

Chapter 6

Dermatologic Manifestations

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Introduction

Involvement of the skin, nails, and oral mucosa are hallmark features of dyskeratosis congenita (DC). In fact, the original description of DC was based upon the clinical triad of reticulated (net-like) skin pigmentation, fingernail and toenail abnormalities, and oral leukoplakia (whitish plaques inside the mouth). However, not all patients have these findings, which may develop over time (Figure 1) [1]. In addition to the diagnostic triad, individuals with DC and related Telomere Biology Disorders (TBDs) may develop numerous other bothersome cutaneous skin-related complications including hair loss, skin cancer, and excessive sweating (hyperhidrosis). The focus of this chapter is to review the dermatologic manifestations in individuals with DC/TBDs and examine management and treatment strategies.

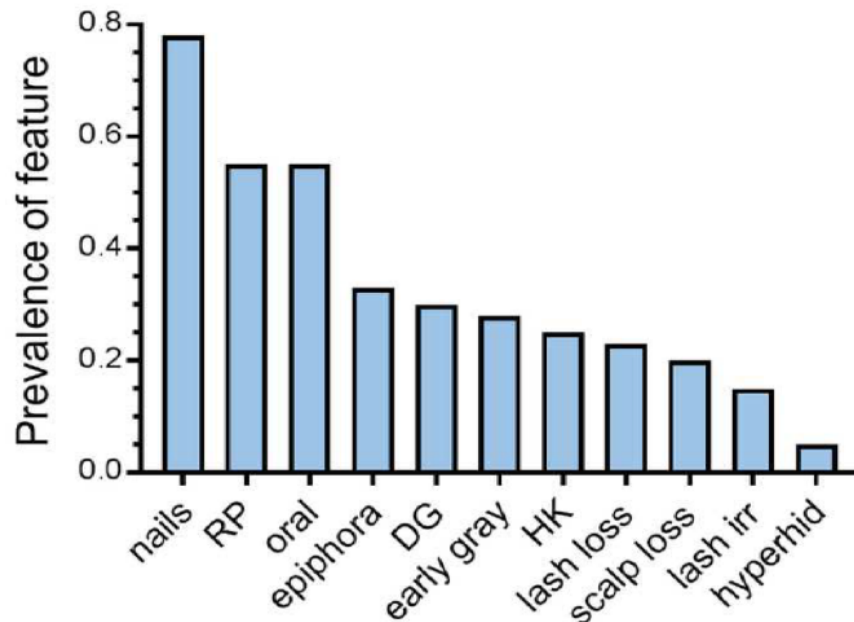


Figure 1. Prevalence of mucocutaneous findings in 60 patients with DC (Adapted from Ward et al, *J Am Acad Dermatol* 2018).

DG, Dermatoglyphic changes; early gray, graying of the hair before the age of 30 years; HK, hyperkeratosis of the palms and/or soles; hyperhid, hyperhidrosis; lash irr, blepharitis or irritation due to eyelashes; lash loss, thinning or sparseness of the eyelashes; nails, nail dystrophy; oral, leukoplakia or oral squamous cell sarcoma; RP, reticulate skin pigmentation; scalp loss, premature hair thinning or balding of the scalp

Skin Cancer

Data from literature reviews and groups (cohorts) of individuals with DC/TBDs have identified an overall increased risk of several cancers for affected individuals [2, 3].

Head and neck squamous cell cancer (HNSCC) and cutaneous squamous cell cancer are the most frequently reported solid organ tumors in this population. Individuals with DC/TBDs tend to develop these malignancies at a younger ages than is typical in the general population [2] In a review of eight individuals with DC/TBDs and cutaneous

squamous cell cancer reported in the literature, the median age at onset was 21 years, significantly earlier than in the general population, with a median age of 68 years old [2].

Squamous cell cancers of the skin generally present as slow-growing pink-to-skin-colored flat growths or raised bumps and may be associated with overlying scales (flaking skin). The most common locations for squamous cell cancers of the skin are areas frequently exposed to sun, including the head and neck, upper trunk, and upper extremities. However, they may occur on any site of the body.

General risk factors for squamous cell cancers include sunlight (ultraviolet light) exposure, radiation, and the chronic use of medications that suppress the immune system (immunosuppressants). Voriconazole, a medication used to treat fungal infections, may also increase the risk of squamous cell cancer [4]. There is also an association between the human papillomavirus (HPV) and squamous cell cancers; however, data suggests individuals with DC/TBDs may develop squamous cell cancers independent of this HPV association [5].

There are multiple surgical (e.g., excision, Mohs micrographic surgery) and non-surgical (e.g., topical chemotherapy, radiation therapy) options to treat skin cancers. The most appropriate treatment depends on factors such as the size and differentiation of the tumor, risk of recurrence, the location on the body, and the anticipated cosmetic appearance following treatment.

Because of the increased risk of skin cancer, prevention strategies are highly recommended for individuals with DC/TBDs. Useful strategies include:

- Regular use of sunscreen or sunblock when outdoors, and use of a daily moisturizing lotion with sunblock
- Wear hats and sun-protective clothing when outdoors to prevent excessive sun exposure
- Limit outdoor time during hours of peak sun exposure (between 10 am and 4pm)

- Be mindful of reflected sun from water and snow when engaging in outdoor activities
- Avoid tanning beds
- Perform regular skin self-examinations to look for new or changing skin growths

In addition, annual full body skin examination by a dermatologist is recommended [6].

Thickening of Palms and Soles

The thickening of the skin on the palms and soles seen in individuals with DC/TBDs may be referred to by the medical term hyperkeratosis. These changes are due to increased thickness of the upper cell layers of the skin overlying these areas (Figure 2).

The mainstay of treatment for hyperkeratosis of the palms and soles is the liberal use of topical moisturizers (emollients) which contain agents that break down keratin, the fundamental component of the excess thickened skin. Agents that may be used for both moisturizing and breakdown of keratin include the following:

- Urea cream
- Salicylic acid cream or compounded ointment
- Cream or lotion containing lactic acid with ammonium hydroxide

Use of a daily moisturizer for maintenance of generally healthy skin on the remainder of the body is also recommended.



Figure 2. Hyperkeratosis: Thickening of the skin of the palm. Image obtained after informed consent from participants in the Cancer in Inherited Bone Marrow Failure Syndromes Study, ClinicalTrials.gov Identifier: NCT00027274. Courtesy of Neelam Giri, MD and Sharon Savage, MD, National Cancer Institute.

Hair Changes

DC/TBDs is associated with several changes in the appearance and quantity of hair. The hair of individuals with DC/TBDs shows structural abnormalities in both the hair shaft and in the hair cuticle, which may contribute to the thin appearance and early hair loss [7].

Individuals with DC/TBDs often experience graying of the hair at an early age. Additionally, hair loss (alopecia) also tends to occur at an early age in DC/TBDs. This may affect the hair of the scalp, eyebrows, eyelashes, or body. Patients with loss of eyelashes may experience an increase in eye irritation from entry of dust particles or other foreign material and may benefit from protective eyewear. To date, no studies have looked specifically at treatments for hair loss in individuals with DC/TBDs. Minoxidil is an over-the-counter topical treatment that may be used for thinning of scalp hair. Side effects of minoxidil include contact dermatitis and unwanted facial hair growth. Bimatoprost is an ophthalmic solution applied to the base of the upper

eyelashes that causes the lashes to grow longer, fuller and darker. Side effects of bimatoprost include pigmentation of the eyelids and iris which may be permanent.

Skin Pigmentation

One of the diagnostic skin changes associated with DC is the net-like pattern of skin pigmentation termed reticulate pigmentation. The common appearance is of gray-brown skin pigmentation along sites of flexion, including the neck, shoulders, arms, and chest, as seen in Figure 3. An additional finding of skin changes in DC/TBDs is poikiloderma, or thinning of the skin (atrophy) accompanied by the formation of fine blood vessels (telangiectasias) and areas of both increased (hyper-) and decreased (hypo-) pigmentation. While these features may aid in the diagnosis of DC/TBDs, there are no studies examining the impact of treatments specifically aimed at reversing these changes. Liberal use of daily moisturizers can be used to decrease roughness associated with symptomatic dry skin.



Figure 3. Reticulated pigmentation on the neck. Images obtained after informed consent from participants in the Cancer in Inherited Bone Marrow Failure Syndromes Study, ClinicalTrials.gov Identifier: NCT00027274. Courtesy of Neelam Giri, MD and Sharon Savage, MD, National Cancer Institute.

Skin changes following allogeneic hematopoietic cell transplantation (HCT) or solid organ transplantation for DC/TBDs have not been extensively examined but deserve close medical attention. Individuals who have undergone transplantation and their caregivers should be attuned to new or changing skin lesions for surveillance of skin cancers. Those who underwent HCT should be carefully followed for the development of cutaneous graft versus host disease, which may closely mimic the poikilodermatous skin and nail changes seen in DC/TBDs [6]. Regular visits with a dermatologist are encouraged for skin cancer screening in patients following transplantation.

Hyperhidrosis

Up to 15% of patients with DC/TBDs experience hyperhidrosis, or excessive sweating [8]. Sweat glands are located in highest concentration in the palms, soles, and axillary regions of the body. Excessive sweating can have a significant impact on an individual's quality of life, and several treatment strategies exist for the management of hyperhidrosis.

Treatments for hyperhidrosis include [9]:

- Avoidance of specific triggers which may worsen hyperhidrosis such as alcohol and spicy foods
- Topical aluminum chloride powder, roll-on, or sprays
- Topical glycopyrronium cloths
- Botulinum toxin injections
- Systemic anticholinergic agents such as oxybutynin or glycopyrrolate
- Iontophoresis with topical anticholinergic agents

No studies have been performed to date specifically examining the efficacy of these treatments in individuals with DC/TBDs, but all have been shown to offer some relief of hyperhidrosis in various clinical scenarios.

Adermatoglyphia

Lack of fingerprints – adermatoglyphia – is another potential dermatologic finding of DC/TBDs (Figure 4). In some individuals it is thought to be secondary to a disorder in formation of the epidermis (the top layer of skin) during development as an embryo. In others, it may develop over time due to the hyperkeratosis of the palms [10, 11] Caregivers and individuals with DC/TBDs should be aware of this potential skin complication, as it may impact such processes as immigration and obtaining government identification [11].

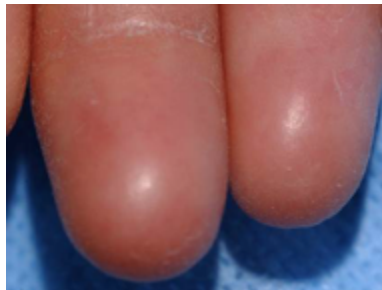


Figure 4. Adermatoglyphia: Loss of fingerprints. Image obtained after informed consent from participants in the Cancer in Inherited Bone Marrow Failure Syndromes Study, ClinicalTrials.gov Identifier: NCT00027274. Courtesy of Neelam Giri, MD and Sharon Savage, MD, National Cancer Institute.

Nails

Nail involvement in DC/TBDs can range from nail malformation (onychodystrophy) to small nails (micronychia) to complete absence of the nail plate (anonychia). Several nail changes are shown in Figure 5. Common forms of onychodystrophy that occur in DC/TBDs include longitudinal grooving of the nail plate (onychorrhexis) as well as splitting of the nail (onychoschizia).



Figure 5. Nail changes in DC: onychoschizia, longitudinal ridging, and micronychia. Images obtained after informed consent from participants in the Cancer in Inherited Bone Marrow Failure Syndromes Study, ClinicalTrials.gov Identifier: NCT00027274. Courtesy of Neelam Giri, MD and Sharon Savage, MD, National Cancer Institute.

As with the skin findings of DC/TBDs, nail involvement may also mimic features of other conditions. The nail changes have been reported to be similar to those in other cutaneous conditions such as lichen planus and graft versus host disease after HCT.¹²

There are limited data on management of nail changes specifically in DC/TBDs. Brittle, fragile nails may also impact quality of life by causing repeated injury or discomfort. Keeping the nails trimmed and use of an emery board to dull rough or sharp nail edges may reduce the discomfort of incidental nail injury during day-to-day activities.

Additional strategies that may be useful for the treatment of fragile nails include [13]:

- Reduce excessive exposure to water, detergents, and prolonged hand washing
- Avoid long-term use of artificial nails from salons
- Nail polishes and lacquers may help to strengthen brittle nails

- Vitamin supplements such as biotin may provide some strength to brittle nails

Daily Skin Care

As the skin is a clearly visible organ to individuals and to the outside world, an unhealthy or abnormal appearance of the skin can have a potential impact on one's quality of life or self-esteem. Strategies to maintain skin health include:

- Review the daily sun protection strategies outlined above in the skin cancer section
- Use a daily moisturizer, applied daily after showering or bathing, to help maintain the skin's natural water content
- Stay well-hydrated throughout the day with adequate water intake
- Avoid abrasive or overly-drying soaps or detergents
- Perform regular skin self-exams for any new or changing skin lesions

In addition, annual full body skin examination by a dermatologist is recommended [5].

Conclusion

The dermatologic manifestations of DC/TBDs may involve the hair, nails, skin, and mucosal surfaces. Given the increased risk of cutaneous cancers in this population and the clinical overlap with other skin conditions, we recommend regular surveillance by a dermatologist for individuals with DC/TBDs for both diagnostic evaluation and therapeutic management.

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