

# OLMSTED SYNDROME

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### INTRODUCTION

Olmsted syndrome is a rare congenital disorder of keratinization characterized by symmetrical sharply defined mutilating palmoplantar keratoderma (1). It was first described in 1927 by H. C. Olmsted. The disorder can also clinically manifest with diffuse alopecia, digital constriction, onychodystrophy, periorificial hyperkeratotic plaques, linear hyperkeratotic follicular streaks, oral leukokeratosis, and acral hyperhidrosis. Other rare findings include ichthyotic lesions, joint laxity, absent premolar teeth, high-frequency hearing loss, and sclerosing cholangitis (2,3). This syndrome typically presents between the neonatal period to early childhood.

### CASE REPORT

A 10-year-old girl from Douglasville, Georgia originally presented with massive painful hyperkeratotic lesions affecting her feet, hands, and knees. On examination, we observed an erythematous sole covered by 3 centimeter-thick fissure hyperkeratosis, and hyperkeratotic lesions between the thumb and index finger, bilaterally (Figure 1). The patient had met normal developmental milestones. The past medical history was noncontributory except for the placement of Eustachian tubes and tonsillectomy. The syndrome first began as a diaper rash, which disappeared. Then lesions started to develop at the age of two. The patient is wheelchair-bound secondary to the painful calluses. At home, she wears knee protectors and crawls on her knees. She is currently going to physical therapy for atrophy of the lower legs.

The patient takes Lortab and Lyrica to control the pain and sees a pain specialist. No other family member was known to have any skin disease. The patient's parents had consulted several dermatologists and infectious disease doctors. She was clinically diagnosed with pachyonychia congenita. She recently was genetically tested and found to be heterozygous for the G573C mutation in the TRPV3 gene that is consistent with Olmsted Syndrome (Figure 2). Her immediate family was also genetically tested and all had negative results. The patient was informed that due to her specific genetic pattern, any offspring she produces would have a 50% chance of having the disease.

The patient has routine foot debridements in the operating room every 5-6 months (Figures 3-5). She is currently 17-years-old and is considering bilateral below-knee amputations due to severe pain and deformity.

### DISCUSSION

Olmsted Syndrome was first described in 1927 as a combination of congenital palmoplantar, keratoderma, and periorificial hyperkeratosis (1). The differential diagnoses include palmoplantar keratoderma, pachyonychia congenita, Mal de Maleda Syndrome, acrodermatitis enteropathica, Papillon-Lefevre Syndrome, Tyrosinemia type II, and Vohwinkel Syndrome (3-6).

Until recently, only 46 individuals with Olmsted had been reported including 36 sporadic cases and 4 families containing 10 affected individuals (7). Only within the last few years have mutations been found in the gene TRPV3. At this time only 7 cases have been reported in the literature with genetic testing to confirm they are caused by mutations in this gene.

The literature reports the majority of cases occur in males, and it is rarely reported in female patients (8). The definite mode of inheritance is still uncertain. However, an X-linked dominant transmission in two monozygotic male twins and a familial case with a possible autosomal dominant transmission have been reported (8, 9). Kress et al found a defect in the expression of mature epidermal keratins (types 1, 10) and persistence of acidic keratins (types 5, 14) in the involved epidermis. Danso-Abeam et al found a variety of immunological disturbances in Olmsted Syndrome,



Figure 1. A 10-year-old girl with Olmsted presurgical debridement.

<i>Test(s) requested:</i>	TRPV3 Gene / Evaluate for G573C Mutation Identified in a Research Laboratory / Olmsted Syndrome
<i>Relevant History:</i>	This individual is heterozygous for the G573C mutation in the TRPV3 gene, as identified by a research laboratory. Confirmation requested.
<i>Result:</i>	<b>POSITIVE. The G573C Mutation in the TRPV3 Gene is PRESENT.</b>  This individual is heterozygous for a G>T nucleotide substitution resulting in the replacement of a Glycine codon (GGC) with a Cysteine codon (TGC) at amino acid position 573. This mutation is denoted c.1717 G>T at the cDNA level or p.Gly573Cys (G573C) at the protein level.
<i>Interpretation:</i>	The presence of the G573C mutation previously identified in a research laboratory was confirmed in the submitted specimen. The interpretation of the clinical significance of this result is deferred to the research laboratory. Mutations elsewhere in the TRPV3 gene would not be identified by this targeted analysis.
<i>Recommendation:</i>	Genetic counseling is recommended.
<i>Methods:</i>	The relevant portion of the TRPV3 gene was PCR-amplified from genomic DNA. Bi-directional sequence was obtained and DNA sequence was analyzed and compared to the published gene sequence. The methods used by GeneDx are expected to be greater than 99% sensitive in detecting mutations identifiable by sequencing.

Figure 2. Genetic testing report.



Figure 3. Same patient at age 11 years. Recurrence 6 months after surgical debridement.



Figure 4. Immediate post debridement of bilateral hyperkeratotic lesions.



Figure 5. Same patient at age 15 years, complete recurrence of deformity.

including frequent dermal infections, hyper IgE levels, chronic eosinophilia, and elevated follicular T cells in the peripheral blood.

The disease typically presents in early childhood, however adult skin lesion onset has been reported (12, 13). In the case report presented, the patient had palmoplantar keratoderma, onychodystrophy, digital constriction, and fissure hyperkeratosis. Other features commonly reported on occasion with Olmsted Syndrome include diffuse alopecia, periorificial hyperkeratotic plaques, linear hyperkeratotic follicular streaks, oral leukokeratosis, and acral hyperhidrosis (1-3). Other findings include ichthyotic lesions, joint laxity, absent premolar teeth, high-frequency hearing loss, anhidrosis, chronic blepharitis, corneal epithelial dysplasia, and sclerosing cholangitis (1-3).

There is a higher susceptibility in patients with Olmsted Syndrome to develop epidermal tumors. These tumors can include squamous cell carcinoma and epithelioma cuniculatum (8, 14). Olmsted Syndrome has a progressively slow course. In this disease, the keratoderma becomes increasingly thickened to the point where normal walking is affected. With severe fissuring, the tissue heals with constricting bands of tissue, known as pseudoainhum formation (8). This formation can lead to autoamputation of the affected digits (8). Periorificial lesions may remain stable or worsen with age (8).

This condition is often difficult to diagnose because of its rarity and clinical overlap. There is no cure for Olmsted Syndrome. Treatment is difficult and includes topical keratolytics, systemic retinoids, and mechanical removal of keratoderma (15, 16). Topical treatments offer temporary pain relief with a high rate of recurrence. Various topicals including salicylic acid, urea, boric acid, corticosteroids, shale oil, emollients, retinoic acid, antimicrobials, wet dressing, and water soaks have been met with varying levels of success

(3, 17). Emollients soften the keratoderma. Systemic retinoids have some benefit in the early stages (18). In severe cases, full-thickness excision of palmoplantar skin is performed with skin grafting (2, 17). Oral treatments with antihistamines, vitamin E and A, antimicrobials, and corticosteroids have also been utilized with no consistent benefit (3, 5, 8). This disease has a chronic and progressive course, and as a result, is extremely resistant to therapy (3, 5, 8).

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