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First Case of Rothmund-Thomson Syndrome Type II Presenting with Osteosarcoma in Palestine: A Case Report and Review of Literature

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Rothmund-Thomson syndrome (RTS), also known as poikiloderma congenitale, is a rare genetic disorder characterized by its pleiotropic nature, affecting multiple organ systems. Key features of RTS include early photosensitivity and facial erythema that progresses to poikiloderma, as well as sparse scalp hair, absent or sparse eyebrows and eyelashes, juvenile cataracts, short stature, and skeletal abnormalities. Patients with RTSII, often attributed to mutations in the RECQL4 helicase gene, are predisposed to osteosarcoma and skin cancer. Herein, we present a case study of an eight-year-old female with heterogeneous mutations in RECQL4. The patient exhibited an exfoliative erythematous rash on face and diaper area at the age of 7- months, along with absent eyelashes and scanty eyebrows. Subsequently, she developed osteosarcoma, and she is currently undergoing treatment.

Introduction

Rothmund-Thomson syndrome (RTS) stands as a rare autosomal recessive disorder characterized by a spectrum of clinical features, chiefly marked by facial erythema evolving into poikiloderma. Individuals affected by RTS often present with sparse scalp hair, absent or scanty eyebrows and eyelashes, juvenile cataracts, short stature, and skeletal abnormalities, which may range from overt frontal bossing and saddle nose to subtle congenital radial ray defects discernible only through radiographic analysis. Premature aging and a predisposition to cancer further outline the syndrome's complexity [1]. Manifesting typically in early infancy, around 3-6 months of age [2], the precise prevalence of RTS remains unclear, though approximately 300 cases have been documented to date [1]. Notably, two clinical subtypes, RTSI and RTSII, have been delineated, each accounting for a respective portion of reported cases. RTSI, constituting 35%-40% of cases, is typified by poikiloderma, ectodermal dysplasia, and juvenile cataracts, with underlying genetic mutations yet to be fully discovered. On the other hand, RTSII, representing 60%-65% of cases, shares the poikilodermic hallmark but is notably associated with congenital bone defects and an elevated risk of osteosarcoma in childhood, followed by an increased susceptibility to skin cancer in later life. RECQL4 helicase gene homozygous or compound heterozygous mutations underlie the pathogenesis of RTSII [1]. Interestingly, our patient had a late diagnosis of RTSIl, and while she was under closes monitoring, she developed osteosarcoma.

The unique clinical heterogeneity and cancer predisposition associated with RTS underscore the importance of heightened clinical suspicion, comprehensive evaluation, and multidisciplinary management to reduce potential complications and ensure optimal outcomes for affected individuals.

Case Presentation

Our patient, a second child of non-consanguineous parents, was delivered via normal delivery with a birth weight of 2 kg. Initially healthy, she developed vomiting and diarrhea at 7 months of age, followed by the gradual onset of exfoliative skin rash affecting her cheeks, diaper area, hands, and feet. Concurrently, she experienced eyebrow and eyelash loss. Despite concerns of zinc deficiency and biotinidase deficiency, laboratory investigations ruled out both diagnosis. The skin rash persisted, resembling livedo reticularis, accompanied by hand and feet swelling, blister formation, and bluish discoloration in cold weather, alongside failure to thrive. Due to financial constraints and logistical hurdles, including obstacles related to accessing medical care in more advanced health facilities, definitive diagnostic tests such as skin biopsy and exome sequencing were delayed until the age of two and a half.

Initial biopsy findings were non-specific, further complicating the diagnostic process. However, subsequent exome sequencing revealed compound heterozygous mutations in the RECQL4 gene, confirming the diagnosis of Rothmund-Thomson syndrome type II. Despite presenting with Rothmund-Thomson syndrome (RTS), our patient exhibited no signs of cataract formation and demonstrated a normal neurological examination upon evaluation. She has normal intellectual development and good school performance. However, the patient's clinical course was marked by skeletal fragility, evidenced by multiple fractures following minor falls, and distinctive cutaneous manifestations, including telangiectatic lesions and severe skin dryness particularly evident on her face (Figure 1), on the palmar and dorsal surface of the hands (Figure 2), knees (Figure 3), and feet (Figure 4).

Figure 1. Frontal View of the Patient, with Notable Observation of Atrophic Erythematous Changes with Partial Telangiectatic Dermal Alterations on the Face. Remarkably, the patient presents with a complete absence of both eyelashes and eyebrows. The eyes have been intentionally blurred, respecting the privacy and confidentiality of the individual, as per the family's request.

Figure 2. Hyperkeratosis and Thickened Palm and Dorsum with a Rough, Wart-like (verrucous) Texture.

Figure 3. Hyperkeratosis of the Knee.

Figure 4. Hyperkeratosis and Thickened Soles with a Rough, Wart-like (verrucous) Texture.

Regular follow-up at the hospital included maintenance on topical ointments for moisturizing. Despite regular follow-up, the patient's health took a significant turn six months ago when she began limping, progressively worsening over time, accompanied by gradual swelling of left leg. Medical consultation revealed a left tibia lesion suggestive of high-grade osteosarcoma, confirmed by subsequent imaging studies (Figure 5) and needle biopsy.

Figure 5. X-ray Shows Left Proximal Tibial Osteosaroma.

Metastatic work up with chest CT revealed no lung lesions. At present, the patient's stature and weight fall below the 3rd percentile, measuring 115 cm in height and 17.6 kg in weight, with a BMI of 13.3. She is currently undergoing treatment following the Children's Oncology Group protocol ASOT 0331 for her diagnosed localized osteosarcoma (doxorubicin, cisplatin and high dose methotrexate). She tolerated the chemotherapy well except for worsening of the skin condition especially after high dose methotrexate. She had a limb salvage resection with tumor necrosis more than 97%.

Discussion

Characteristic findings of RTS include early photosensitivity and facial erythema progressing to poikiloderma, as well as sparse scalp hair, absent or sparse eyebrows and eyelashes, short stature, and skeletal abnormalities [3]. This syndrome is often diagnosed later in life due to its subtle presentation. Our patient was diagnosed at 2.5 years of age after suffering for 2 years with exfoliative skin rash. She developed osteosarcoma at the age of 8. A study involving 33 RTS patients revealed that 11 of them developed osteosarcoma (33%), all having at least one truncating mutation in RECQL4 [3]. Another study showed that RTS patients with osteosarcoma have a similar clinical course, location (with the distal femur and tibia being the most common locations), and histology of osteosarcoma similar to sporadic cases, but they present at an earlier age with a mean of 11 years [4] and a bimodal distribution peaking at 18 and 60 years in the remaining population [5]. It also indicates a similar response to treatment, except for enhanced doxorubicin sensitivity leading to severe mucositis requiring a 25% dose reduction [4]. This syndrome is also associated with other skeletal anomalies other than osteosarcoma, some of which may go unnoticed.

A study was performed on 41 patients with RECQL4 mutation, 20 of whom underwent radiographic skeletal survey, 75% of them show at least one notable skeletal anomaly, however, only 20% of them were able to be detected clinically. The most frequent skeletal anomalies encountered are: abnormal metaphyseal trabeculation, brachymesophalangy, thumb aplasia or hypoplasia, osteopenia, radial head dislocation, radial aplasia or hypoplasia, and patellar ossification defects. An analysis of genotype-phenotype with Fisher's exact test revealed a significant association between RECQL4 mutational status and the occurrence of skeletal abnormalities ($p < 0.0001$) [6]. RTS is also associated with an increased risk of basal cell carcinoma, squamous cell carcinoma, and osteosarcoma, certain recommendations have been published, including regular skin examinations and care, cataract screening and management by ophthalmologists, routine dental check-ups, minimizing radiation exposure, employing sun protection, and monitoring skin for abnormalities. Individuals with RECQL4 pathogenic variants are advised to undergo a skeletal survey before the age of 5 to detect any skeletal anomalies and should be educated about the potential risk of osteosarcoma, remaining alert for associated signs and symptoms, and seeking prompt medical attention if detected. Comparing new imaging, such as X-rays, with the baseline skeletal survey can guide further evaluation. The efficacy of routine osteosarcoma screening remains undetermined, with factors such as timing, duration, modality, and cost needed to be taken into consideration [7].

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Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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