

Case Report

Diagnostic Challenges of Rothmund-Thomson Syndrome in Infancy: A Case Report from a Resource-Limited Setting

Marcella Anggatama ^{1,2}, Hanggoro Tri Rinonce ^{2,3}, Dwinanda Almira Rizkiani ^{1,2}, Eddy Supriyadi ^{2,4}, Raden Roro Rini Andayani ^{1,2}, Yohanes Widodo Wirohadidjojo ^{1,2}, Retno Danarti ^{1,2,*}

1. Department of Dermatology and Venereology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; E-Mails: marcellaanggatama@gmail.com; dwinanda.almira@gmail.com; rr.riniandayani@gmail.com; yohanes.widodo@ugm.ac.id; danarti@ugm.ac.id; ORCID: 0000-0001-7594-184X
2. Sardjito Hospital, Yogyakarta, Indonesia; E-Mails: hanggoro_rinonce@ugm.ac.id; e.supriyadi@ugm.ac.id
3. Department of Anatomical Pathology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
4. Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

* **Correspondence:** Retno Danarti; E-Mail: danarti@ugm.ac.id; ORCID: 0000-0001-7594-184X

Academic Editor: Fabrizio Stasolla

Collection: [Rare Genetic Syndromes: From Diagnosis to Treatment](#)

OBM Genetics

2025, volume 9, issue 4

doi:10.21926/obm.genet.2504320

Received: October 26, 2025

Accepted: December 07, 2025

Published: December 11, 2025

Abstract

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive disorder characterized by early-onset poikiloderma and multisystem abnormalities. Diagnosis is often confirmed through genetic testing, but in many resource-limited settings, molecular studies are unavailable, necessitating reliance on clinical and histopathological evaluation. We report a 1-year-old boy referred for assessment of progressive pigmented skin lesions. The patient was referred by a pediatrician with febrile neutropenia, bicytopenia suspicious for acute lymphoblastic leukemia, undescended testes, severe malnutrition, and growth retardation.



© 2025 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

Dermatological examination revealed poikilodermatous changes on sun-exposed areas and extremities. Differential diagnoses included Rothmund–Thomson syndrome, dyskeratosis congenita, Bloom syndrome, livedo racemosa, livedo reticularis, poikiloderma with neutrophilia, Kindler syndrome, and cutis marmorata telangiectatica congenita. Histopathology demonstrated epidermal atrophy, basal cell vacuolization, melanin incontinence, and telangiectasia, consistent with congenital poikiloderma. Immunofluorescence excluded Bloom syndrome. In correlation with clinical and pathological findings, RTS was determined to be the most likely diagnosis. This case highlights the complexity of diagnosing RTS in the absence of genetic testing. It underscores the importance of integrating clinical, dermatological, and histopathological findings, even though a definitive diagnosis remains based on genetic testing results. Early recognition is critical given the risk of malignancy and the need for lifelong surveillance and multidisciplinary care.

Keywords

Dyskeratosis congenita; poikiloderma; resource-limited; Rothmund-Thomson syndrome

1. Introduction

Rothmund–Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis, first described by Rothmund in 1868 and later expanded by Thomson in 1923, characterized by early-onset poikiloderma and multisystem abnormalities [1]. Rothmund–Thomson syndrome (RTS) is genetically heterogeneous, comprising four recognized subtypes associated with mutation in *ANAPC1* (RTS type 1), *RECQL4* (RTS type 2), *CRIPT* (RTS type 3), and *DNA2* (RTS type 4) [1-3].

In clinical practice, diagnosis relies on recognition of the characteristic progression of poikiloderma from infancy, together with growth retardation and ectodermal features [2, 4]. Diagnosing RTS can be challenging due to its phenotypic overlap with other inherited poikilodermatous syndromes, such as dyskeratosis congenita, Bloom syndrome, and livedoid dermatosis [5]. In well-resourced settings, confirmation is achieved through genetic testing [6]; however, in resource-limited settings where genetic testing is unavailable, distinguishing RTS from phenotypically similar disorders such as dyskeratosis congenita, Bloom syndrome, or poikiloderma with neutropenia poses a significant challenge and requires careful clinicopathological correlation.

This case report describes a 1-year-old boy with multisystem involvement and progressive poikiloderma. We highlight the complexity of establishing a clinical diagnosis of RTS in a resource-limited setting where genetic testing was unavailable, and emphasize the importance of a multidisciplinary approach to management.

2. Case Report

A 1-year-old boy was referred to the Department of Dermatology and Venereology for consultation from the Department of Pediatrics. The primary reason for referral was evaluation of progressive pigmented skin lesions. The pediatric team had admitted the patient with an initial diagnosis of febrile neutropenia with suspicion of acute lymphoblastic leukemia (ALL) due to

recurrent fever for the past 3 months, undescended testes, and severe malnutrition characterized by both severe underweight and severe stunting.

The mother first noticed hypopigmented patches on the left cheek three months before admission, which gradually became bilateral and developed a reticulated pattern. The lesions darkened when exposed to cold air and became erythematous with sun exposure. One month before admission, she visited a local dermatologist for new net-like hyperpigmented patches on the limbs; a topical agent of unknown composition was prescribed, but lesions progressed further and extended to the trunk, buttocks, and genital area. The child was born at term, weighing 2.2 kg and measuring 42 cm. Additional history revealed poor weight and height gain since infancy, delayed eruption of primary teeth, and sparse scalp hair, along with thinning of the eyebrows and eyelashes. There was no delay in psychomotor development, and there was no history of severe infections aside from the recurrent febrile episode, and no family history of similar skin or systemic problems.

On the day of admission, the physical examination showed an undernourished boy weighing 6.6 kg with a height of 66 cm. Anthropometric indices revealed WAZ = -3.64 and HAZ = -4.61, consistent with severe underweight and stunting. Vital signs were within normal limits. General examination noted hepatomegaly (4 cm below the costal margin) and impalpable testes. Dermatological examination revealed multiple patches of hyperpigmentation and hypopigmentation forming a reticulate pattern over the bilateral malar regions, arms, trunk, gluteal area, and both lower extremities, consistent with poikilodermatous changes (Figure 1). We also found sparse hair, sparse eyelashes, and unerupted teeth. We found no abnormalities on the nails and oral mucosa. The differential diagnoses based on clinical manifestation for this patient were Rothmund–Thomson syndrome, dyskeratosis congenita, Bloom syndrome, livedo racemosa, livedo reticularis, poikiloderma with neutrophilia, Kindler syndrome, and cutis marmorata telangiectatica congenita.



Figure 1 Clinical manifestation of the patient. A-C: Poikilodermatous changes on both cheeks and sparse hair. D-E: Poikilodermatous changes on both legs, F-H: Poikilodermatous changes on both arms. I: No lesion on the abdominal area. J: Hyperpigmented patches on the back. K: No abnormalities in the genital area. Red Arrow: Reticulated pattern of poikilodermatous changes.

Supporting examination revealed that on the day of admission, the leukocyte count was 3700/ μ L (leukopenia) and the neutrophil count was 1100/ μ L, which did not support the initial suspicion from the pediatric department of ALL. Further bone marrow examination also did not match ALL findings, as there was <20% of blast cells. Further neutrophil counts were 1280/ μ L and 1300/ μ L on the third and sixth day of admission, suggesting only transient neutropenia. Our pediatrician concluded that the condition was related to infection rather than hematological malignancy, and we disregarded the possibility of dyskeratosis congenita based on regular bone marrow findings. Histopathological examination of a skin biopsy from the right femoral region showed epidermal orthokeratosis with a basket-weave pattern, focal epidermal atrophy, spongiosis, and basal cell vacuolization. The upper dermis demonstrated melanin incontinence, dilated blood vessels, and patchy lymphohistiocytic infiltration with scattered neutrophils. No vascular occlusion or malignancy was identified (Figure 2). These histopathological features were consistent with congenital poikiloderma, suggesting RTS or Bloom syndrome. Direct immunofluorescence studies showed no deposition of C3c, IgG, IgM, or IgA at the dermoepidermal junction, findings arguing against congenital telangiectatic erythema (Bloom's syndrome), and led to the final diagnosis of RTS. Further X-rays of the upper and lower limbs did not reveal any abnormalities. No radial ray defects, metaphyseal dysplasia, osteopenia, or pathologic fractures were identified. The thumbs were well formed without hypoplasia, and there were no signs of delayed bone maturation or structural deformities.

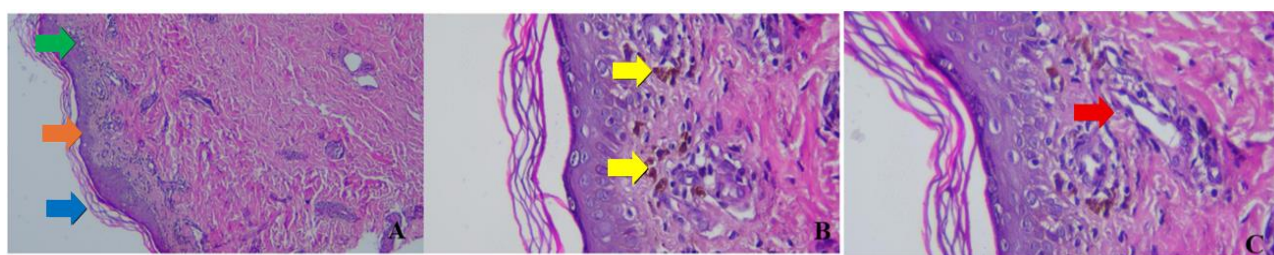


Figure 2 Histopathological findings with H&E Staining (A) Orthokeratosis with a basket weave pattern (blue arrow), focal atrophy (orange arrow), spongiosis, and focal basal cell vacuolization (green arrow). (B) Pigment incontinence is seen within the upper dermis (yellow arrow). (C) The dermis shows vascular dilatation accompanied by patchy infiltration of inflammatory cells (red arrow).

Differentiating between RTS types 1–4 was limited by the unavailability of molecular testing. Genetic tests for *RECQL4*, *ANAPC1*, *CRIP1*, and *DNA2* are not accessible in our clinical setting, and sending samples abroad was financially prohibitive for the family. Thus, diagnosis relied on clinical features—infancy-onset poikiloderma, ectodermal findings (sparse hair, delayed dentition), congenital growth failure, and histopathology—making RTS type 1 or RTS type 2 the most likely possibilities.

The patient received dermatologic therapy consisting of pseudoceramide lotion, topical hydrocortisone 0.1% for gluteal erythema, and broad-spectrum photoprotection (SPF 33). Pediatric management included intravenous ciprofloxacin for infection, correction of hyponatremia, micronutrient supplementation, and high-calorie nutritional support. The multidisciplinary evaluation included dental, nutritional, and orthopedic consultations.

Follow-up was limited due to socioeconomic constraints. A telephone interview two weeks after discharge revealed that poikiloderma persisted but had not progressed, and the child had no

recurrent fever or infection. Laboratory follow-up was not available. This limited follow-up reflects the challenges of managing rare genetic disorders in low-resource settings.

2.1 Ethics Statement

Written informed consent for publication, including the use of clinical images, was obtained from the patient's legal guardian. Ethical standards were maintained throughout the patient's evaluation and treatment.

3. Discussion

The diagnosis of RTS in this patient illustrates the complexity of evaluating rare genetic syndromes in settings without access to molecular diagnostics [2, 6]. While genetic testing remains the gold standard for confirmation, it was unavailable in this case due to the inaccessibility of the testing in our clinical setting, and sending samples abroad was financially prohibitive for the family. Therefore, the diagnostic process required integrating clinical features and histopathological findings while excluding differential diagnoses.

Clinically, we considered several differential diagnoses, including Rothmund–Thomson syndrome, dyskeratosis congenita, Bloom syndrome, livedo racemosa, livedo reticularis, poikiloderma with neutrophilia, Kindler syndrome, and cutis marmorata telangiectatica congenita.

Rothmund–Thomson syndrome often presents in infancy with erythematous facial lesions that gradually evolve into poikiloderma involving sun-exposed areas. Our patient demonstrated this classical pattern of cutaneous progression. Additional systemic findings, including congenital-onset growth retardation, delayed dentition, and sparse hair, further supported the diagnosis of RTS. These ectodermal abnormalities are consistent with both RTS Type 1 and RTS Type 2; however, the severity of growth failure and multisystem involvement observed in this case is more typical of the RTS Type 2 spectrum, although the absence of skeletal abnormalities makes precise subtyping difficult in the absence of genetic testing [6, 7].

The overlap with other poikilodermatous syndromes complicated the diagnostic pathway. Dyskeratosis congenita was considered because of the patient's cytopenia; however, the absence of nail dystrophy and oral leukoplakia argued against this diagnosis [8]. Bloom syndrome was suspected based on poikiloderma and growth retardation, but was excluded based on negative immunofluorescence results and the absence of recurrent infections or narrow facial features. Livedo racemosa and livedo reticularis were less likely since histopathology showed no vascular occlusion or thrombosis. Poikiloderma with neutrophilia was ruled out because the patient did not exhibit persistent neutropenia or palmoplantar keratoderma. Cutis marmorata telangiectatica congenita was excluded due to the absence of congenital vascular malformations and localized skin atrophy. Kindler syndrome was also considered, given the early-onset poikiloderma, but no trauma-induced blisters, mucosal fragility, or acral atrophy were observed, making this diagnosis unlikely. Considering the combination of early-onset poikiloderma on sun-exposed areas, growth retardation, sparse hair, and compatible histopathological findings, the most plausible diagnosis was Rothmund–Thomson syndrome [6, 9]. Histopathology also played an essential role in differentiating differential diagnoses in patients with poikiloderma. The biopsy in our patient showed epidermal atrophy, basal vacuolar alteration, telangiectasia, and pigment incontinence, features consistent with congenital poikiloderma typically seen in RTS [6]. Notably, there was no subepidermal blistering or dermo-

epidermal separation, which argues strongly against Kindler syndrome. Kindler syndrome characteristically shows trauma-induced subepidermal clefts, vacuolar degeneration of the basal layer, pigment incontinence, and ultrastructural abnormalities of the basement membrane (including reduplication of the lamina densa, widening of the lamina lucida, and multiple cleavage planes), none of which were present in our specimen [10]. In contrast, Bloom syndrome may show a *lupus-like interface dermatitis* with prominent basal vacuolar changes, basement membrane thickening, perifollicular infiltrates, and colloid bodies; however, our biopsy demonstrated only focal basal vacuolization without interface dermatitis or basement membrane thickening, making Bloom syndrome unlikely. Further direct immunofluorescence test also revealed no deposition of C3c, IgG, IgM, or IgA along the dermoepidermal junction [11]. Taken together, the absence of subepidermal blistering, lack of basement membrane disruption, and the presence of classic poikilodermatous features support RTS over Kindler syndrome and Bloom syndrome in this case. Immunofluorescence further narrowed the possibilities, allowing Bloom syndrome to be excluded [12]. Eventually, we summarized the differential diagnosis in this case in Table 1. Our final diagnosis was RTS, but the type was not determined yet since no genetic testing was done in our patient.

Table 1 Features distinguishing differential diagnosis of clinical poikilodermatous changes in the skin.

Feature	RTS Type 1 [2]	RTS Type 2 [2]	PN [6]	Dyskeratosis Congenita [6, 8]	Bloom Syndrome [11, 12]	Kindler Syndrome [6, 10]	Our Patient
Genetic Basis	<i>ANAPC1</i> mutation, Autosomal Recessive	<i>RECQL4</i> mutation, Autosomal Recessive	<i>USB1</i> mutation	Multiple genes (<i>DKC1</i> common)	<i>BLM</i> mutation, Autosomal recessive	<i>FERMT1</i> mutation, Autosomal recessive	Not tested (unavailable)
Onset of Poikiloderma	Infancy	Infancy (<6 months)	Infancy	Childhood/adolescence	Infancy: early childhood	Early childhood (may start with blistering)	Infancy (~6-7 months)
Pattern of Poikiloderma	Face then spread to limbs	Face then spread limbs	Generalized early	Reticulated; progressive	Telangiectatic erythema develops into poikiloderma	Acral to generalized; associated with trauma	Face to limbs, did not associate with trauma
Early Skin Findings	Facial erythema	Facial erythema	None specific	Nail & mucosal changes	Telangiectatic erythema	Trauma-induced blisters, acral fragility	Erythematous patches when exposed to the sun
Hair Abnormalities	Sparse scalp/brows/lashes	Sparse scalp/brows/lashes	Absent (normal hair)	Variable	Mild	Normal or mildly sparse	Sparse hair + eyebrows thinning
Nail Changes	None or mild	Absent	None	Nail dystrophy typical	Normal	Nail dystrophy may occur	Normal
Dental Abnormalities	Delayed eruption, microdontia	Delayed eruption, microdontia	Absent	Frequent	Mild	Not characteristic	Delayed eruption

Skeletal Abnormalities	Typically absent	Characteristic: radial ray defects, osteopenia	Absent	Absent	Absent	Absent	Normal skeletal examination
Growth Pattern	Mild–moderate failure to thrive	Severe congenital failure to thrive	Mild–moderate	Present	Severe proportional short stature	Normal or mild ↓	Failure to thrive
Hematologic Features	Generally normal	Possible mild cytopenias	Persistent severe neutropenia	Bone marrow failure/pancytopenia	Immunodeficiency possible	None	Transient neutropenia
Infection Susceptibility	Normal	Mild	Recurrent infections	Recurrent infections	Recurrent infections	No ↑	Mild
GI Symptoms	None	None	Chronic diarrhea	Variable	Rare	None typical	None
Photosensitivity	Present	Present	Not typical	Variable	Marked	Possible	Present
Histopathology	Poikiloderma	Poikiloderma	Non-specific	Atrophy + fibrosis	Telangiectasia	Dermal–epidermal separation; reduplication of the basement membrane	Congenital poikiloderma
Key Distinguishing Clues	Poikiloderma + ectodermal findings; no skeletal defects	Poikiloderma + skeletal anomalies + cancer risk	Persistent neutropenia + diarrhea + normal hair	Nail dystrophy + leukoplakia + marrow failure	Narrow facies + telangiectasia + infections	Acral blistering, mucosal fragility, trauma-induced changes	Fits RTS Type 1 or atypical Type 2; no blistering = not Kindler; excludes PN, DC, BS

This case underscores the diagnostic importance of a multidisciplinary approach in resource-limited environments where genetic testing is limited [13, 14]. Pediatricians, dermatologists, and pathologists collaborated to refine the differential diagnosis and establish a working conclusion of RTS. Recognizing RTS has critical implications beyond dermatological management. Affected children face a high lifetime risk of malignancy, especially osteosarcoma in RTS type 2, and therefore require long-term cancer surveillance involving a multidisciplinary approach [6]. Supportive care, such as strict photoprotection, nutritional support, dental monitoring, and endocrine evaluation, is equally vital in optimizing quality of life [4, 15].

4. Conclusion

Rothmund-Thomson syndrome is a rare inherited disorder that presents significant diagnostic challenges in resource-limited settings where genetic testing is unavailable. In such cases, careful correlation of clinical features, histopathology, and immunopathology remains essential to guide diagnosis. This case highlights the importance of maintaining a high index of suspicion for RTS in infants with poikiloderma and growth abnormalities. Early recognition is vital, as timely interventions, cancer surveillance, and multidisciplinary management can substantially alter prognosis and quality of life.

Author Contributions

Marcella Anggatama was responsible for patients' data collection, drafted the case report manuscript, and reviewed and approved the final version for publication. Hanggoro Tri Rinonce contributed to the histopathological evaluation and interpretation of the skin biopsy findings, providing essential input for establishing the final diagnosis. Dwinanda Almira Rizkiani, Raden Roro Rini Andayani, and Yohanes Widodo Wirohadidjojo assisted in drafting the manuscript and reviewed and approved the final version for publication. Eddy Supriyadi contributed to the interpretation of clinical data, assisted in drafting the manuscript, and reviewed and approved the final version for publication. Retno Danarti was responsible for providing oversight and guidance in case report preparation, assisting in interpreting clinical data, revising the manuscript critically for intellectual content, and finalizing and approving the manuscript for submission and publication. All authors have read and approved the published version of the manuscript.

Funding

The authors have received no financial support for the research, authorship, or publication of this article.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Gökten DB, Mercan R. Rothmund-Thomson syndrome: Unpacking a rare diagnosis. *Rom Med J.* 2024; 71: 55.

2. Martins DJ, Di Lazzaro Filho R, Bertola DR, Hoch NC. Rothmund-Thomson syndrome, a disorder far from solved. *Front Aging*. 2023; 4: 1296409.
3. Wang T, Chen L, She Q, Dong Y, Deng Y. Four novel RECQL4 mutations in four Chinese patients with Rothmund-Thomson syndrome and analysis of RECQL4 mRNA expression level in one typical patient. *J Dermatol Sci*. 2018; 91: 335-337.
4. Sánchez-Padilla AP, Valencia-Herrera AM, Toledo-Bahena ME, Mena-Cedillos CA, Toussaint-Caire S. Rothmund-Thomson syndrome: A case series from a tertiary pediatric hospital in Mexico. *Bol Med Hosp Infant Mex*. 2022; 79: 56-61.
5. Demerdjieva Z, Trifunova BK, Damevska S. A pediatric case presenting with poikiloderma. In: *Clinical cases in pediatric skin cancers*. Cham: Springer International Publishing; 2022. pp. 61-68.
6. Rayinda T, van Steensel M, Danarti R. Inherited skin disorders presenting with poikiloderma. *Int J Dermatol*. 2021; 60: 1343-1353.
7. Memiş S, Demirtaş MS. A rare case of limb anomalies: Rothmund-Thomson syndrome. *Acta Fac Med Naissensis*. 2024; 41: 569-574.
8. Callea M, Martinelli D, Cammarata-Scalisi F, Grimaldi C, Jilani H, Grimaldi P, et al. Multisystemic manifestations in rare diseases: The experience of dyskeratosis congenita. *Genes*. 2022; 13: 496.
9. Kaneko H, Takemoto M, Murakami H, Ihara K, Kosaki R, Motegi SI, et al. Rothmund-Thomson syndrome investigated by two nationwide surveys in Japan. *Pediatr Int*. 2022; 64: e15120.
10. Mendes L, Nogueira L, Vilasboas V, Talhari C, Talhari S, Santos M. Kindler syndrome: Report of two cases. *An Bras Dermatol*. 2012; 87: 779-781.
11. McGowan J, Maize J, Cook J. Lupus-like histopathology in bloom syndrome: Reexamining the clinical and histologic implications of photosensitivity. *Am J Dermatopathol*. 2009; 31: 786-791.
12. Kasap B, Guclu-Geyik F, Alkaya DU, Cetin G, Tuysuz B. Two novel variants and follow-up findings in four children with Bloom syndrome from two families. *Clin Dysmorphol*. 2022; 31: 31-35.
13. Uslu A, Çekmen N. Perioperative management in Rothmund–Thomson syndrome: A case report. *Bali J Anesthesiol*. 2023; 7: 43-46.
14. Ay B, Akgun-Dogan O, Taylan F, Marcelis C, Abali S, Lim JY, et al. Undiagnosed hackathon ends diagnostic odyssey in a patient with *DNA2*-related Rothmund–Thomson syndrome. *Am J Med Genet A*. 2025; 197: e64179.
15. Cheung K, Shakeel M, Parkin D, Ayer J. PD14 The first documented case of Rothmund–Thomson syndrome with ultraviolet B photosensitivity confirmed by phototesting. *Br J Dermatol*. 2025; 193: ljaf085-266.