Case report

**Rothmund-Thomson Syndrome Type II: A Case Report with Genetic and Dermoscopic Insights**

.

ABSTRACT

|  |
| --- |
| **Background: Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis characterized by poikiloderma, sparse hair, skeletal anomalies, and an increased risk of malignancies, particularly osteosarcoma and skin cancers. RTS is classified into two types: Type I with an unknown genetic cause and Type II associated with mutations in the RECQL4 gene.**  **Case Report: We report the case of an 11-year-old male born to first-degree consanguineous parents, who presented with coarse, sparse hair and erythematous facial lesions since infancy, evolving into hypo- and hyperpigmented macules. Clinical examination revealed poikiloderma affecting the hands, buttocks, and feet, with skin atrophy, telangiectasias, eyebrow and eyelash alopecia, plantar hyperkeratosis, thumb hypoplasia, and psychomotor developmental delay. Dermoscopic evaluation demonstrated heterogeneous pigmentation with fine arborizing telangiectasias, without malignant features. Genetic analysis identified a pathogenic c.2335\_2356del, p.(Asp779Cysfs\*57) mutation in the RECQL4 gene, confirming the diagnosis of RTS Type II.**  **Conclusion: This case highlights the importance of considering RTS in pediatric patients presenting with poikiloderma and developmental anomalies, particularly in consanguineous populations. Genetic confirmation is essential for accurate diagnosis, and long-term surveillance is crucial due to the increased risk of malignancies associated with RTS Type II.** |

*Keywords: Rothmund-Thomson syndrome, RECQL4 mutation, poikiloderma, dermoscopy, genodermatosis, pediatric dermatology*.

1. INTRODUCTION

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis characterized by poikilodermas, sparse hair, skeletal abnormalities, and a higher risk of malignanciesnamely, osteosarcoma and skin cancers [1,2]. There are basically two types of RTS: Type I with unknown genetic cause and II, associated with mutations in RECQL4 gene [3]. This is a case in point of a Type II RTS in an 11-year-old boy which highlights the clinical features, the diagnostic process, dermoscopic findings, genetic confirmation, and a comprehensive discussion of the syndrome.

2. **Case presentation**

An 11-year-old male, born to first-degree consanguinity, came to the dermatology department of CHU Ibn-Sina, Rabat. The condition had first been noticed when he was 3 months old, with abnormal and coarse hair of slight length, along with erythematous lesions on the face, which progressively turned into macules of hypopigmented and hyperpigmented changes (Figure 1).

Clinical examination revealed poikiloderma of the hands, buttocks, and feet, characterized by the skin atrophy, mixed leucodermic and melanodermic background, and telangiectasia on the cheeks and nose. Noticing the expression of eyebrow and eyelashes alopecia, dorsal hand atrophy with changes in pigmentation, plantar hyperkeratosis, and a hypoplastic, adducted thumb. The patient was also psychomotor-delayed.

Dermoscopy was performed using a polarized dermatoscope. It showed a patchwork pattern of pigmentation with areas of hypopigmentation and hyperpigmentation studded with fine, largely linear, and arborizing vessels on the malar region. No dermoscopic features suggestive of malignancy were noted, such as atypical patterns of vascularization, irregular pigment networks, or blue-whitish veils [4].

A standard karyotype was unremarkable. In genomic tests, a c.2335\_2356del, p.(Asp779Cysfs\*57) mutation in the RECQL4 gene was identified, cementing RTS Type II diagnosis. Other analyses, including isotonic serum, echocardiography, electrolyte analysis, thyroid profile, and abdominal ultrasound, yielded completely normal results.

3. discussion

Rothmund-Thomson syndrome (RTS) is a genetically heterogeneous disorder with great clinical variability. Type II RTS arises in most genetically confirmed cases due to mutations of RECQL4 [3]. The RECQL4 gene encodes a DNA helicase involved in DNA replication, repair, and stability. A mutation within this gene causes genomic instability, leading to susceptibility to malignancies, particularly osteosarcoma and certain skin cancers [5].

This skin disorder was initially identified by Auguste Rothmund in 1868, followed by a detailed description from British dermatologist Sydney Thomson in 1923. The term "Rothmund-Thomson syndrome" (RTS) was officially introduced by William Taylor in 1957, and it remains the recognized name for the condition. RTS shows a higher prevalence in males, with an observed male-to-female ratio of 2:1 [1,6].

In general, RTS presents itself in two clinical forms. Type I manifests with poikiloderma-like skin changes, ectodermal dysplasia characteristics, and early infantile cataracts. Type II is recognized with poikiloderma, congenital skeletal abnormalities, predisposition to osteosarcoma, and neoplasms of the skin. RTS follows an autosomal recessive pattern of inheritance combined with genetic heterogeneity: Type II is associated with biallelic mutations (both homozygous and compound heterozygous) in the RECQL4 gene mapping to chromosome 8q24.3 for a helicase whose gene product is useful for DNA replication and repair; as such 65% of people tested have mutations in that gene. On the other hand, the genetic basis of Type I is unknown. RECQL4 mutations render the patient at increased risk for neoplastic development.

The clinical onset of RTS is generally in infancy with poikiloderma, which subsequently later involves the extremities and buttocks. Other features are hypoplasia of the scalp hair, eyebrows, and eyelashes, limb and skeletal malformations such as radial ray defects, dental anomalies, and growth retardation [1]. Photosensitivity, affecting about 30% of RTS patients, leads to the formation of blistering skin lesions upon exposure to sunlight. Over the years, warty keratoses could appear in other sun-keeping areas and eventually develop into skin cancers, basal cell carcinoma in the majority of cases. Also, an increase of incidence of melanoma can be seen generally from ages 20 to 30. RTS increases the risk of other neoplasms in addition to the common skin cancers, including hematologic malignancies, gastrointestinal tumors, and osteosarcoma. Our patient contained features that match the classical picture of RTS Type II-including poikiloderma, sparse hair, thumb hypoplasia, and developmental delay [5,7].

Individuals with RTS often present with various skeletal abnormalities, including shortened bones, an increased tendency for fractures, metaphyseal growth disturbances, and dysplastic alterations in the phalanges. Additionally, there may be underdevelopment (hypoplasia) of the forearm or thumb bones, as well as partial or complete absence of the patella [8]. When these osseous anomalies are observed together, they can provide important diagnostic clues. The most severe complication is the development of osteosarcoma, which is exclusively linked to patients harboring mutations in the RECQL4 gene [9]. Table 1 describes the main manifestations of RTS and their frequency of presentation.

Dermoscopy in RTS is not extensively described in the literature, but it can aid in differentiating poikiloderma from other pigmentary disorders. In our case, dermoscopy underscored the telangiectatic element of poikiloderma and heterogeneous pigmentation, correlating with chronic cutaneous changes due to atrophies and vascular dilatation [4]. The absence of malignant dermoscopic features is reassuring but does not take away from the need for close monitoring.

The diagnosis of RTS depends on clinical features and combination testing; poikiloderma is typical but, due to its non-specific nature, genetic confirmation should always be undertaken in unusual cases [3]. Other genodermatoses would be differential diagnoses within the group, whereby these would include Bloom syndrome, Cockayne syndrome, and dyskeratosis congenita.

Histopathological examination revealed features consistent with poikiloderma, including hyperkeratosis, epidermal thinning (atrophy), and vacuolar degeneration at the basal layer. Occasional apoptotic keratinocytes were identified within the basal layer. The dermis exhibited numerous telangiectatic blood vessels, scattered melanophages, and a variable inflammatory infiltrate predominantly located in the upper dermis [10,11].

Type II of RTS presents with a very high rate of cancer, with the most common being osteosarcoma, where this often presents during the teenage years. Other derived cancers also include squamous cell carcinoma and basal cell carcinoma [1,2]. Both of these warrant regular dermatology screenings along with imaging studies, which would seek a likely early detection. The prognosis of RTS largely depends on the development of malignant neoplasms. Despite this risk, there have been documented cases of individuals living beyond 50 years of age, indicating that long-term survival is possible, particularly in the absence of severe cancer-related complications [12].

The management of RTS patients relies on a multidisciplinary approach combined with genetic counseling to facilitate the early detection of syndrome-associated manifestations. This strategy ensures close monitoring to identify any signs of neoplastic development at an early stage [13]. For cutaneous lesions, the primary focus is on avoiding ultraviolet (UV) exposure through rigorous photoprotection measures. Recent evidence suggests that telangiectatic lesions respond well to treatment with pulsed dye laser [14]. In the absence of malignant tumor development, patients typically have a normal life expectancy [15].

**Table 1. The main manifestations of RTS and their frequency of presentation [16].**

|  |  |
| --- | --- |
| **Clinical manifestations** | **Percentage** |
| Skin   * Erythema and facial edema, in early ages, evolving to poikiloderma changes: atrophy, telangiectasias, hyperpigmentation, or hypopigmentation * Photosensitivity, blistering * Hyperkeratosis on hands, feet, knees * Calcinosis cutis, actinic keratosis | 90% |
| Hair  – Fine, sparse, progressing to partial or total alopecia, absence of eyebrows and eyelashes | 30% |
| Nails  – Nail dystrophy, anonychia | 30% |
| Dental disorders  – Caries, microdontia, conical teeth | 40% |
| Skeletal alterations  – Saddle nose, prognathism, agenesis of carpus and thumb, syndactyly, osteogenesis imperfecta, hyperostosis, osteoporosis | 70% |
| Ocular alterations  – Cataracts, keratoconus, coloboma, strabismus, amblyopia, microphthalmia, optic nerve atrophy, exophthalmos, glaucoma, photophobia, hypertelorism | 50% |
| Neoplasms  – Osteosarcomas, basal cell carcinoma, squamous cell carcinoma, melanoma, fibrosarcoma, lymphoma, gastric carcinoma, myelodysplastic syndrome, acute myelocytic leukemia. | 3-32% |
| Others  – Low birth weight, growth retardation, short stature, hypogonadism | 20-50% |

**Une image contenant personne, peau, lunettes de soleil, Visage humain

Le contenu généré par l’IA peut être incorrect.**

**Fig 1:  
A. Facial skin atrophy, leukoderma-hyperpigmentation, and telangiectasias involving the cheeks and nose.  
B. Leukoderma-hyperpigmentation with associated atrophy on the dorsal aspect of both hands.  
C. Poikiloderma on the buttocks.  
D. Hypoplastic and adducted thumb.**

4. Conclusion

This case underscores the importance of considering RTS in children with poikiloderma and developmental anomalies, particularly in consanguineous populations. Genetic testing for RECQL4 mutations is crucial for definitive diagnosis. Long-term surveillance for malignancies remains a cornerstone of RTS management.

Consent (where ever applicable)

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval (where ever applicable)

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

References

1. Wang LL, Levy ML, Lewis RA, Chintagumpala MM, Lev D, Rogers M, Plon SE. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am J Med Genet A. 2001;102(1):11-17.
2. Larizza L, Roversi G, Volpi L. Rothmund-Thomson syndrome. Orphanet J Rare Dis. 2010;5:2.
3. Siitonen HA, Kopra O, Kaariainen H, Haravuori H, Winter RM, Saamanen AM, Kestila M, Peltonen L. Molecular defect of RAPADILINO syndrome expands the phenotype spectrum of RECQL4 defects. Hum Mol Genet. 2003;12(21):2837-2844.
4. de Souza TA, Piva MR, Castro LS, Nakano MY. Clinical and genetic aspects of Rothmund-Thomson syndrome: A review. An Bras Dermatol. 2019;94(4):417-425.
5. Sangrithi MN, Bernal JA, Madine MA, Laskey RA, Carroll J, Venkitaraman AR. Initiation of DNA replication requires the RECQL4 protein mutated in Rothmund-Thomson syndrome. Cell. 2005;121(6):887-898.
6. Silverberg NB, Biro DE, Laude TA. What syndrome is this? Rothmund-Thomson syndrome (poikiloderma congenitale). Pediatr Dermatol. 1999;16:59-61.
7. Lu L, Jin W, Wang LL. RECQ DNA helicases and osteosarcoma. Adv Exp Med Biol. 2020;1258:37-54.
8. Simon T, Kohlhase J, Wilhelm C, Kochanek M, De Carolis B, Berthold F. Multiple malignant diseases in a patient with Rothmund-Thomson syndrome with RECQL4 mutations: case report and literature review. Am J Med Genet A. 2010;152A:1575-9. 11.
9. Piquero-Casals J, Okubo AY, Nico MM. Rothmund-Thomson syndrome in three siblings and development of cutaneous squamous cell carcinoma. Pediatr Dermatol.
10. Gupta S, De S, Srivastava V, Hussain M, Kumari J, Muniyappa K, et al. RECQL4 and p53 potentiate the activity of polymerase and maintain the integrity of the human mitochondrial genome. Carcinogenesis. 2014;35:34-45.
11. Green JS, Rickett AB. Rothmund-Thomson syndrome complicated by osteosarcoma. Pediatr Radiol. 1998;28:48-50.
12. Potozkin JR, Geronemus RG. Treatment of the poikilodermatous component of the Rothmund-Thomson syndrome with the flashlamp-pumped pulsed dye laser: a case report. Pediatr Dermatol. 1991;8:162-5
13. Ciloglu S, Duran A, Pekcan SY, Buyukdogan H. Leg ulcer in a patient with Rothmund-Thomson syndrome. Springerplus. 2015;4:572
14. Yves Sznajer H, Siitonen A, Roversi G, Dangoisse C, Scaillon M, Ziereisen F, et al. Atypical Rothmund-Thomson syndrome in a patient with compound heterozygous mutations in RECQL4 gene and phenotypic features in RECQL4 syndromes. Eur J Pediatr. 2008;167:175-81.
15. Romero Flórez A. Síndrome de Rothmund-Thomson o poiquilodermia congénita. Dermatol Rev Mex. 2012;56:354-7
16. Alicia P. Sánchez-Padilla, Adriana M. Valencia-Herrera, Mirna E. Toledo-Bahena, Carlos A. Mena-Cedillos, and Sonia Toussaint-Caire Rothmund-Thomson syndrome: a case series from a tertiary pediatric hospital in Mexico