**Primary cutaneous malignant melanoma in Rett syndrome: Report of a case with nuclear features resembling herpes simplex virus cytopathic effects—a hitherto unrecognized morphological variant**

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**Abstract**

Rett syndrome (RTT) is a progressive neurological disorder, affecting females with mutations in the X-linked gene methyl-CpG-binding protein 2 (MECP2). While MECP2 has been implicated in cancers of the breast, colon, and prostate, cancer in patients with RTT is rare. We present a case of malignant melanoma in a patient with RTT, which additionally, displayed hitherto undescribed nuclear features, resembling herpes simplex virus cytopathic effects.

**KEYWORDS**
herpes simplex virus cytopathic effects, malignant melanoma, MECP2, Rett syndrome

1 | INTRODUCTION

Methyl-CpG-binding protein (MECP2) is an X-chromosome-linked gene. Since its discovery over two decades ago, it has been implicated in pathological conditions linked with Rett syndrome (RTT)\(^1\) and other disorders including autism, neonatal encephalopathy, and X-linked retardation.\(^2\) Cancers in patients with RTT have been occasionally documented,\(^3\) and mutations in MECP2 gene are thought to be associated with breast, colon, and prostate cancers.\(^2\) We describe herein a patient with RTT who presented with a subungual melanoma. The nuclear features of the melanoma, resembling herpes simplex virus (HSV) inclusions, were unusual and have not been described in melanomas previously.

2 | CASE REPORT

A 29-year-old female with RTT presented with an irregularly pigmented subungual lesion on the left thumb. The lesion was recently noticed by her caretakers who were concerned by its appearance. Due to her severe autism, complete physical examination was difficult. Nevertheless, surgical excision of the lesion was carried out with minimal clinical margins. Light microscopic examination of hematoxylin-eosin-stained slides from the pigmented lesion revealed features of a malignant melanoma displaying nuclear morphology that, as far as we are aware, has not been previously described. The malignant melanocytes had ground-glass and clear nuclei, with multinucleation, nuclear molding, and chromatin margination. The histopathological appearances bore a striking resemblance to HSV inclusions (Figures 1-4). These malignant melanocytes were positive for S100 protein (Figures 4 and 5) and Melan-A, and were negative for cytokeratins, HSV1 and 2 (Figure 6) and varicella zoster virus (VZV) immunostains.

The melanoma was focally ulcerated and had a Breslow thickness of 4 mm with positive margins. Following discussion in the multi-disciplinary team meeting, the patient underwent disarticulation of the left thumb at the level of the interphalangeal joint. Sentinel lymph node was not performed due to her clinical condition. Examination of this re-excision specimen showed residual melanoma, which was now completely excised, with no evidence of bone invasion. Molecular
FIGURE 1  Diffuse infiltration of skin by malignant melanoma with surface ulceration (hematoxylin-eosin ×20)

FIGURE 2  Medium-power view showing diffuse infiltration of the dermis by malignant melanoma (hematoxylin-eosin ×100)

FIGURE 3  Higher power view reveals the highly unusual nuclear morphology (hematoxylin-eosin ×400)

FIGURE 4  The nuclei demonstrate nuclear molding, clearing, and multinucleation, simulating features seen in herpes simplex infection (hematoxylin-eosin ×600)

FIGURE 5  S100 highlighting the malignant melanocytes (×200)

FIGURE 6  Herpes simplex virus (HSV) immunostain is negative (×100)
analysis was negative for BRAF or NRAS mutations. Her staging computed tomography imaging did not reveal any metastatic focus.

Following the surgery, the patient was followed up every 3 months for 3 years. During this period, her caretakers were asked to examine her axilla on a regular basis, as physical examination was deemed to be difficult during her follow-up visits. Unfortunately, 3 years postsurgery, the patient developed multiple subcutaneous deposits of metastatic melanoma in the breast, back, left axilla, and left lower abdominal wall. Due to her severe autism, she was not considered to be a candidate for systemic therapy and is currently managed conservatively.

3 | DISCUSSION

We describe a rare case of malignant melanoma in a patient with RTT. Initially described by Andreas Rett, an Austrian pediatric neurologist in 1966, RTT is a progressive neurodevelopmental disorder, caused by mutations in the X-linked gene MECP2, a ubiquitously expressed transcriptional regulator. It is one of the most common causes of mental retardation in females. There are limited options for treatment and most of these are based around symptom relief. Malignancy in patients with RTT is documented in rare case reports, although recent studies have described an additional role for MECP2 during carcinogenesis. As far as we are aware, melanoma in RTT has never been reported previously. Interestingly, our case also showed a previously undescribed morphological variant, with nuclear features resembling HSV cytopathic effects.

It is well known that malignant melanoma has various histopathological morphologies, some more common than others. Our case adds to these morphological variants, where the tumor nuclei display ground glass appearance with chromatin margination, nuclear molding and multinucleation—features that are usually associated with HSV cytopathic effects in keratinocytes. The cause for this highly unusual morphology is unclear, but in the context of the patient’s clinical background, one is inclined to propose that the presence of mutations in MECP2 may have played a role. The exact mechanism is uncertain, but as MECP2 is considered as a predicted epigenetic regulator, it is possible that the unusual nuclear changes may have arisen from defects in the epigenetic mechanisms resulting from MECP2 mutations. As more cancer cases are reported in patients with RTT, further studies highlighting the role of MECP2 gene in the etiology of malignancies in these patients may illuminate the molecular basis of this highly unusual morphology.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
Data available on request from the authors

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