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Case Report

Atypical meningioma as a solitary malignancy in a patient with Rothmund-Thompson syndrome

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Abstract

Background: Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive disorder characterized by genomic instability and increased risk of various malignancies, especially osteosarcoma and squamous cell carcinoma. We report the first RTS patient who developed a central nervous system (CNS)-related neoplasm.

Case description: A 28-year-old male, previously diagnosed with RTS, developed a massive parasagital lesion, detected by magnetic resonance imaging. The tumor was surgically removed and histologically diagnosed as atypical meningioma. Preoperative symptoms were dramatically improved.

Conclusions: This is the first description of a CNS-related malignancy in RTS patients. Although rare, the genomic instability and additional risk factors of this syndrome should be considered in choosing the course of treatment.

Key Words: Meningioma, RECQL4, Pothmund-Thomson syndrome

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INTRODUCTION

Rothmund-Thomson syndrome (RTS) is an autosomal recessive disorder characterized by cutaneous rash, sparse hair, small stature, skeletal and dental abnormalities, cataracts, premature aging, and an increased risk for cancer, especially malignancies originating from bone and skin tissue.[33] RTS is an extremely rare disease. Approximately 300 patients have been recorded in the literature to date.[13] Several types of malignancies have been described in RTS patients, of which osteosarcoma (OS) was the most common, followed by squamous cell carcinoma (SCC).[29] Other types of malignancies documented in RTS patients include different types of mesenchymal cancers, epithelial skin cancers, and hematological malignancies.[33] Recently, mutations in the *RECQL4* gene have been associated with RTS.[11] This finding has opened a new window into the molecular mechanisms underlying this intriguing phenomenon. Here we present a RTS patient who developed an atypical meningioma as a primary malignancy at the age of 28. This is the first report of a malignancy related to the CNS in a RTS patient.

CASE REPORT

History

This 28-year-old male, diagnosed with RTS, presented with severe headaches in the last six months accompanied by intermittent dizziness, gait instability, occasional blurry vision, and tinnitus in both ears. No seizures or other neurological symptoms were described. The patient suffered from poikiloderma, thin skin, and sparse hair

continuously from the first year of life. Several years prior to the current episode, he underwent a number of leg extension operations using Ilizarov apparatuses due to short stature. Ongoing dental supervision was required from an early age due to dental malformations. His cognitive functions were preserved. No history of malignancies was reported.

Examination

A nonspecific defect in the visual field, more on the left side and accompanied by anisocoria, was identified. The rest of the general and neurological examinations were normal. MR imaging revealed a parietal, extra-axial lesion on the right hemisphere, diagnosed as a parasagital meningioma. Lesion size was approximately 50 × 60 × 64 mm, placing significant stress on the adjacent sulci, right trigone and right hippocampus. Mild posterior trans-tentorial herniation, compressing the midbrain from the right side and resulting in increased aqueduct pressure with no enlargement of the third ventricle, was demonstrated [Figures 1a and b]. No flow was demonstrated in the posterior part of the superior sagittal sinus above torcula level. Mild crowding of the cerebellar tonsils at the level of the foramen magnum was also noted, with slight forward compression of the medulla.

Operation

Under general anesthesia, with the aid of standard navigation and microsurgical techniques, the tumor was gross totally removed [Figures 1c and d]. The postoperative course was uneventful, with improvement of the preoperative symptoms and papilledema.

Pathological findings

Pathological examination of the removed tumor demonstrated grade II atypical meningioma (WHO) with mean mitotic count of 10 per 5-mm field and positive Ki67 in 5% of cells.

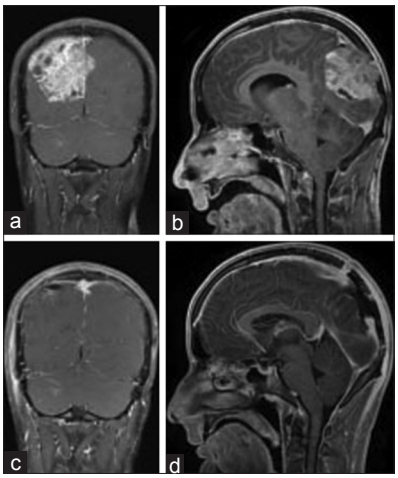

Figure 1: A coronal T1-contrasted fast spin echo MR scans, and midline sagital 3D incoherent gradient echo MR scans 2 weeks prior to (a,b), and 1 month following the operation (c,d)

DISCUSSION

This is the first report of a brain tumor as a single malignancy in a RTS patient. RTS was first described in 1868 by August Rothmund, a German ophthalmologist, as a syndrome consisting of a unique rash associated with bilateral juvenile cataract.[23] In 1923, a British dermatologist named Sydney Thomson coined the term "poikiloderma congenital" regarding a patient with similar rash and skeletal abnormalities but no cataract.[31] In 1957 it was recognized that both disorders were merely two variants of the same syndrome, identified from that point on as RTS.[30] RTS type-I is characterized by poikiloderma, ectodermal dysplasia, and juvenile cataracts, while RTS type-II is characterized by poikiloderma, congenital bony defects, and predisposition to osteosarcoma.[13,29,33] The main hallmark of the disease is a cutaneous rash, appearing in the first year of life as an erythema that later swells and blisters. The rash usually starts on the face and then spreads to the extremities. Over time, a chronic phase emerges, characterized by telangiectatic regions, depigmentation, and punctate atrophy. These changes, which persist throughout life, were termed poikiloderma.[13] Bone defects include pathological fractures, osteopenia, dislocations, abnormal trabeculation, irregular metaphysis, hypoplasia or agenesis of various bones, and others.[13,15,33] Bone anomalies may contribute to the short stature frequently seen in RTS patients. Hair is commonly affected; brittle or missing scalp hair and diminished eyelashes and/or eyebrows were seen in most cases of RTS.[33] Documented dental abnormalities include a variety of malformations such as hypoplastic teeth, multiple crown formations, microdontia, and others.[9,20,22] Bilateral cataracts, usually developed early in life, are the most common ocular lesions seen in RTS patients. Other eye defects include congenital bilateral glaucoma, exophthalmia, corneal atrophy, or scleralization.[6,14,16,17] About two-third of RTS patients suffers from symmetrical growth retardation, of which in most cases the levels of growth hormone are normal.[13,33] Sporadic case reports documented RTS patients who presented with other manifestations such as deafness,[1] gastrointestinal tract malformations,[2] and symptoms in the respiratory and hematological systems.[19,21,28]

Recently, mutations in the *RECQL4* gene were associated with RTS type-II.[11] The protein encoded by *RECQL4* is a DNA helicase that belongs to the RecQ helicase family. DNA helicases unwind double-stranded DNA into single-stranded DNAs and are involved in various basic cellular processes. Aberrations of their function reduce genomic stability and thus predispose to cancer.[7,24-26] The rate of malignancies, both primary and secondary, is significantly higher among patients with RTS type-II. OS is the most frequently seen malignancy in RTS

patients. It usually occurs in the second decade of life, earlier than in sporadic nonsyndromic OS, even though they have the same clinical features and histological characteristics.[13] The estimated prevalence of OS in RTS patients is 30%.[13] Most of OS cases were isolated; usually involving the femur and tibia, though several cases of multicentric OS were also described.[13,29] The specific mechanism of this substantial predisposition towards developing OS relative to other malignancies is still poorly understood. It is presumed that aside from its basic cellular functions, RECQL4 also plays a role as a regulatory protein in differentiation and proliferation of osteoblast progenitors.[35] This notion is reinforced by the pronounced skeletal defects frequently observed in RTS patients. Epithelial tumors of the skin, most commonly SCC, affect approximately 5% of RTS patients and usually develop later in life compared to OS (usually closer to the mid-third decade). Other types of malignancies have been previously documented in RTS patients. These include different types of mesenchymal cancers such as malignant fibrous histiocytoma and fibrosarcoma,[4] skin cancers such as basal cell carcinoma,[3] Bowen's disease,[8] and verrucous carcinoma,[4] and also hematological malignancies as acute myeloid leukemia,[19] myelodysplasia,[18] and Hodgkin's sarcoma.[13,29] Previous reports also documented single cases of gastric carcinoma,[5] malignant eccrine poroma,[32] parathyroid adenoma,[34] and amelanotic melanoma.[10] Moreover, RTS patients appear to have a higher risk for second malignant diseases compared to patients without a predisposition to cancer, and many of these patients suffered from secondary malignancies of the types previously described.[29]

In the case presented here, the patient developed an atypical meningioma as a solitary malignancy. This is the first report of a nervous system related malignancy developing in a RTS patient. Of course, the possibility that the development of this cancer was merely coincidental with the RTS should be taken under consideration. However, both the patient's young age and the fact that this is his only malignancy point to a causative relationship between the two. Syndromes that are characterized by genomic instability often show increased sensitivity to radiotherapy and chemotherapy. RTS patients have a higher risk of secondary malignancies than patients without a cancer predisposition, and several studies demonstrated increased sensitivity of RTS-derived cells to radiation due to reduced DNA repair abilities.[12,27] Hence, for cases in which postoperative radiotherapy is needed, this risk factor should be taken into account.

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