

# Rothmund-Thomson syndrome: Unpacking a rare diagnosis

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## ABSTRACT

Rothmund-Thomson syndrome (RTS), also known as congenital poikiloderma, is a genodermatosis that appears in infancy and is characterized by poikilodermatous changes in the skin. It is a very rare and complex genetic disorder that can present with a wide range of symptoms and affect multiple systems in the body. The syndrome is inherited in an autosomal recessive manner. A 21-year-old female patient presented to our rheumatology outpatient clinic with swelling of the hands, sclerodactyly, and stiffness of the fingers with preliminary diagnosis of systemic sclerosis. She has had deformities in her feet and hands since the age of one year. Physical examination revealed poikiloderma and extremity deformities. She also had neutropenia in her bloodstream. She was diagnosed with Rothmund Thomson syndrome after genetic test results, prescribed colchicine and followed up regularly every three months. After two years of follow-up, she was diagnosed with ovarian cancer.

**Keywords:** Rothmund–Thomson syndrome, poikiloderma, deformities, cancer, RECQL4

## INTRODUCTION

Rothmund-Thomson syndrome (RTS), also known as congenital poikiloderma, is a genodermatosis that appears in infancy and is characterized by poikilodermatous changes in the skin. It is a very uncommon autosomal recessive condition marked by an early childhood facial rash, delayed growth leading to diminished height, and occasionally, intrauterine growth restriction during pregnancy, though detailed information on the fetal stage is not available [1]. It was first described by Auguste Rothmund in 1868 and then by Sydney Thomson in 1923. Two variants of the disease are recognized: RTS 1, which is less common with a prevalence of 30-35%, and RTS 2, which is more frequent, accounting for 60-65% of cases [2]. The global prevalence of RTS 2 is estimated to be fewer than one in a million. RTS 1 includes poikiloderma, ectodermal dysplasia, sparse hair and juvenile cataracts. RTS 2 is defined by poikiloderma, skeletal abnormalities and an increased risk of cancer. Diagnosing RTS hinges on clinical assessments combined with the detection of biallelic pathogenic mutations in either RECQL4 or ANAPC1 using molecular genetic tests. Type II RTS is linked to either compound heterozygous or homozygous mutations in

the RECQL4 gene. About 60% of RTS diagnoses trace back to abnormalities in RECQL4, with ANAPC1 mutations contributing to another 10%. The genetic causes for the final 30% of RTS cases are currently unknown [3]. These genetic mutations result in a defect in DNA repair, includes features such as alopecia, short stature, ectodermal changes, skeletal deformities, juvenile cataracts and a predisposition to cancer. It is a rare and complex genetic disorder that can present with a wide range of symptoms and affect multiple systems in the body [4].

RTS, characterized by hypopigmentation and hyperpigmentation of the skin named poikiloderma, is one of the syndromes associated with the aforementioned genetic mutation. At birth, patients' skin is normal, but by the third month, a red rash emerges on the cheeks. This rash then expands to the arms and legs before spreading to the buttocks. Over time, this condition progresses to include skin atrophy and the development of permanent telangiectasias, leading to the distinctive appearance observed during follow-up [5].

The syndrome is also characterized by hypogonadism, amenorrhoea, abnormalities of the radius, ulna and patella, osteopenia and bone marrow defects, which may lead to neutropenia and anemia [6]. One

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prevalent complication in RTS is cancer, particularly osteosarcoma, which affects two-thirds of patients with RECQL4 mutations. Nonetheless, other cancers are commonly observed, and the development of hematological and additional malignancies in these patients remains incompletely understood [7].

In this case report, we aim to share our insights on RTS, a condition that has been reported as extremely rare globally.

## CASE

A 21-year-old woman presented to the rheumatology clinic with various complaints, including dry and

wrinkled skin, hearing loss, digital ulcers, sclerodactyly, poikiloderma (both hypo- and hyperpigmented areas on the skin), joint pain and limb deformities with preliminary diagnosis of systemic sclerosis. (as seen in Figure 1, Figure 2). The general physical examination revealed short stature (height 152 cm), dry, transparent and wrinkled skin, stiffness and pain in the hands, foot deformities, sparse eyebrows, leg muscle atrophy and weakness, ulnar deviation and a flat nose. Her blood sample was positive for Anti-Nuclear Antibodies (ANA) with a fine mottled nucleolar pattern. An extractable nuclear antigen (ENA) panel was performed and was negative. The patient's capilleroscopic examination was not com-



**FIGURE 1.** Widespread poikilodermatous changes in skin of our patient



**FIGURE 2.** Limb deformities in our patient

patible with scleroderma. Although sclerodactyly, thickening of the skin, digital ulcers can also be seen in scleroderma, the absence of Raynaud's phenomenon seems to distract us from this diagnosis. Since the patient did not have Raynaud's phenomenon and the capillaroscopic examination and ENA profile did not seem compatible with scleroderma, genetic testing was requested for the patient. According to the genetic test results, a compound heterozygous mutation in the RECQL4 gene was detected in the patient, she was diagnosed with Rothmund-Thomson syndrome. Further investigations were performed for malignancy, cardiac, respiratory, ocular and sensorineural systems.

Cardiac examination revealed a normal ejection fraction of 65% with no cardiac defects. Pulmonary function tests showed a reduced FEV1/FVC of 0.84, and high-resolution computed tomography (HRCT) showed mosaic attenuation in both lungs and fibrotic changes in bilateral posterobasal segments.

The patient's eyes were examined by an ophthalmologist and no ocular defects were found. Sensorineural hearing loss was noted in her left ear after evaluation by an ENT specialist.

The patient was prescribed colchicine and followed up in the outpatient clinic every three months. During the follow-up period, she developed neutropenia and anemia and was prescribed granulocyte colony stimulating factor (G-CSF) by the hematology department to increase her white blood cell count.

After two years of follow-up, the patient complained of abdominal pain, particularly in the groin region. A contrast-enhanced abdominal scan was performed, which revealed a 46 mm lesion in her right adnexal region. The obstetrics and gynecology department decided to proceed with surgery, which led to the diagnosis of ovarian cancer.

## DISCUSSION

To date, approximately 400 patients have been diagnosed with Rothmund-Thomson syndrome [8]. Clinical features are highly variable between patients, making diagnosis difficult and patients may be missed. The syndrome is characterised by poikiloderma, i.e. hypo- and hyperpigmented areas of skin, telangiectasias and wrinkles [9]. Other anomalies include microdontia, periodontal pathology, uvula bifida, sparse eyebrows, hypogonadism, radial and ulnar deviation, saddle nose, palmoplantar hyperkeratosis, premature hair greying and dystrophic nails [10].

Consistent with the literature, our patient had extensive poikilodermatous lesions on the skin, deformities of the feet and hands, a saddle nose, sparse eyebrows, premature greying of the hair and dystrophic nails.

Ocular manifestations in the course of RTS are not well-defined. Case reports indicate various ocular issues associated with this syndrome, including bilateral ocular hypertension, bilateral iris dysgenesis, retinal and corneal atrophies, as well as corneal opacities [11]. Although patients may experience photosensitivity and develop juvenile cataracts, our patient did not exhibit any ocular findings [12].

Hematological and respiratory abnormalities, such as anemia and neutropenia, have also been reported in a few cases. In terms of respiratory findings, the literature notes an association between lower respiratory tract infections and RTS. Some case reports have detailed the coexistence of syndrome and bronchiectasis [13]. Sensorineural deafness has been reported in one patient, and we also found a sensorineural hearing loss [14].

In syndromes characterized by significant phenotypic variation and clinical diversity, mutation screening becomes a crucial tool. An example of such syndromes is RECQL4-related disorders [15]. In mutations of the RECQL4 gene, there is not a clear-cut genotype-phenotype relationship that can predict clinical outcomes based on the specific type of mutation. However, truncating mutations in this gene are particularly associated with RTS [16]. The precise function of the RECQL4 gene remains not completely understood, but it is known to play a critical role in DNA repair and maintenance of genomic stability [17]. Individuals with mutations in RECQL4 or other similar genes are at increased risk of developing cancers at a younger age due to their inability to effectively repair DNA damage. This underscores the need for regular monitoring and possibly earlier intervention for individuals with known predispositions to genomic instability due to defective DNA repair genes [18].

The diagnosis of the syndrome depends on its recognition in clinical practice, which can be challenging for clinicians due to its rarity. The diagnosis is established through clinical findings, including the age of onset, prevalence, and appearance of poikiloderma, along with supporting genetic testing [19].

Long-term management of this syndrome involves a multidisciplinary team consisting of dermatologists, orthopedists, pulmonologists, oncologists, and ophthalmologists. Management of the condition includes laser treatment for telangiectatic lesions, periodic ophthalmologic evaluations, and radiological assessments for symptoms that could indicate underlying issues.

The primary complication of this syndrome is cancer and prognosis varies depending on the development of malignant tumours [20]. Our patient has ovarian cancer and the prognosis depends on this diagnosis.



## CONCLUSION

We have highlighted the features of Rothmund-Thomson syndrome and defined one of the first cases in our country. The significance of this article lies in generating ideas for the identification of the syndrome. If we can identify the syndrome based on these findings, patients can be monitored early, and we can remain vigilant for any potential devel-

opment of malignancies. Early diagnosis may enhance the life expectancy of these patients.

### Conflicts of interest:

We undersign, certificate that we do not have any financial or personal relationships that might bias the content of this work.

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