Dermatologic (and other) Manifestations of Rothmund-Thomson Syndrome

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A member of the Seton Family of Hospitals

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Case History

- 3 month old girl with fine hair, lashes, brows and missing thumbs
- Seen again at 13 yrs
- Again with same findings; in addition was found to have differences in skin pigmentation, absent carpal bones, decreased bone density, palmoplantar hyperkeratoses, RECQL4 mutations

Case History

Case Rep Dermatol 2014;6:176

Rothmund-Thomson Syndrome

- AR
- Poikiloderma
- Cataracts
- Short stature
- Limb defects
- Malignancy

RTS

- Erythema within 1st six months
  -90% in first year of life
  -Face, extremities, buttocks
- Photosensitivity???; Inconsistent data regarding sensitivity to UV/IR
- Heat intolerance
- Swelling

Br J Dermatol 2011;164:245
GeneReviews 2016

RTS

- Blistering

- Poikiloderma (atrophy [thinning], dyspigmentation, telangiectasia [fine superficial vessels]) develops later;
  -can be in adulthood (?)

- Hyperkeratoses [thickening of skin]; ~ 30% as early as 2 yrs

Rothmund-Thompson Syndrome

- Ectodermal defects/differences

  -Skin, Nails
  -Hair
  -Teeth

- Eyes
- Gastrointestinal
- Malignancies; bone, skin, others
- ? Link to aging and cancer susceptibility (RECQ/RECQL)

Rothmund-Thomson Syndrome and Aging

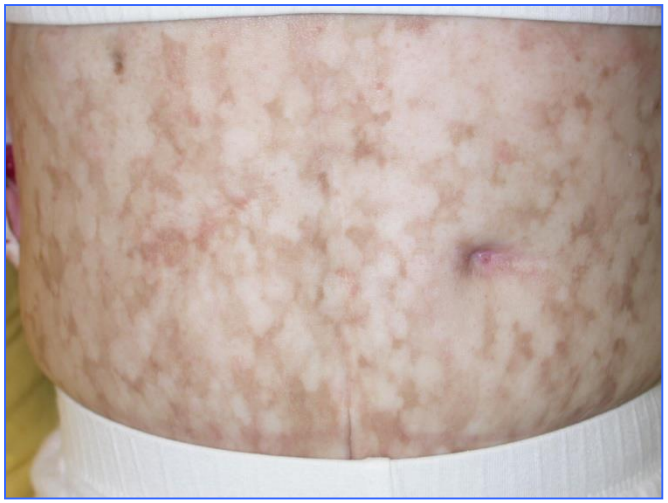
Table 1
Clinical features of aging in RTS patients

	Clinical findings
Skin	Poikiloderma (atrophy and irregular pigmentation, telangiectases)
Skin Accessories	Sparse scalp hair, alopecia, sparse eye brows and lashes
Eye	Cataracts
Skeletal System	Osteoporosis, frequent fractures
Malignancy	Osteosarcoma, skin cancer (squamous and basal cell carcinomas)

Ageing Res Rev 2017

Rothmund-Thomson Syndrome Differential Diagnosis

- Baller-Gerold syndrome; craniosynostosis
- Clericuzio poikiloderma; neutropenia, infections
- Bloom's (telangiectasia) and Werner's
- Hereditary sclerosing poikiloderma; with sclerodermatous plaques on palms/soles
- Kindler syndrome; bullous disease
- Progressive reticulated telangiectatic erythema
- Others



Baller-Gerold Syndrome

-Craniosynostosis w/radial defects
-AR
-Short stature
-CHD, GU abnl
-MR

RECQL Syndromes

Rothmund-Thomson

- **Poikiloderma**, **Sparse hair**, Short stature, Long bone differences
- **Palmoplantar keratoderma**, Osteosarcoma, **Skin CA**

Bloom Syndrome

- Microcephaly, Immunodeficiency, Malignancies (leukemia, lymphoma)
- **Poikiloderma**, **Telangiectasia** central face/neck ("butterfly" distribution), **Café au lait**

Werner Syndrome

- **Graying of hair**, Short stature,**Sclerodermatous skin** changes (firm areas)
- Ulcers on feet, ankles
- Malignancies

Rothmund-Thomson
Poikiloderma

Hyper-/Hypopigmentation

Telangiectasia (fine, discrete, small vessels)

Atrophy (thinning)

Skin Hyperpigmentation

RTS

Rothmund-Thompson/Hair

- Fine, thinned
- Brows, lashes 1st
- Alopecia; partial or total
- One report of pili annulati (a diff. of hair shaft appearance under microscope; may be spangled; may be prone to breakage

  JEADV 2108;32:e208

Rothmund-Thompson/Nails

- Dystrophic (different growth)

  -30%

  -Thinned

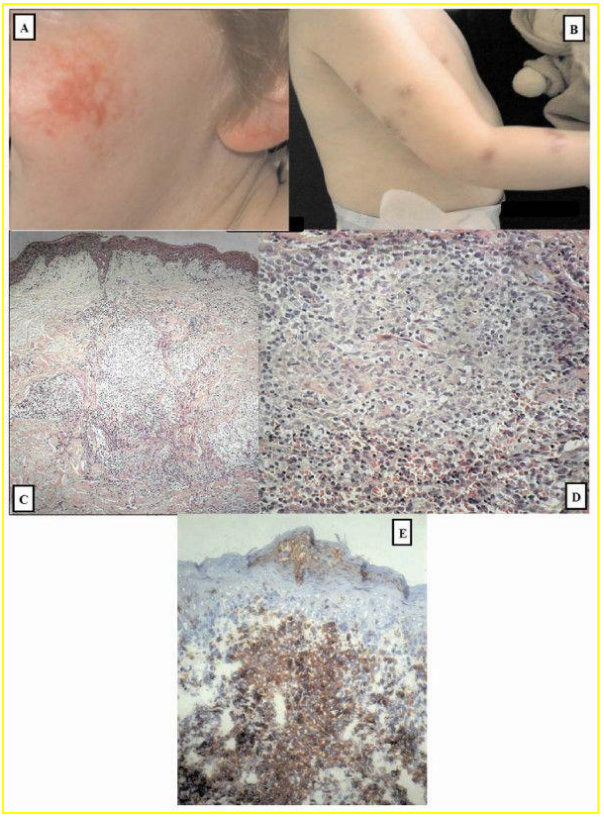
RTS - Hyperkeratosis

Often painful! Occur in ≅ 30%
With nail changes, speaks to difference in keratin function…
- (possible therapeutic options)

RTS – Granulomatous Lesions

- Have been reported previously in patients with immunodeficiency states
- Thickened areas of skin growths
- SOME reports of immunodeficiency (RARE) in RTS

  Orphanet J Rare Dis 2010;5:37



Rothmund Thomson Syndrome Dental

- Caries; pulp involvement by radiography*
- Congenital anodontia*
- Microdontia
- Overall incidence of dental/RTS:
  - 27%-59%

BMJ Case Rep 2015;doi:10.1136/bcr-2015-209994

Rothmund-Thomson Syndrome

Rothmund-Thomson Syndrome and Mouse Model Findings

Table 2. Comparison of reported symptoms of Rothmund–Thomson syndrome and *Recql4*-deficient mice

	Recql4-deficient mice				Rothmund–Thomson syndrome	Premature aging
	Frequency (%)	(*n*)	Examination	pc26/pc107[a]		
Skin changes						
Poikiloderma	0	(4)	Histologic	+/NT[d]	+	
Skin atrophy	100	(4)	Histologic	+/NT[d]	+	+
Colorless hair	65	(23)	Macroscopic	+/+	+	+
Hair loss	52	(23)	Macroscopic	+/+	+	+
Short stature	100	(23)	Macroscopic	+/+	+	+
Bone dysplasia	100	(4)	Microscopic, X-ray	+/+	+	+
Dystrophic teeth	100	(4)	Microscopic, X-ray	+/+	+	+
Cataracts	0	(23)	Macroscopic[b]	+/+	+	+
Immunological abnormality	100	(6)	Shrunken thymus	+/+	Rare	+
Malignancies	0	(16)	Macroscopic	+/+	+	+
X-ray high sensitivity	0	(2)	Cytologic (MEF)[c]	+/+	?[e]	
UV high sensitivity	0	(2)	Cytologic (MEF)[c]	+/+	?[e]	

Note: Poikiloderma not seen in this mouse model
Not all RTS cells are Xray/UV sensitive

Hum Mol Genet 2003

RTS and Malignancies

TABLE I. Patients With RTS and Multiple Malignant Diseases Reported in the Literature

Refs.	Number of RTS patients	Age at diagnosis of first malignant disease (years)	Primary malignant disease	Second malignant diseases
Borg et al. [1998]	1	26	Multiple skin cancers	Squamous cell carcinoma of the tongue, subsequent lung metastases
Davies [1982]	1	32	Squamous cell carcinoma	Fibrosarcoma
Hicks et al. [2007], Wang et al. [2001]	41	4–18	13 osteosarcoma	1 patient developed Hodgkin's lymphoma B-cell type and subsequent squamous carcinoma of esophagus, 1 patient developed squamous carcinoma in situ of the skin
Spurney et al. [1998], Aung et al. [2002]	1	15	Multifocal osteosarcoma	Secondary nasopharyngeal non-Hodgkin lymphoma
Stinco et al. [2008]	1	63	Basal cell carcinoma	Basal cell carcinoma and squamous cell carcinoma
Werder et al. [1975]	1	32	Squamous cell carcinoma	Parathyroid adenoma

Other malignancies rarely reported

Am J Med Genet Part A 2010;152A:1575

Rothmund-Thompson
Skin Malignancy

- Squamous cell CA
  -Verrucous CA
  -Tongue*
- Bowen's disease
- Basal cell CA

  May occur at younger age

  AJMG A 2010;152A:1575
  J Dermatol 2008;35:154
  *Br J Plast Surg 1998;51:646

Rothmund-Thomson-
Skin Management

- Photoprotection; ? Necessary (YES!)
- Emollients (dry skin, routine)
- ? Topical retinoids (hyperkeratoses)
- ? Topical salicylic acid (hyperkeratoses)
- ? Filing methods (hyperkeratoses/nails)
- Laser; Pulsed-dye, other lasers
  -ectatic/dilated vessels
  -hyperpigmentation
  -textural skin changes
- F/U of discrete skin lesions !!!

Eucerin®

Aquaphor
HEALING OINTMENT

EpiCeram
Skin Barrier Emulsion

Vaseline

Cost of Moisturizers

Vaseline	$4.17	13 oz
Eucerin	$15.00	16 oz
Cetaphil	$13.00	16 oz
Cetaphil Restoraderm	$18.00 +	10 oz
Aquaphor	$13.00	14 oz
Aveeno Eczema Care	$12.00	6 oz
Cerave	$17.00	16 oz
Vanicream	$14.00 +	16 oz
Atopiclair (Rx)	$36-$89.00	100 ml
Epiceram (Rx)	$89.00-$241	90 gm/3.2 oz

Drug Facts

Active Ingredients	Purpose
Avobenzone 3% Homosalate 10% Octyl methoxycinnamate 7.5%	Sunscreen

Uses

- helps prevent sunburn
- if used as directed with other sun protection measures (see **Directions**), decreases the risk of skin cancer and early skin aging caused by the sun

Warnings

For external use only

Do not use on damaged or broken skin

When using this product keep out of eyes. Rinse with water to remove.

Stop use and ask a doctor if rash occurs

Keep out of reach of children. If product is swallowed, get medical help or contact a Poison Control Center right away.

Directions

- apply liberally 15 minutes before sun exposure
- reapply:
  - after 40 minutes of swimming or sweating
  - immediately after towel drying
  - at least every 2 hours
- **Sun Protection Measures.** Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a broad spectrum SPF of 15 or higher and other sun protection measures including:
  - limit time in the sun, especially from 10 a.m. – 2 p.m.
  - wear long-sleeve shirts, pants, hats, and sunglasses
- children under 6 months: Ask a doctor

Inactive ingredients

aloe extract, barium sulfate, benzyl alcohol, carbomer, dimethicone, disodium EDTA, jojoba oil, methylparaben, octadecene/MA copolymer, polyglyceryl-3 distearate, phenethyl alcohol, propylparaben, sorbitan isostearate, sorbitol, stearic acid, tocopherol (vitamin E), triethanolamine, water

Other information

- protect this product from excessive heat and direct sun

Questions or comments?

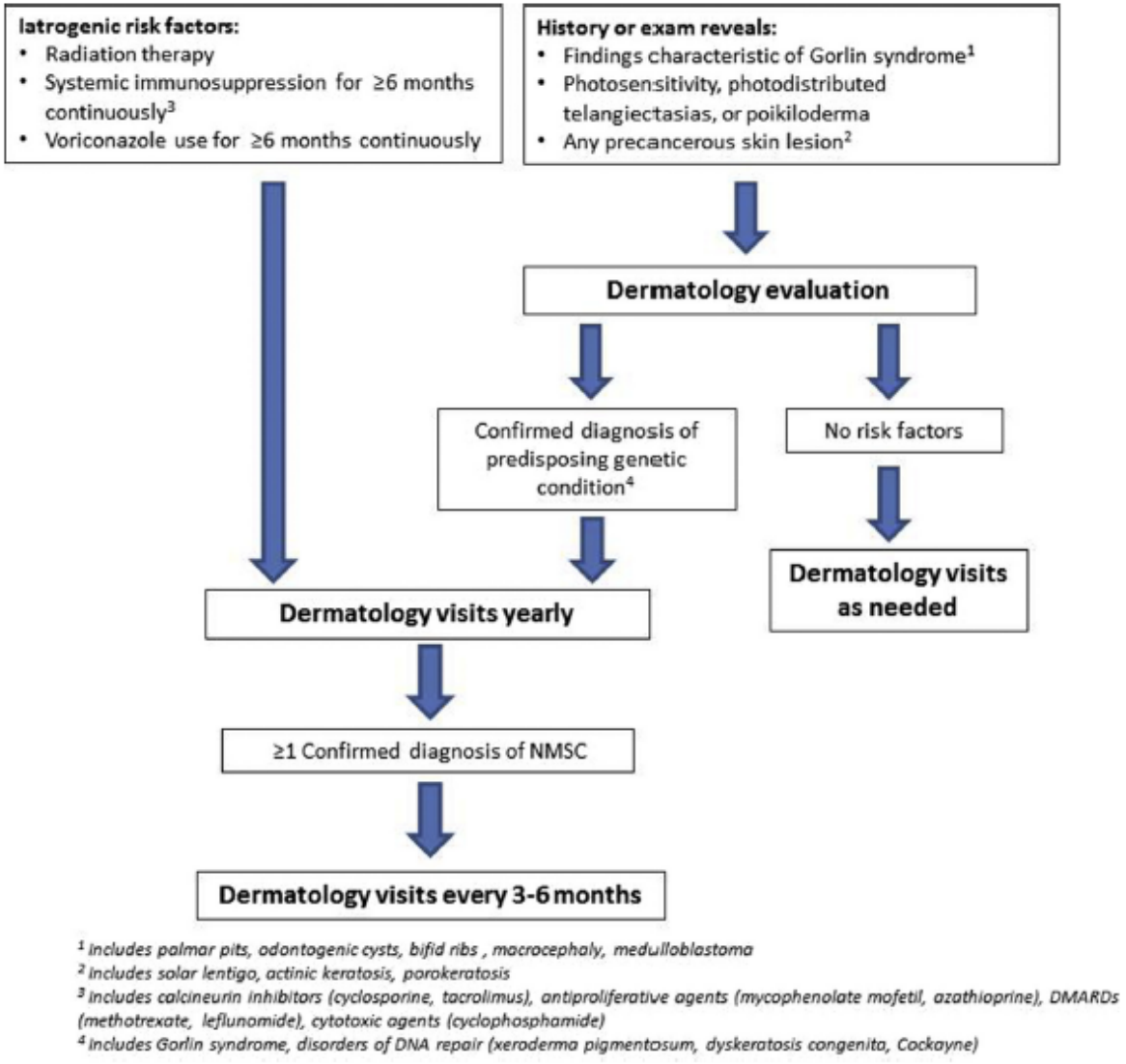
Call toll free 1-800-XXX-XXXX

Sunscreen Labeling and Sun Protection

- Broad Spectrum; requires both UVA coverage AND SPF 15 or higher
  - ultimately max SPF 50+
- No “waterproof”, “sweatproof”, “sunblock” claims
- Water resistant: 40 mins or 80 mins
- Clothing and hats

Skin Tumors

- Biopsy of suspicious growths
- Excision
  - Mohs' surgery
- Systemic therapies
- Topical management
  - Imiquimod
  - 5-Fluorouracil (5-FU)
  - Others!



[1] *includes palmar pits, odontogenic cysts, bifid ribs , macrocephaly, medulloblastoma*
[2] *includes solar lentigo, actinic keratosis, porokeratosis*
[3] *includes calcineurin inhibitors (cyclosporine, tacrolimus), antiproliferative agents (mycophenolate mofetil, azathioprine), DMARDs (methotrexate, leflunomide), cytotoxic agents (cyclophosphamide)*
[4] *includes Gorlin syndrome, disorders of DNA repair (xeroderma pigmentosum, dyskeratosis congenita, Cockayne)*

Pediatric (Non-melanoma) Screening Recommendations (Gorlin/Basal Cell Nevus Syndrome)
J Pediatr 2019

Management – Skin CA*

Non-surgical treatment	Treatment course	1-y BCC clearance rate (adult)
5-Fluorouracil (topical)[a]	Twice daily for 12 wk	90%-93%
Imiquimod (topical)	5 times weekly for 6 wk	75%-87%
Solasodine glycoalkaloids (topical)	Twice daily under occlusion for 8 wk	78%
Ingenol mebutate (topical)[a]	Once daily (+/– occlusion) for 7 d	63%
Tazarotene (topical)	Once daily for 24 wk	28%-64%
5-Fluorouracil (intralesional)	Once weekly for 6 wk	91%
Laser therapy[b]	4 treatments at 3-wk intervals	79%-100%
ALA photodynamic therapy	2 illuminations at 1-h intervals	89%-97%
MAL photodynamic therapy	2 illuminations at 1-h intervals	75%-85%

Additional: curettage, excision, oral retinoids, vismodegib, sonidegib

Pediatr Dermatol 2020

Transformative Teams in Healthcare

Communication and Collaboration Seminar

- Students in: Medicine, Nursing, Social Work, Pharmacy, Educational Psychology

- Parents help facilitate discussion
  -Experience with dx
  -What has gone well… what went badly
  -What could be better
  -Did the “team” function as a team?
  -What were key things having greatest impact?

Looking ahead

- Quality
- Clinical and economic outcomes
- Cross-disciplinary relationships (as part of disease models)
- Patients/Families !!!

RECQ-Management

- Multidisciplinary !!!

  -Dermatology
  -Ophthalmology
  -Genetics
  -Oncology
  -Orthopedics
  -*Psychosocial*
  -? Dental
  -Others… *Patients and Families!!!*

To close

- "The good physician knows his (her) patients through and through… Time, sympathy and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, *for the secret of the care of the patient is in caring for the patient*."

Peabody FW. JAMA 1927