1] The differential diagnosis should primarily include oral candidiasis, frictional leukokeratosis, leukoedema, leukoplakia, and lichen planus.[1,2]

Although WSN is a benign and asymptomatic disease, its effects on mucosa texture and aesthetics are a source of discomfort for many patients. Multiple treatments have been tested for WSN (Table 1). Some have proven of little benefit, producing variable results, and there is no well-defined therapeutic protocol.

Partial and complete responses have been described in patients treated with topical tetracyclines. The best results have been described in patients treated with 0.025% tetracycline rinses 2 times per day for 12 weeks. However, good responses have been reported in 2 cases treated with oral tetracyclines, in line with our findings. The paucity of publications makes it difficult to establish the best route of tetracycline administration. In WSN, the beneficial effect of second-generation tetracyclines such as doxycycline and minocycline can be attributed both to their anti-inflammatory effects and their modulation of epithelial keratinization.[1] These properties constitute an advantage over tetracycline.[10]

Although WSN is not considered of microbiological origin, most of the treatments for which good outcomes have been reported to date are antimicrobial therapies, including oral and topical antibiotics and antiseptics such as chlorhexidine.[8] This suggests that certain microorganisms may play a role in disease expression in genetically predisposed individuals. However, further evidence is required to support this hypothesis.

Analysis of therapeutic response as a function of a family history of WSN suggests that the absence of a family history does not greatly increase the likelihood of a response to treatment, but is associated with a greater clinical response.

The new WSN case presented here, in which the patient showed a satisfactory clinical response to oral doxycycline (100 mg/d for 6 weeks), provides additional data on the use of oral tetracyclines to treat this condition. We believe it is important to have a knowledge of the clinical evidence supporting the different treatments used to date to ensure selection of the most appropriate therapies for these patients.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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https://doi.org/10.1016/j.adengl.2019.10.014

Buschke Scleroderma Refractory to Conventional Treatment: Response to UV-A1 Phototherapy☆

Escleredema de Buschke refractario a terapia convencional. Respuesta a UVA1

To the Editor:

Scleredema belongs to the diffuse cutaneous mucinosis group of disorders. It is also known as adult scleredema or Buschke scleredema, after the dermatologist who first described it in 1902 in a patient with the classic manifestations of the disease. It is considered a rare disease and its prevalence is unknown. No race-or sex-related differences in prevalence have been reported, and it has been described in both pediatric and adult populations.

A 62-year-old man with a personal history of long-standing hypertension, dyslipidemia, and type II diabetes mellitus with good metabolic control was initially evaluated in the digestive system unit for dysphagia for solids that had begun several months earlier. Endoscopy had been performed, but showed no evidence of disease. However, a subsequent cervical thoracic abdominal pelvic computed tomography (CT) scan revealed edema of cervical, axillary, and thoracic subcutaneous cellular tissue. The patient was admitted to the internal medicine unit. Examination revealed diffuse skin induration in the cervical region, shoulders, back, and buttocks (Fig. 1B).

Blood tests showed an increase in free lambda chains (570 mg/L) and immunofixation revealed a monoclonal component. The pathological examination revealed no epidermal lesions and diffuse thickening in the middle and deep dermis, with an increase in mucopolysaccharides between collagen bundles and an absence of inflammatory infiltrate (Fig. 2B).

Once the suspected diagnosis of adult scleredema was confirmed, different treatments were performed successively, without response, and the patient's clinical signs progressively worsened, hindering the full range of movements involving the shoulder and pelvic girdles. The treatments administered included the following: prednisone (tapering dose starting at 40 mg/d); methotrexate (15 mg/wk for 4 months); methylprednisolone (6 pulses of 500 mg); intravenous immunoglobulin (3 g/wk for 3 cycles, with little improvement); and cyclophosphamide.

Treatment was started with ultraviolet A1 (UV-A1; UVA 302 L lamp, Waldmann®, Villingen-Schwenningen, Germany) at an initial dose of 5 J/cm^2, increasing in 10% increments up to a maximum dose of 20 J/cm^2, administered in 3 sessions per week for a total of 28 sessions (cumulative dose, 291.09 J/cm^2). This regimen had no adverse effects and resulted in improvements in dysphagia and mobility and a reduction in skin stiffness on the neck but not the buttocks. Comparison of pre- and post-treatment elastography findings showed a decrease in skin stiffness (Fig. 2C and D).

Scleredema in adults is a rare disease of the connective tissue, the clinical presentation of which depends on the disease with which it is associated.[1] Scleredema associated with diabetes mellitus is considered the most common form, and affects obese adults with poorly controlled and advanced diabetes. It begins insidiously, typically affecting the posterior area of the neck and thorax, sparing the extremities. Scleredema associated with a monoclonal gammopathy is the least common form. The clinical presentation is similar to that described in diabetes mellitus patients, but the disease course is variable: spontaneous resolution has been described in some cases, while in others the disease can be refractory to treatment and can become chronic. In our patient, we identified 2 well-established clinical and etiological factors.

Scleredema appears to be caused by irreversible collagen glycosylation in the diabetes mellitus-associated form, sensitization to collagen in the form associated with streptococcal infection, and chronic immune stimulation in the form associated with monoclonal gammopathy.[2]

Treatment poses a real challenge for the clinician. Treatment with immunosuppressants, intravenous immunoglobulins,[3] and extracorporeal photopheresis[4] has been described, with variable responses. However, phototherapy has always been considered a fundamental component of the treatment of adult scleredema. Due to its lower cost, greater accessibility, and, according to some authors, faster treatment response compared with other types of phototherapy,[5] narrowband ultraviolet B (UV-B) has been the most commonly used modality.

UV-A1 phototherapy (340–400 nm) appears to offer a better response and lower rates of recurrence, as described

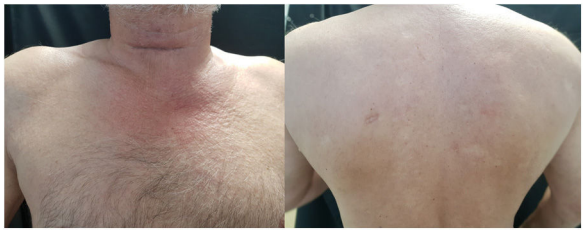

Figure 1 A, Increased skin stiffness on the chest with papules and peau d'orange in a V-shaped pattern. B, Waxy stiffness of the skin of the back.

☆ Please cite this article as: L. Linares-González, T. Ródenas-Herranz, J.L. Espelt-Otero et al., Escleredema de Buschke refractario a terapia convencional. Respuesta a UVA1, ACTAS Dermo-Sifiliográficas, 2021;112:466–468.