Beta-Catenin Mutation with Complex Chromosomal Changes in Desmoid Tumor of the Scalp: A Case Report

Gary Liu, BS^{1,3} Howard L. Weiner, MD² William C. Pederson, MD¹ Lesley Davies, PA-C¹
Edward P. Buchanan, MD, FACS, FAAS¹

¹ Department of Plastic Surgery, Baylor College of Medicine, Houston, Texas

² Department of Neurosurgery, Baylor College of Medicine, Houston, Texas

³ Medical Scientist Training Program, Baylor College of Medicine, Houston, Texas

Address for correspondence Edward P. Buchanan, MD, FACS, FAAS, Chief, Division of Plastic Surgery, Department of Plastic Surgery, Baylor College of Medicine, 6701 Fannin, Suite 610.00, Houston, TX 77030 (e-mail: ebuchana@bcm.edu; btung@bcm.edu).

Craniofacial Trauma Reconstruction 2019;12:146–149

Abstract

Gain-of-function mutations in the beta-catenin gene (*CTNNB1*) drive genomic instability within different cancers. However, it is unclear whether alterations in beta-catenin signaling can still lead to chromosomal rearrangements in neoplasms without metastatic potential. Here, we report a unique case, whereby a desmoid tumor of the scalp contains a missense mutation in *CTNNB1*. This mutation is located at the T41 phosphorylation site—previously reported to be necessary for proper beta-catenin degradation. Online database analysis then revealed that our mutation is likely causative of many different cancers and also absent in the healthy public. Karyotyping of the desmoid tumor cells then showed complex chromosomal changes in 16 out of 20 cells examined. To treat this patient, we surgically removed both the neoplasm and underlying calvarium and then successfully reconstructed the skull and scalp. Taken together, our data suggest that increased beta-catenin signaling can lead to genomic instability in the absence of metastatic potential.

Keywords

- Desmoid Tumor
- benign cancer
- *CTNNB1*
- Wnt

The human beta-catenin gene (*CTNNB1*) is a transcription factor within the canonical Wnt signaling pathway to regulate many aspects of cell division and growth. Gain-of-function mutations in *CTNNB1* and/or disruptions in its negative regulators are associated with different malignancies, including colorectal cancer, acute myelogenous leukemia, and melanoma.¹

One hypothesis for how increased beta-catenin signaling leads to cancer is by inducing chromosomal instability. Uncontrolled Wnt signaling activation has been previously linked to multiple cancers with complex chromosomal rearrangements.² Furthermore, overexpressing beta-catenin in mice promotes increased genomic instability by altering DNA damage repair.³ Thus, aberrant beta-catenin signaling is considered a key driver in carcinogenesis.

Interestingly, mutations in the *CTNNB1* gene are also associated with neoplasms that do not have metastatic potential.⁴ One such disease is desmoid tumors, which are aggressive noncancerous neoplasms that can occur any-

where in the body.⁵ A previous study found *CTNNB1* mutations in 88% of 260 desmoid tumors.⁶ Because aberrant Wnt signaling leads to chromosomal instability, a typical hallmark of cancer, these findings bring about a fundamental question: Does increased beta-catenin signaling affect neoplasms differently based on their metastatic potential? For example, will nonmalignant tumors still develop genomic instability due to aberrant beta-catenin signaling? Here, we report a unique case whereby a desmoid tumor of the scalp contains both a somatic mutation in the T41 phosphorylation site of the *CTNNB1* gene, which regulate protein stability, and complex chromosomal rearrangements.

Preoperative

A 20-month-old male first presented to our office with a left skull mass over the parietal, temporal, and occipital area. The mass, which was present at birth, has grown considerably in the

received

August 14, 2018

accepted after revision

October 13, 2018

published online

November 16, 2018

Copyright © 2019 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0038-1676078>.
ISSN 1943-3875.

Fig. 1 CTNNB1 mutation leads to unique phenotype in our patient. (a) Axial MRI of patient 10 months prior to surgery shows desmoid tumor measuring 6.6 cm craniocaudal $\times$ 2.8 cm transverse $\times$ 7.5 cm anterior posterior. (b) Four months before surgery, the tumor grew to 9.2 cm $\times$ 4.9 cm $\times$ 8.6 cm. (c) One month before surgery, MRA shows tumor at 10 cm $\times$ 5.7 cm $\times$ 8.3 cm and normal intracranial arterial vasculature. (d) MRV of patient also shows no intracranial venous abnormalities. Table: 9 out of 9 reported cases on Clinvar show malignancies resulting from threonine to isoleucine substitution at codon 41 of CTNNB1, the same mutation as our patient's benign tumor.

last 8 months ($\rightarrow$ Fig. 1a, b), leading to erosion of the subjacent skull. Needle core biopsy showed a low-grade spindle cell proliferation, most suggestive of a desmoid tumor. Both magnetic resonance angiography ($\rightarrow$ Fig. 1c) and magnetic resonance venography ($\rightarrow$ Fig. 1d) showed normal intracranial vasculature with the left external carotid artery supplying the desmoid tumor.

Cells from the neoplasm were then sequenced at the CTNNB1 locus, a known positive regulator for tumorigenesis. We discovered a missense mutation at codon 41 (122C > T), which resulted in an amino acid substitution from threonine to isoleucine. This single base pair change removed a phosphorylation site previously reported to facilitate the destabilization of β -catenin protein and is therefore necessary for downregulation of Wnt signaling.⁷⁻⁹ Immunohistochemistry then revealed increased nuclear beta-catenin staining in the tumor cells (data not shown).

To investigate the potential pathogenicity of this coding change, we searched for patients with the same somatic mutation on the Clinvar database. Interestingly, all nine reported cases with our mutation resulted in malignant tumors ($\rightarrow$ Fig. 1, table). According to Clinvar database,¹⁰ while many other mutations in CTNNB1 were likely benign, all patients with our mutation had malignancies. Furthermore, in the Gnomad database¹¹ where more than 100,000 phenotypically normal patients were sequenced, no amino acid changes at T41 could be found (data not shown). Therefore, while this somatic mutation is found in multiple tumor types, it does not appear to be a germline mutation in the human population. Taken together, our data suggest that the T41 mutation is the likely cause of our patient's phenotype.

To investigate how this mutation may influence DNA stability, we performed karyotyping in 8- to 9-day primary culture tumor cells. We discovered unbalanced chromosomal aberrations in 16 out of 20 cells examined. These changes include loss of chromosomes Y and 6; gain of chromosome 4;

additional materials on chromosomes 4q35, 6p23, and 21p11.2; and dicentric chromosomes (5; 15 and 4; unresolvable). At this point, our team proceeded with operations to resect and reconstruct the defect.

Operation

Our team began the operation by resecting the desmoid tumor. We then proceeded with craniectomy to remove the involved bone. To adequately determine the tumor margins, we temporarily covered the exposed dura with a resorbable mesh and wound VAC and waited for a definitive pathology report ($\rightarrow$ Fig. 2a). Five days later, we returned to the operating room and resected all remaining tumors. The dura was stripped away from the inner table of the skull with a Penfield dissector and dental instrument and the wound irrigated. We left the dura intact and harvested an autologous craniotomy flap to reconstruct the left calvarium ($\rightarrow$ Fig. 2b).

To reconstruct the left scalp, we first harvested a chimeric flap consisting of the patient's latissimus dorsi and two lower slips of his serratus anterior ($\rightarrow$ Fig. 2c). The thoracodorsal and subscapular arteries were dissected out. Preauricular incision was then made to explore the temporal vessels. After identifying those vessels, we removed the muscles out from the back and then rearranged them to cover the wound. Using microsurgical techniques, we further dissected out the temporal vessels and an end-to-end anastomosis between donor and recipient was performed. The remainder of the flap was sutured in place and a flat Jackson-Pratt drain was brought through an incision behind the ear until it reached under the flap. We finished by harvesting several strips of meshed skin graft from the thigh and sutured them over the graft ($\rightarrow$ Fig. 2d). Unfortunately, a thrombus at the anastomosis site developed 6 days later, which required thrombectomy and a reverse saphenous vein graft to reconnect donor to recipient arteries. The artery was noted to be patent using Doppler ultrasonography and despite this complication, the patient recovered well.

Fig. 2 Tumor resection with cranial and scalp reconstruction. (a) Following tumor and subjacent calvarium resection, a resorbable mesh and wound VAC was placed over exposed dura. (b) Left calvarium was reconstructed using an autologous craniotomy flap. (c) Chimeric flap showing latissimus dorsi and two lower slips of serratus anterior. (d) Sutured meshed skin graft from thigh.

Fig. 3 Pre- and postsurgical comparison shows successful treatment. (a) Axial CT just prior to surgery. (b) Picture of patient's skull just prior to surgery. (c) Axial CT 2 months after surgery. (d) Picture of patient's skull 2 months after surgery.

Postoperative

Our patient was managed in the ICU for the next 15 days and eventually discharged under stable condition. Follow-up MRI and CT scan 2 months later revealed no residual tumor or intracranial abnormalities and a successful scalp and calvarial reconstruction (► Fig. 3a–d).

Discussion

Gain-of-function mutations in beta-catenin can lead to genomic instability in different forms of cancer. However, it is unclear how increased beta-catenin signaling may affect chromosomal stability in benign tumors. Our case report suggests that a T41 somatic mutation, which leads to increased CTNNB1 stability, can result in both chromosomal rearrangements and neoplasm without metastatic potential.

Through our report, one interesting question that arises is why this mutation leads to a desmoid tumor when it is carcinogenic in other contexts. A simple answer is that another mutation is required for cancer. For example, increased beta-catenin signaling may be the driver for increased cell division. However, to achieve metastatic potential, another mutation which leads to increased cell mobility, may be required. This classical “hallmark of cancer” is fundamental to our understanding for how malignancy develops.¹²

Although our patient probably escaped a second hit mutation which leads to cancer, it is interesting that the complex chromosomal rearrangements did not lead to metastatic potential. In fact, other cases of desmoid tumors also show a similar loss in genomic stability.¹³ Therefore, this demonstrates that simply losing, gaining, or breaking the chromosome at random locations may be statistically improbable in causing cancer. More likely, targeted mutation in a very small subset of locations is how cancer arises.

Overall, our patient tolerated the surgery well and has returned to normal function. Given that desmoid tumors do not become malignant, he has a very favorable prognosis and we hope for his continued health.

Conflict of Interest

None.

References

- 1 Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene* 2017;36(11):1461–1473
- 2 Rao CV, Asch AS, Yamada HY. Frequently mutated genes/pathways and genomic instability as prevention targets in liver cancer. *Carcinogenesis* 2017;38(01):2–11
- 3 Dose M, Emmanuel AO, Chaumeil J, et al. β -Catenin induces T-cell transformation by promoting genomic instability. *Proc Natl Acad Sci U S A* 2014;111(01):391–396
- 4 Alman BA, Li C, Pajerski ME, Diaz-Cano S, Wolfe HJ. Increased beta-catenin protein and somatic APC mutations in sporadic aggressive fibromatoses (desmoid tumors). *Am J Pathol* 1997; 151(02):329–334
- 5 Martínez-Lage JF, Acosta J, Sola J, Poza M. Congenital desmoid tumor of the scalp: a histologically benign lesion with aggressive clinical behavior. *Childs Nerv Syst* 1996;12(07):409–412
- 6 Le Guellec S, Soubeyran I, Rochaix P, et al. CTNNB1 mutation analysis is a useful tool for the diagnosis of desmoid tumors: a study of 260 desmoid tumors and 191 potential morphologic mimics. *Mod Pathol* 2012;25(12):1551–1558
- 7 Bodenmiller B, Aebersold R. Quantitative analysis of protein phosphorylation on a system-wide scale by mass spectrometry-based proteomics. *Methods Enzymol* 2010;470:317–334
- 8 Wang Z, Vogelstein B, Kinzler KW. Phosphorylation of β -catenin at S33, S37, or T41 can occur in the absence of phosphorylation at T45 in colon cancer cells. *Cancer Res* 2003;63(17):5234–5235
- 9 Liu C, Li Y, Semenov M, et al. Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism. *Cell* 2002;108(06):837–847
- 10 Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res* 2018;46(D1):D1062–D1067
- 11 Lek M, Karczewski KJ, Minikel EV, et al; Exome Aggregation Consortium. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016;536(7616):285–291
- 12 Knudson AG. Two genetic hits (more or less) to cancer. *Nat Rev Cancer* 2001;1(02):157–162
- 13 Bridge JA, Sreekantaiah C, Mouron B, Neff JR, Sandberg AA, Wolman SR. Clonal chromosomal abnormalities in desmoid tumors. Implications for histopathogenesis. *Cancer* 1992;69(02):430–436