Novel *BRD2::NUTM1* Fusion in NUT Carcinoma With Exceptional Response to Chemotherapy: A Case Report

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ABSTRACT

We present the first known case of a patient with *BRD2::NUTM1*-driven NUT carcinoma. A 59-year-old woman presented with poorly differentiated squamous cell lung cancer metastatic to the pleura. Eventually, a positive NUT immunohistochemistry, NUT fluorescence in situ hybridization, and RNA next-generation sequencing with a *BRD2::NUTM1* fusion led to the diagnosis of NUT carcinoma. She received multiple lines of chemotherapy with response and is still alive at 2 years postdiagnosis. This report expands on the known fusions in NUT carcinoma and highlights potential differences in patient prognosis on the basis of gene fusion partners.

Keywords: Case report; NUT carcinoma; *BRD2::NUTM1* gene fusion; Non–small cell lung cancer

Introduction

NUT carcinoma is a rare and aggressive poorly differentiated squamous cell carcinoma that affects patients of all ages. It carries a poor prognosis, with a median overall survival (OS) of 6.7 months.[1,2] The defining feature is rearrangement of the *NUTM1* gene with different fusion partners, most frequently *BRD4*, followed by *BRD3*.[2] Both *BRD4* and *BRD3* are members of the BET family, which also includes *BRD2* and *BRDT*. Despite the frequency of *BRD4::NUTM1* and *BRD3::NUTM1* gene fusions, there have been no reported fusions with the other BET genes. Herein, we present the first known case of an individual with NUT carcinoma with a *BRD2::NUTM1* gene fusion.

Case Presentation

A 59-year-old woman with a never smoking history presented with an incidentally noted 2.7 × 3.0 cm left lower lobe (LLL) mass on computed tomography (CT) in February 2021 (Figs. 1 and 2*A* and *B*). A positron emission tomography (PET) scan revealed avidity in the LLL mass (standardized uptake value [SUV] 6.8 units) and regional lymph nodes (LNs) (SUV 3.1–4.9 units). A brain magnetic resonance imaging scan was negative for metastatic disease. Biopsies

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Cite this article as: Wu SJ, Kim JJ, Huang Y, et al. Novel *BRD2::NUTM1* fusion in NUT carcinoma with exceptional response to chemotherapy: a case report. *JTO Clin Res Rep*. 2024;5:100625.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100625

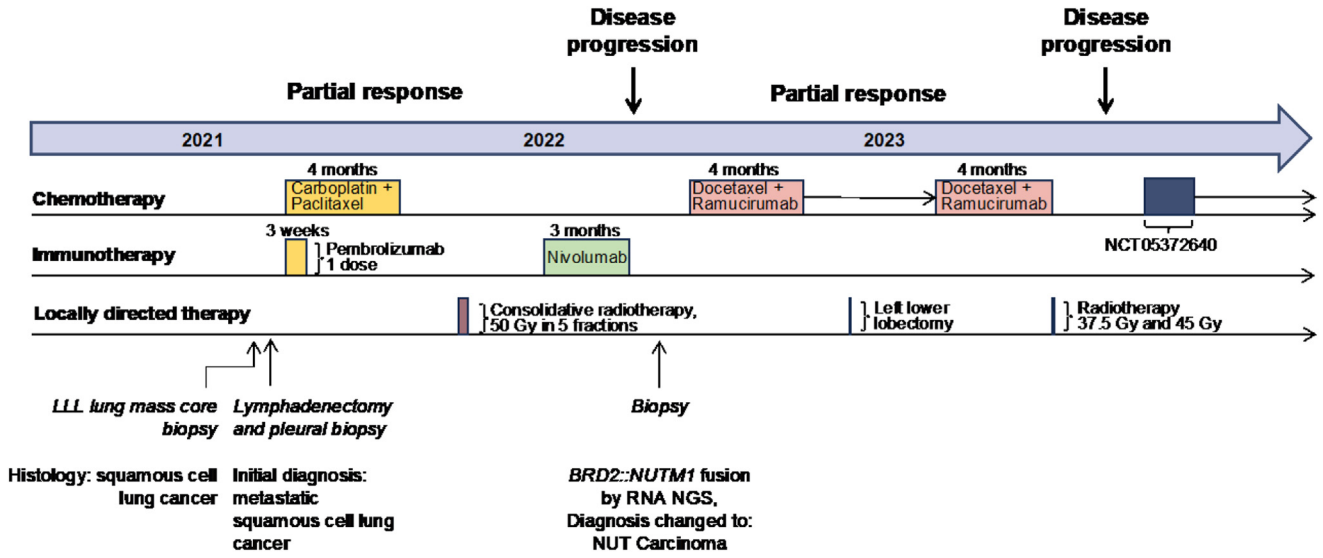

Figure 1. Clinical timeline from initial diagnosis (February 2021) to the most recent follow-up (September 2023).

revealed poorly differentiated squamous cell carcinoma with metastasis to the pleura, stage cT3N2M1a/IVa (Fig. 2*C–E*).

She started carboplatin, paclitaxel, and pembrolizumab on March 2021. A chest CT on completion of four cycles revealed that the LLL mass had decreased to 1.5 × 1.4 cm. The mass was consolidated with 50 Gy of radiation.

Chest CT 3 months after revealed that the LLL mass increased to 2.0 cm with new left hilar lymphadenopathy. Nivolumab was started in December 2021. After 3 months of nivolumab, a chest CT revealed that the LLL mass had increased to 3.4 cm with new left infrahilar adenopathy.

A biopsy of the LLL mass was performed; a *BRD2::NUTM1* gene fusion was identified by RNA-based

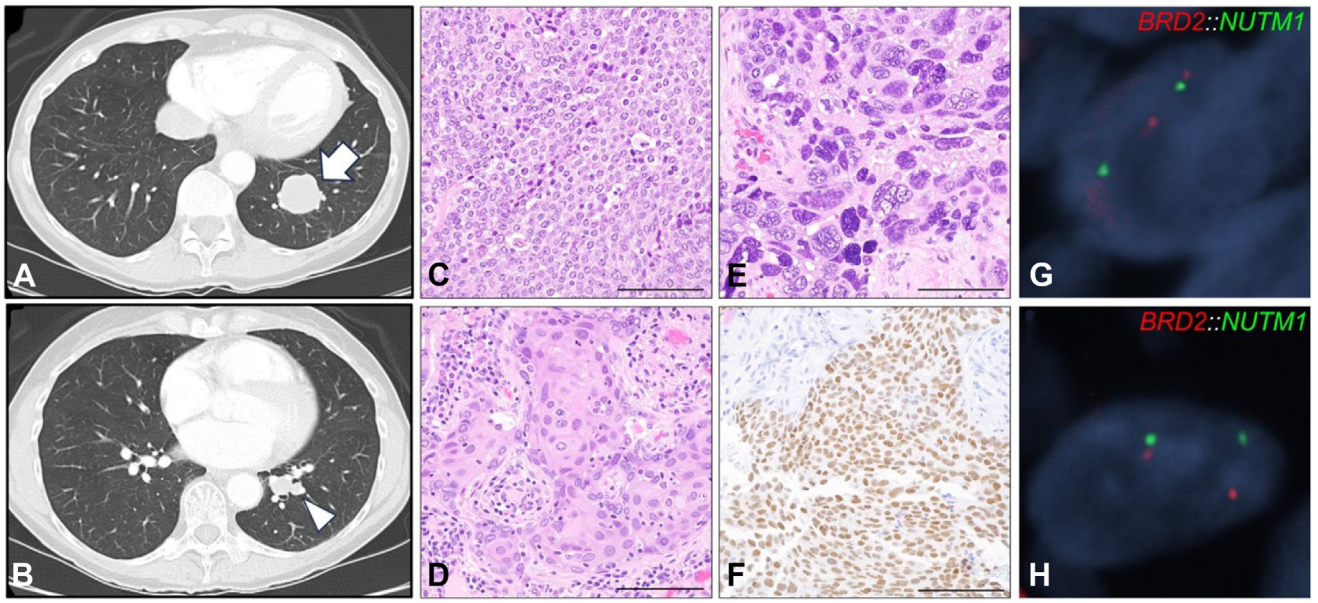

Figure 2. Initial CT scan imaging revealing the (*A*, arrow) left lower lobe mass and (*B*, arrowhead) hilar lymphadenopathy. (*C*) HE staining of the left lower lobe lung resection revealing monomorphic phenotype, (*D*) pleomorphic areas, and (*E*) squamous differentiation. (*F*) Immunohistochemistry for NUT revealing nuclear speckled staining. (*G*, *H*) BRD2::NUTM1 dual color bring-together FISH performed on the patient's core biopsy. The red-green doublet identifies the BRD2-NUTM1 allele, and single red and green signals identify normal BRD2 and NUTM1 alleles, respectively. The horizontal scale bar represents 100 μM. CT, computed tomography; FISH, fluorescence in situ hybridization.

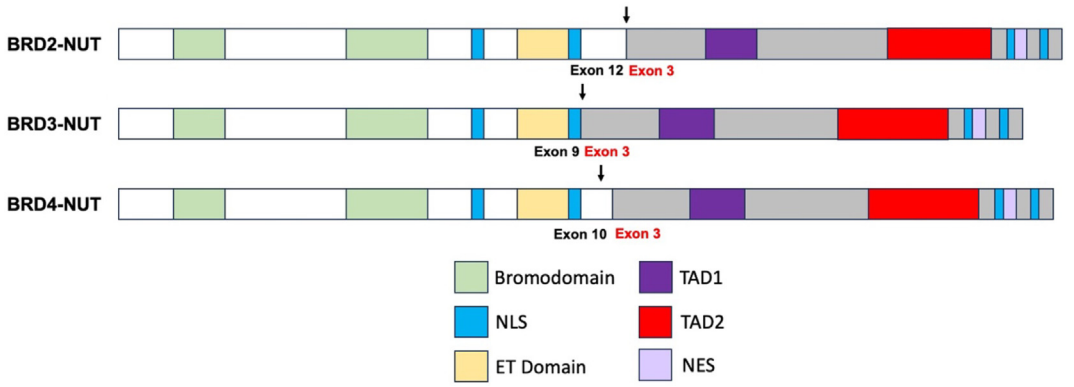

Figure 3. Schematic of the BRD2-NUT fusion protein identified in this case in comparison to the most common BRD3-NUT and BRD4-NUT proteins. The black arrows indicate the location of translocation-associated break points. NLS, nuclear localization signal; ET, extraterminal; TAD1, transcriptional activation domain 1; TAD2, transcriptional activation domain 2; NES, nuclear export signal.

next-generation sequencing (NGS). Immunohistochemistry (IHC) for NUT was positive. These findings altered the diagnosis to NUT carcinoma.

Docetaxel and ramucirumab were started in May 2022. After 4 months of treatment, a chest CT revealed a stable LLL mass. The patient underwent a LLL lobectomy with mediastinal lymphadenectomy in October 2022. The histopathology revealed 2.5 cm residual NUT carcinoma and metastatic disease in six of eight LNs. The resection specimen had treatment effect and areas of abrupt keratinization. IHC for NUT revealed positive nuclear dot-like staining in the tumor cells, and fluorescence in situ hybridization (FISH) confirmed a fusion between *NUTM1* and *BRD2* (Fig. 2*F–H*; Supplementary Methods).

In January 2023, docetaxel and ramucirumab were resumed and discontinued in May 2023 owing to neuropathy. A PET scan revealed residual avidity in a left upper lobe (LUL) nodule, mediastinal, hilar, and supraclavicular LN; 45 Gy and 37.5 Gy of radiation were delivered to the LUL and LN, respectively. A PET scan in August 2023 revealed stable treated disease but new lung nodules, avid subcarinal adenopathy, and an avid right acetabular bone lesion. The patient has since started on a clinical trial for NUT carcinoma (NCT05372640). Written informed consent was provided by the patient for this case report.

Discussion

We present the first known case of NUT carcinoma harboring a *BRD2::NUTM1* fusion oncogene. The case highlights diagnostic challenges and a clinical course with a remarkably good outcome for NUT carcinoma.

Our case illustrates the challenge of diagnosing NUT carcinoma upfront. The diagnosis necessitates demonstration of rearrangement of the *NUTM1* gene by either (1) nuclear IHC staining for NUT,[3] (2) FISH testing, or (3) PCR-based or NGS, preferably RNA-based NGS. Diagnosis is often delayed owing to under-recognition, nonspecific histologic features, and disease aggressiveness.

This case highlights the first known case of NUT carcinoma with a *BRD2::NUTM1* fusion. BRD2, BRD3, and BRD4 are BET proteins,[4,5] a family characterized by the presence of two acetyl-histone–binding bromodomains and an extraterminal protein-interaction domain. These domains allow BET proteins to bind to regions of active, acetylated chromatin, facilitating the transcriptional elongation of associated genes. The oncogenic function of BRD2-NUT is predicted to be similar to that of BRD4-NUT as it retains all known functional domains of BRD4-NUT, including the highly homologous dual bromodomains, extraterminal domain, and nearly the entire NUT protein with its two p300-binding transcriptional activation domains (TAD1, TAD2)[6,7] (Fig. 3). *BRD4::NUTM1* has been found to promote tumorigenesis through multiple mechanisms that block differentiation and maintain growth, including up-regulation of the proto-oncogenes *MYC*[6] and *SOX2* through formation of megadomains near these loci.[7]

The clinical course of this patient may shed light on the natural history and treatment response of BRD2-NUT–driven NUT carcinoma. This patient has a thoracic primary tumor, which has a median OS of 4.4 months.[2] In our recent report of responses to chemotherapy in NUT carcinoma, the objective response rate was only 31%.[8] Among head/neck origin NUT carcinoma, non–BRD4-NUT-driven disease has improved prognosis compared with BRD4-NUT–driven disease. In clinical trials of targeted BET bromodomain inhibitors for NUT carcinoma (molibresib, RO6870810, and Bristol-Myers Squibb-986158), patients with partial responses were limited to those with non–*BRD4::NUTM1*-driven tumors.[1,2] These data suggest that the specific *NUTM1*

fusion partner is both prognostic and predictive. In contrast to most NUT carcinomas, this patient with BRD2-NUT-driven NUT carcinoma has an OS of greater than 2 years since diagnosis and responded to multiple lines of chemotherapy. This favorable outcome stands out and may reflect that *BRD2::NUTM1* fusions have a more chemotherapy-sensitive or less aggressive disease biology. Ultimately, the prognostic and predictive implications of *NUTM1* fusion partners will have to be characterized in larger data sets.

With increased diagnostic awareness and clinical trial development for NUT carcinoma, investigators should take disease heterogeneity into account. In particular, all patients should have fusion partner testing locally or free-of-charge through the International NUT Carcinoma Registry (NC-Registry.org). Current NUT carcinoma targeted therapy trials are focused on combinations with BET bromodomain inhibitors. For example, CTEP 10507 (NCT05019716) tests the addition of chemotherapy to the BET bromodomain inhibitor ZEN-3694 and has a non-*BRD4*, nonthoracic exploratory cohort that adds chemotherapy later to account for disease heterogeneity.

Conclusions

We describe a patient presenting with NUT carcinoma harboring a novel *BRD2::NUTM1* fusion. The biological significance of this rearrangement is yet to be elucidated; however, disease response to multiple chemotherapies and patient survival at 2 years post-diagnosis may suggest a more favorable prognosis but would necessitate further evaluation.

CRediT Authorship Contribution Statement

Sarah J. Wu: Data curation, Visualization, Writing—original draft, Writing—review and editing.

Justin J. Kim: Data curation, Visualization, Writing—original draft, Writing—review and editing.

Yeying Huang: Data curation, Writing—review and editing.

R. Taylor Durall: Data curation, Writing—review and editing.

Simone Becker: Data curation, Writing—review and editing.

Stephanie Canty: Data curation, Writing—review and editing.

Stefania Molinaro: Data curation, Writing—review and editing.

Evan Pisick: Data curation, Writing—review and editing.

Geoffrey I. Shapiro: Writing—review and editing.

Christopher A. French: Conceptualization, Resources, Supervision, Writing—review and editing.

Jia Luo: Conceptualization, Resources, Data curation, Supervision, Visualization, Writing—original draft, Writing—review and editing.

Disclosure

Dr. Shapiro reports receiving grants and personal fees from Merck KGaA/EMD-Serono; grants from Tango, Bristol-Myers Squibb, Pfizer, and Eli Lilly; receiving personal fees from Bicycle Therapeutics, Cybrexa Therapeutics, Boehringer Ingelheim, Bayer, ImmunoMet, Concarlo Holdings, Syros, Zentalis, CytomX Therapeutics, Blueprint Medicines, Kymera Therapeutics, Janssen, Xinthera, and Artios outside the submitted work; having a patent for "Dosage regimen for sapacitabine and seliciclib" issued to Cyclacel Pharmaceuticals and Geoffrey Shapiro and a patent for "Compositions and methods for predicting response and resistance to CDK4/6 inhibition" issued to Liam Cornell and Geoffrey Shapiro. Dr. French reports receiving research funding from Boehringer Ingelheim and consultant fees from Boehringer Ingelheim. Dr. Luo reports receiving research support to her institution from Erasca, Genentech, Kronos Bio, Novartis, and Revolution Medicines; honoraria from Targeted Oncology, Physicians' Education Resource, VJ Oncology, Cancer GRACE, and Community Cancer Education, Inc.; having advisory board participation from AstraZeneca and Amgen; receiving personal fees from Erasca, Blueprint Medicines, and Daiichi Sankyo; and having a pending patent filed by Memorial Sloan Kettering related to multimodal features to predict response to immunotherapy (PCT/US2023/115872). The remaining authors declare no conflict of interest.

Acknowledgments

Written informed consent was obtained from the patient to publish this report. The authors acknowledge funding and support from the Lowe Center for Thoracic Oncology, NIH/NCI R01CA124633-16, DF/HCC Lung Spore Career Enhancement Program, Friends of Jay Dion, Ryan Richards Foundation, McDevitt Strong, and the Max Vincze Foundation.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2023.100625.

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