Dermatologic (and other) Manifestations of Rothmund-Thomson Syndrome

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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
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

- \( \text{? Link to aging and cancer susceptibility (RECQ/RECQL)} \)
Rothmund-Thomson Syndrome and Aging

Table 1
Clinical features of aging in RTS patients

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

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>
<thead>
<tr>
<th>Skin changes</th>
<th>Recql4-deficient mice</th>
<th>n</th>
<th>Examination</th>
<th>pc26/pc107</th>
<th>Rothmund–Thomson syndrome</th>
<th>Premature aging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poikiloderma</td>
<td>0</td>
<td></td>
<td>Histologic</td>
<td>+/-NTd</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin atrophy</td>
<td>100</td>
<td></td>
<td>Histologic</td>
<td>+/-NTd</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Colorless hair</td>
<td>65</td>
<td></td>
<td>Macroscopic</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hair loss</td>
<td>52</td>
<td></td>
<td>Macroscopic</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Short stature</td>
<td>100</td>
<td></td>
<td>Macroscopic</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone dysplasia</td>
<td>100</td>
<td></td>
<td>Microscopic, X-ray</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dystrophic teeth</td>
<td>100</td>
<td></td>
<td>Microscopic, X-ray</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cataracts</td>
<td>0</td>
<td></td>
<td>Macroscopicb</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunological abnormality</td>
<td>100</td>
<td></td>
<td>Shrunken thymus</td>
<td>+/-</td>
<td>Rare</td>
<td>+</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0</td>
<td></td>
<td>Macroscopic</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>X-ray high sensitivity</td>
<td>0</td>
<td></td>
<td>Cytologic (MEF)c</td>
<td>+/-</td>
<td>?c</td>
<td></td>
</tr>
<tr>
<td>UV high sensitivity</td>
<td>0</td>
<td></td>
<td>Cytologic (MEF)c</td>
<td>+/-</td>
<td>?c</td>
<td></td>
</tr>
</tbody>
</table>

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

Hum Mol Genet 2003
RTS and Malignancies

Other malignancies rarely reported


<table>
<thead>
<tr>
<th>Refs.</th>
<th>Number of RTS patients</th>
<th>Age at diagnosis of first malignant disease (years)</th>
<th>Primary malignant disease</th>
<th>Second malignant diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borg et al. [1998]</td>
<td>1</td>
<td>26</td>
<td>Multiple skin cancers</td>
<td>Squamous cell carcinoma of the tongue, subsequent lung metastases</td>
</tr>
<tr>
<td>Davies [1982]</td>
<td>1</td>
<td>32</td>
<td>Squamous cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Hicks et al. [2007], Wang et al. [2001]</td>
<td>41</td>
<td>4–18</td>
<td>13 osteosarcoma</td>
<td>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</td>
</tr>
<tr>
<td>Spurney et al. [1998], Aung et al. [2002], Stinco et al. [2008]</td>
<td>1</td>
<td>15</td>
<td>Multifocal osteosarcoma</td>
<td>Secondary nasopharyngeal non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Werder et al. [1975]</td>
<td>1</td>
<td>32</td>
<td>Basal cell carcinoma</td>
<td>Basal cell carcinoma and squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parathyroid adenoma</td>
</tr>
</tbody>
</table>
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 !!!
## Cost of Moisturizers

<table>
<thead>
<tr>
<th>Moisturizer</th>
<th>Price</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaseline</td>
<td>$4.17</td>
<td>13 oz</td>
</tr>
<tr>
<td>Eucerin</td>
<td>$15.00</td>
<td>16 oz</td>
</tr>
<tr>
<td>Cetaphil</td>
<td>$13.00</td>
<td>16 oz</td>
</tr>
<tr>
<td>Cetaphil Restoraderm</td>
<td>$18.00 +</td>
<td>10 oz</td>
</tr>
<tr>
<td>Aquaphor</td>
<td>$13.00</td>
<td>14 oz</td>
</tr>
<tr>
<td>Aveeno Eczema Care</td>
<td>$12.00</td>
<td>6 oz</td>
</tr>
<tr>
<td>Cerave</td>
<td>$17.00</td>
<td>16 oz</td>
</tr>
<tr>
<td>Vanicream</td>
<td>$14.00 +</td>
<td>16 oz</td>
</tr>
<tr>
<td>Atopiclair (Rx)</td>
<td>$36-$89.00</td>
<td>100 ml</td>
</tr>
<tr>
<td>Epiceram (Rx)</td>
<td>$89.00-$241</td>
<td>90 gm/3.2 oz</td>
</tr>
</tbody>
</table>
**Drug Facts**

**Active Ingredients**
- Avobenzone 3%
- Homosalate 10%
- Octyl methoxycinnamate 7.5%

**Purpose**
- 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. to 2 p.m.
  - Wear long-sleeve shirts, pants, hats, and sunglasses
  - Children under 6 months: Ask a doctor

**Inactive ingredients**
- Aloe extract, benzyl alcohol, carbenzolate, dimethicone, disodium EDTA, jojoba oil, methylparaben, octadecone/MA copolymer, polyglyceryl-3 distearate, phenethyl alcohol, propylparaben, sorbitan stearate, 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-XXX
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!
Pediatric (Non-melanoma) Screening Recommendations (Gorlin/Basal Cell Nevus Syndrome)

J Pediatr 2019
## Management – Skin CA*

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

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