First case report of neck malignant triton tumor coexisting with NF1 and FANCD2 gene mutations

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Abstract

This clinical case first time reports a coexistence of FANCD2 and NF1 mutations in malignant triton tumor (MTT) patient and as the initial operation, the complete resection has crucial influences on the prognosis and recurrence of MTT.

First case report of neckmalignant triton tumor coexisting with NF1 and FANCD2 gene mutations

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Key Clinical Message

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Abstract

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KEYWORDS

Malignant triton tumors, Malignant peripheral nerve sheath tumors,NF1 gene

mutation,FANCD2 gene mutation

1 | INTRODUCTION

Malignant triton tumors (MTTs) are a rare rhabdomyosarcoma-like differentiated subtype in malignant peripheral nerve sheath tumors (MPNSTs), accounting for 5% of all MPNSTs.[1] As many as 50% of MPNSTs occur in patients with neurofibromatosis type 1 (NF-1).[2] MTTs are aggressive, often difficult to completely remove, and the prognosis are poor, which may be related to certain gene mutations.[3] It is known that individuals with mutations in the NF1 tumor suppressor gene will develop into NF- I and MPNSTs. However, few cytogenetic studies specific to MTTs have been performed. At present, the relationship between the genetic test results of MTTs and clinical manifestations is not completely clear. Here, we report a rare case of neck MTTs with mutations in NF1 and FANCD2 genes, without clinical manifestations of NF- I. As far as we know, this is the first case of MTT with mutations in the NF1 and FANCD2 genes, without clinical manifestations of NF- 1.

2 | CASE

A 27-year-old female patient found a mass at the right back neck, which was with a size similar to a "fava bean" without tenderness, redness, or swelling, and with no growth or disappearance seven months ago. The patient described that the size of the mass gradually increased to like an "adult fist", which was accompanied with mild tenderness one month ago (Fig.1). She was diagnosed as fibroma in the local hospital and underwent major resection. Postoperative pathology revealed high dysplasia of the tumor, and then the pathological section was sent to the "West China Hospital of Sichuan University" for pathological examination. The immunohistochemistry results showed: S-100 (+), CD34 (+), desmin (+), H3K27Me3 (-), myogenin (+), MyoD1 (+), SMA (-), STAT-6 (-), P53 (+), NF (-), ALK-1 (-), TRK (-), and the Ki-67 positive rate was 40%. Immunophenotypic testing revealed the presence of more rhabdomyosarcoma components, which was combined with extensive loss of H3K27Me3 protein. Therefore, malignant triton tumor (MTT) was diagnosed.

However, three weeks after the diagnosis, tumor recurrence was observed and the tumor was rapidly increased to the size of an "adult fist" again. She visited our hospital for surgical treatment. The physical examination showed a mass of approximately 6.4cm×6.5cm×8.9cm at the right back neck. Magnetic Resonance Imaging (MRI) showed a mass of soft tissue that occupied the shadow at the right back neck (Fig.2). On September 18, 2020, we performed surgery to completely remove the tumor. Postoperative pathological analysis by our hospital confirmed MTT (Fig.3). The postoperative tumor specimens were sent to "Beijing Genetron Health Medical Laboratory Co., Ltd." for genetic testing. The results showed FANCD2 and NF1 gene mutations. No tumor recurrence was observed during the postoperative follow-up, and the patient is currently receiving chemotherapy and radiotherapy regularly.

3 | DISCUSSION

MTT is malignant peripheral nerve sheath tumor (MPNST) with rhabdomyosarcomatous differentiation.[4] MPNSTs usually appear in patients with autosomal dominant disease, neurofibromatosis type 1 (NF-1), with sporadic occurrence.[5] NF1 gene frameshift mutation was detected in the tumor specimen of the patient, while no evidence of clinical manifestations of NF-1 was found.

The occurrence of MTT is related to missense mutation and loss of heterozygosity of NF1 gene. As a tumor suppressor gene, NF1 gene is located on the long arm of chromosome 17 (17q11.2) and encodes class I neurofibroma protein.[6]Mutations in NF1 gene can cause abnormal activation of RAS signaling pathways and activate the PI3K/AKT/mTOR signaling pathways. It is suggested that tumors with NF1 mutations are sensitive to inhibitors targeting mTOR and MEK. The protein encoded by NF1 gene of the tumor sample from the patient displayed a frameshift mutation at the 1488th amino acid, with a gene mutation frequency of 90.2%. The NF1-p.Thr1488LysfsTer5 mutation carried by the tumor sample of the patient was a frameshift mutation, which had not been included in Catalogue of Somatic Mutations in Cancer (COSMIC). Frameshift mutations can lead to premature stop codons to encode truncated protein products, which may affect the protein functions.

Neurofibromatosis is associated with an increased risk of many individual cancers, including breast cancer[7]. FANCD2 gene is breast cancer susceptibility and FANCD2 is a potential risk factor of breast cancer.[8]Once FANCD2 gene was ubiquitinated, it participates in the transduction and regulation of various biological processes such as DNA damage repair, cell cycle regulation, gene transcription, etc. via the FA/BRCA pathway.[9] FANCD2 gene mutation leading to defects in DNA damage repair may be one of the causes of MTT occurrence and recurrence. The 1178th amino acid of FANCD2 gene-encoded protein in the patient changed from serine to cysteine, with a gene mutation frequency of 24.7%. The FANCD2-p.Ser1178Cys mutation carried by the tumor sample of the patient was a missense mutation, which had not been included in COSMIC, and its impact on protein functions is still unknown.

This is the first case reporting the coexistence of FANCD2 and NF1 mutations in MTT, while the relationship between the genetic testing results of MTT and its clinical manifestations is still unclear, which requires further research. It is worth noting that radical surgical resection of MTT, whether combined with chemotherapy and radiotherapy, results in a significantly better prognosis than subtotal resection.[10-11] Therefore, as the initial operation, the complete resection has crucial influences on the prognosis and recurrence of MTT, which deserves special attention by clinicians.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Guangtang Chen discovered what was special about this case and wrote the paper,Ming Li provided pathological images ,Qiujing He supervised the findings of this work. All authors discussed the clinical case and contributed to the final manuscript.

ETHICAL APPROVAL

This clinical case report was approved by the ethical committee of the Second People's Hospital of Guiyang City. The patient gave her informed consent. This research was conducted under the Declaration of Helsinki code of ethics.

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figure legends

FIGURE 1 The huge mass on the right back neck of the patient.

FIGURE 2 Neck MRI plain scan and enhancement showing: Massive soft tissue occupying the shadow in the right back neck; mixed weak signal on the T1 enhanced image; large flaky liquefied necrosis area in the center of the lesion; the largest area of the lesion was approximately 64mm×65mm×89mm; adjacent soft tissues were pushed and displaced. The focus of the enhanced scan showed rosette enhancement (A-C). T2WI image of neck MRI showing a large sheet of liquefied necrosis in the center of the mass of soft tissue lesion at the right back neck, with liquid-liquid flat shadow (D).

FIGURE 3 H&E staining showing that oval cells with eosinophilic cytoplasm are morphologically consistent with rhabdoid differentiation identified in the background of malignant peripheral nerve sheath tumor (A). Immumohistochemical staining showing that the tumor cells are diffusely positive for S-100 (B), desmin (C), and myogenin (D).