JCEM Case Reports, 2024, **2**, 1–5
https://doi.org/10.1210/jcemcr/luae037
Advance access publication 22 March 2024
Case Report

A Rare Case of NUT Carcinoma of the Thyroid

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Abstract

NUT carcinoma is an aggressive, poorly differentiated squamous cell carcinoma, defined by rearrangement of the *NUTM1* (Nuclear Protein in Testis) gene. Diagnosis is challenging due to histologic similarities with other poorly differentiated tumors requiring advanced diagnostic techniques. There is no established treatment, and prognosis remains extremely poor. A 27-year-old woman without known medical history presented with a rapidly enlarging neck mass and compressive symptoms. Chemotherapy for presumed squamous cell carcinoma with a component of anaplastic thyroid cancer based on pathology was initiated. Next-generation sequencing revealed thyroid NUT carcinoma with high *PD-L1* expression, prompting PD-1 targeted therapy. The patient expired shortly afterwards from progressive disease. NUT carcinoma of thyroid origin is an extremely rare disease. This case brings awareness to the disease, highlights the importance of advanced diagnostic techniques and complexities in managing patients with NUT carcinoma.

Key Words: NUT carcinoma, thyroid cancer, squamous cell cancer, *NSD3-NUTM1* fusion, next-generation sequencing, *PD-L1*

Abbreviations: BET, bromodomain and extraterminal domain; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; IV, intravenous; NGS, next-generation sequencing; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TSH, thyrotropin (thyroid stimulating hormone).

Introduction

NUT carcinoma is a rare and aggressive type of poorly differentiated squamous cell carcinoma. It predominantly affects young adults, with NUT carcinoma of the thyroid being an even more rare entity (1). It was originally termed NUT midline carcinoma since it typically arises from structures in the thorax, head, and neck (1, 2). NUT carcinoma is defined by rearrangement of the *NUTM1* (Nuclear Protein in Testis) gene, usually involving fusion with the *BRD4* gene in most cases, but other gene fusions are described (1, 3). The histologic appearance of NUT carcinoma can overlap with that of other poorly differentiated tumors, which makes the diagnosis challenging. Increased utilization of advanced diagnostic techniques (immunohistochemical [IHC] and molecular analysis) has led to increased diagnosis of this under-recognized and elusive disease (1). Currently, there is no standard treatment for NUT carcinoma and prognosis is extremely poor, with a median survival of 6.7 months (1-3).

Here we present a rare case of a 27-year-old woman with NUT carcinoma originating from the thyroid, diagnosed via next-generation gene sequencing (NGS). While securing a diagnosis was important, this case also demonstrates the complexities of managing such a rare entity without definitive guidelines. An institutional review board approval was not obtained as it was not required per our institutional policy for a single-case study.

Case Presentation

A 27-year-old woman with no significant medical history presented to the hospital with an enlarging right-sided neck mass for 1 month, associated with difficulty swallowing and hoarseness. There was no family history of thyroid disease or cancer.

Diagnostic Assessment

A cervical lymph node biopsy prior to admission showed poorly differentiated squamous cell carcinoma with associated lymphoid tissue consistent with metastatic squamous cell carcinoma.

Physical examination was remarkable for a firm and immobile right-sided neck mass, extending from the anterior sternocleidomastoid to the midline of the neck, with a markedly enlarged and firm thyroid gland and hoarse voice. Flexible laryngoscopy was unremarkable except for some post-cricoid secretions. Computed tomography (CT) scan of the neck showed a diffusely enlarged heterogeneous thyroid gland with necrosis, right greater than left, with extrathyroidal extension into the tracheoesophageal groove, with the right lobe being indistinct from the strap muscles (Fig. 1). Extensive necrotic cervical adenopathy was observed. No evidence of another head and neck mucosal primary malignancy was seen. The findings were suspicious for an aggressive thyroid neoplasm with nodal metastatic disease and extrathyroidal tumor extension. CT with intravenous contrast of the chest, abdomen,

Received: 6 December 2023. **Editorial Decision:** 23 February 2024. **Corrected and Typeset:** 22 March 2024

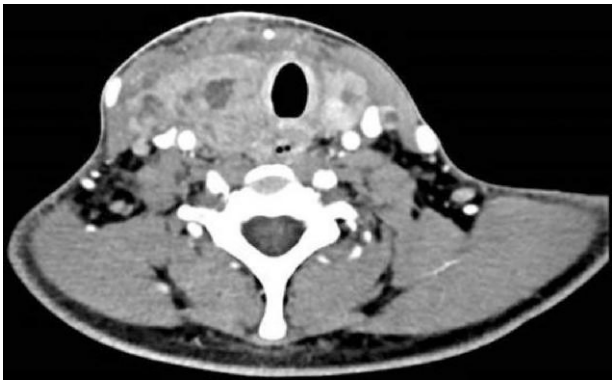

Figure 1. CT scan of the neck showing nodal metastatic disease and a diffusely enlarged heterogenous thyroid gland with necrosis, right greater than left, with extrathyroidal extension into the tracheoesophageal groove, and the right lobe indistinct from the strap muscles.

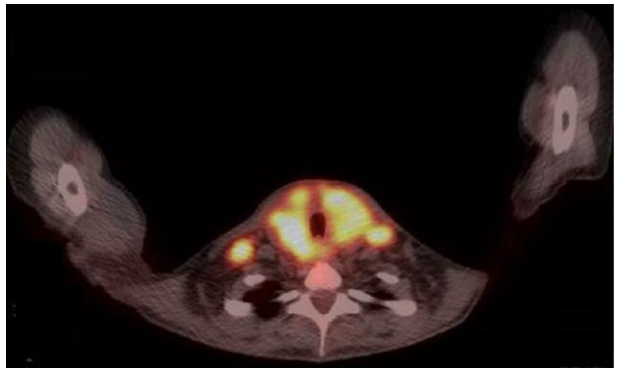

Figure 2. PET/CT performed 1 month after diagnosis showing a fluorodeoxyglucose (FDG) avid thyroid gland, FDG-avid bilateral retropharyngeal and cervical lymphadenopathy.

and pelvis, showed a few scattered bilateral pulmonary nodules, nonspecific, measuring up to 0.5 cm in diameter. CT of the head did not show any metastasis, and magnetic resonance imaging of the head was not performed.

The patient was found to have a suppressed thyroid stimulating hormone (TSH) of < 0.1 ulU/L (< 0.1 mIU/L) (normal reference range, 0.27-4.2 uIU/L; 0.27-4.2 mIU/L), and elevated free thyroxine (T4) of 2.3 ng/dL (29.6 pmol/L) (normal reference range, 0.9-1.8 ng/dL; 11.6-23.2 pmol/L). Thyroid stimulating immunoglobulin and TSH receptor antibodies were negative. Endocrinology, oncology, and ear, nose, and throat (ENT) services were consulted for thyroiditis, possibly secondary to mass effect from the thyroid tumor. Fine needle aspiration (FNA) of the thyroid was nondiagnostic so open excisional biopsy was pursued, which initially showed necrotic tissue replacing the thyroid without evidence of malignancy on intraoperative frozen section, concerning for severe thyroiditis.

Treatment

Prednisone 40 mg daily was started for concern for thyroiditis but after thyroid function tests normalized after one week and the patient developed hypothyroidism, levothyroxine 50 mcg titrated up to 100 mcg was initiated. The final pathology of the left thyroid open excisional biopsy revealed skeletal muscle and soft tissue with acute and chronic inflammation, necrosis, and clusters of inflamed atypical squamous epithelium, consistent with squamous cell carcinoma, primary rather than metastatic. Tumor cells were positive for *p40*, *p53*, and *EGFR*, and the Ki-67 labeling index was high (40%-70%). Scattered tumor cells were weakly positive for *PAX8,* and rare tumor cells were positive for *TTF-1*. These findings raised the possibility that the squamous cell carcinoma found in the specimen might be a component of anaplastic thyroid carcinoma. Steroids were subsequently tapered off and the patient was started on 5 cycles of carboplatin (AUC 2 = 163 mg intravenous [IV] on day 1) and paclitaxel (50 mg/m^2 = 70 mg IV on day 1) for presumed anaplastic thyroid cancer. The patient was deemed to not be a surgical candidate because of involvement of vital surrounding structures including the trachea and esophagus. IHC analysis of the open excisional biopsy specimen demonstrated programmed cell death ligand 1 (*PD-L1*) expression to be 100%. Given high *PD-L1* expression of the tumor, pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, was added, dosed at 200 mg every 3 weeks for 3 months. Next-generation sequencing (NGS) via Guardant subsequently was negative for a *BRAF V600E* mutation but NGS via Foundation Medicine showed a *NSD3-NUTM1* fusion, which classified the squamous cell carcinoma as a NUT "midline" carcinoma.

Outcome and Follow-Up

Positron emission tomography (PET)/CT scan done 1 month after diagnosis showed a fluorodeoxyglucose (FDG)-avid thyroid gland, FDG-avid bilateral retropharyngeal and cervical lymphadenopathy, FDG-avid bilateral lung nodules, FDG-avid L2 vertebrae, with a superior mediastinum focus (Fig. 2); findings compatible with metastatic disease. Magnetic resonance imaging of the pelvis after 2 months showed metastatic lesions to the left iliac wing, L5 vertebral body, and L2 transverse process. The patient received radiation therapy for this. Follow-up CT of the neck and chest after 4 months demonstrated new pleural effusions and a new nodular structure at the lower level of the thyroid gland, concerning for worsening neoplasm. Formal restaging was not performed due to multiple hospitalizations and inability to achieve outpatient follow-up. Her clinical course was complicated by recurrent infections requiring hospitalization and secondary adrenal insufficiency from intermittent glucocorticoid use with chemotherapy, requiring steroid hormone replacement. Her functional status significantly declined, and the decision was eventually made to stop chemotherapy and transition to inpatient hospice. She died approximately 5 months after initial presentation, 6 months after symptom onset.

Discussion

NUT carcinoma, especially of thyroid origin is an extremely rare entity with only 7 other published cases of thyroid-origin NUT carcinoma reported in the literature (Table 1) (4-9). An international NUT carcinoma registry exists to increase awareness of the disease and support future research. Our case brings awareness to this disease and broadens the differential of poorly differentiated thyroid cancer and anaplastic thyroid carcinoma, while also highlighting the importance of advanced diagnostic techniques.

NUT carcinoma is a rare and aggressive subtype of poorly differentiated squamous cell carcinoma typically arising

Table 1. Published cases of NUT carcinoma of thyroid

Article	Mutation	PD-L1%	Age, y	Sex	Extent of disease	Treatment	Outcome
Kuo et al 2021 (4)	*NSD3-NUTM1*	Not listed	34	Male	Thyroid with b/l central and lateral nodal metastases	Radical debulking surgery followed by chemotherapy, RT, and pembrolizumab.	No evidence of disease at 38 months postop
Scherman et al 2022 (5)	*NSD3-NUTM*	Not listed	38	Male	Thyroid with neck and mediastinal nodal metastases	Neoadjuvant chemotherapy and RT followed by left lobectomy for left level IV nodal recurrence followed by short trial of molibresib (BRD4-targeted therapy), discontinued due to drug induced cardiomyopathy. Carboplatin-taxol chemotherapy added for 2 cycles.	Died 21 months after initial diagnosis
Scherman et al 2022 (5)	*NSD3-NUTM1*	Not listed	37	Female	Extensive right-sided neck and thoracic nodal metastases	History of total thyroidectomy with central lymph node dissection plus RAI for PTC (47 mm pT3aN1a) with repeat surgery × 2 for recurrent PTC. Recurrent LAD 7 years after diagnosis of PTC led to 4th surgery—right level IV neck dissection and axillary dissection—revealing diagnosis of NC.	Unknown
Allison et al 2022 (6)	*NSD3-NUTM1*	Not listed	72	Female	Right and left thyroid lobe with extension into the isthmus causing tracheal deviation and vascular invasion	Total thyroidectomy, central lymph node dissection, and RAI.	Unknown
Agaimy et al 2021 (7)	*NSD3-NUTM1*	Not listed	42	Female	Right cervical region with infiltration of the thyroid bed and displacement of the trachea	Radiation with 70 Gy, chemotherapy with cisplatin, etoposide with partial remission. Treatment with molibresib (bromodomain and extraterminal domain protein inhibitor) for compassionate use, treatment stopped due to adverse effects (hepatotoxicity, thrombocytopenia, nausea).	Last known to be tumor free on imaging
Zhou et al 2022 (8)	*BRD4-NUTM1*	30%	38	Male	Left thyroid lobe with lateral cervical lymph node metastasis and bone metastasis on the 8th rib and L2 vertebra	Epirubicin, paclitaxel liposomes, and an engineered anti-programmed death 1 (PD-1) antibody (camrelizumab) and surgery.	Death 10 months after surgery (not described)
Shotton et al 2022 (9)	*BRD4-NUTM1*	Not listed	23	Male	Right thyroid with right lateral neck nodal metastases and lung metastases	Lobectomy with b/l central neck dissection followed by RAI, followed by repeat surgery.	Unknown
Case Presented In This Article	*NSD3-NUTM1*	100%	27	Female	Right greater than left thyroid involvement with extrathyroidal extension into the tracheoesophageal groove, cervical lymph nodes, lung metastases, metastases to iliac crest and lumbar spine	Prednisone, carboplatin, paclitaxel, pembrolizumab, and radiation.	Death 5 months after symptom onset

Abbreviations: b/l, bilateral; IV, intravenous; LAD, lymphadenopathy; NC, NUT carcinoma; PD-L1, programmed cell death ligand 1; postop, postoperative; PTC, papillary thyroid cancer; RAI, radioactive iodine, RT, radiation therapy.

from midline structures such as the thorax, head, and neck, although it can arise from any organ (1). Male and female individuals are affected equally and the median age at diagnosis is 16 to 22 years (2). The disease is characterized by rearrangement of the *NUTM1* gene on chromosome 15 (1-3). In about 70% of cases, the *NUTM1* gene is fused with the *BRD4* gene on chromosome 19 (1). *BRD4-NUTM1* complexes form large and expansive regions of chromatin termed *mega domains*, which cause aberrant transcription, leading to blocking of cellular differentiation and promotion of uncontrolled tumor cell growth (1). The *BRD4* gene is a part of the bromodomain and extraterminal domain (BET) family of proteins, also consisting of *BRD2*, *BRD3*, and *BRDT* (10). In the remaining 30% of cases, *NUTM1* is fused with other genes, such as *BRD3* and *NSD3* (1). This patient had a *NSD3-NUTM1* fusion. *NSD3* is a histone methyltransferase that binds to the extraterminal domain of BET proteins (11). The *NSD3-NUTM1* complex leads to increased transcription of specific genes while halting tumor suppressor genes (12, 13).

The histologic appearance of NUT carcinoma is distinctive but not diagnostic as it can overlap with that of other poorly differentiated tumors, such as nasopharyngeal carcinoma,

Table 2. Summary of the phase I BET inhibitor trials in patients with NUT carcinoma

Trial	Drug/dosing	Total n for NUT carcinoma	Noncomplete response (n)	Partial response (n)	Stable disease (n)	Progressive disease (n)	Not evaluable (n)
Lewin et al 2018 (18)	Birabresib 80 mg PO daily	9	Not applicable	3	3	2	1
Piha-Paul et al 2019 (19)	Molibresib 80 mg PO daily	19	1	4 (2 confirmed)	7	4	3
Ameratunga et al 2020 (20)	ODM-207 0.6-2 mg/kg PO daily	4	Not applicable	Not applicable	1	3	Not applicable
Shapiro et al 2021 (21)	RO6870810 0.65 mg/kg subcutaneous daily	7	Not applicable	2	4	1	Not applicable

Abbreviations: BET, bromodomain and extraterminal domain; n, number of participants; PO, oral.

small cell carcinoma, and lymphoma, making it a challenging diagnosis (1). NUT carcinoma has been underdiagnosed and misdiagnosed due to low awareness of the disease, but the increasing availability of advanced diagnostic testing has helped improve this issue (1, 2). IHC staining of greater than 50% of tumor nuclei is the recommended first-line test for diagnosis, with a high specificity and sensitivity (2). Testing for NUT carcinoma should be considered in poorly differentiated carcinomas without glandular differentiation arising in the chest, head, and neck (2). Molecular analysis can also establish the diagnosis, as well as identify the fusion partner to *NUTM1* (1). In this case, the diagnosis was made by NGS testing, identifying a *NSD3-NUTM1* fusion. Identifying the fusion partner to *NUTM1* is helpful as *NSD3-NUTM1* and *BRD3-NUTM1* fusions are associated with a significantly improved survival compared with *BRD4-NUTM1* fusions (3). In this case, IHC analysis of the thyroid excisional biopsy specimen also revealed a high *PD-L1* expression, prompting the addition of PD-1 targeted therapy.

NUT carcinomas are extremely aggressive and often widely metastatic on diagnosis, conferring a very poor prognosis, with a median survival of 6.7 months (2, 3). Thoracic tumors and *BRD4-NUTM1* fusions are associated with a worse survival (3). Currently, there is no standard treatment of NUT carcinoma, given that only minimal literature is reported. If feasible, local surgical resection and radiotherapy should be attempted, as they are both associated with improved 2-year overall survival. The patient was deemed not to be a candidate for surgical resection or debulking due to the gross extension into surrounding vital structures, including the trachea and esophagus; however, this decision was made when the patient was presumed to have anaplastic thyroid cancer. Surgical debulking possibly should have been reconsidered after the diagnosis of NUT carcinoma was revealed, given the data on improved outcomes with surgery. Chemotherapy with either platinum-containing regimens or Ewing sarcoma protocol are commonly used despite lack of evidence (1, 2). Targeted therapy for the *BRD4* portion has demonstrated efficacy in several phase 1 trials, however no cures were achieved (1, 2). PD-1 inhibitors may be beneficial in certain subtypes of NUT carcinoma.

BET bromodomain inhibitors were first studied in NUT carcinoma in 2010 (14). These inhibitors lead to the separation of *BRD4-NUTM1* as well as other *BRD4*-dependent *NUTM1* fusion partners, such as *BRD3-NUTM1*, *NSD3-NUTM1*, and *ZNF532-NUTM1* from chromatin, leading to the arrest of cell growth and differentiation of the tumor (11, 14-17). Several phase I trials of BET inhibitors have been undertaken in patients with NUT carcinoma (Table 2) (18-21). In the birabresib trial at a dose of 80 mg daily in participants with NUT carcinoma, a third of the patients demonstrated a partial response (18). The molibresib trial at a dose of 80 mg daily in participants with NUT carcinoma showed an overall response rate of 11% (19). The phase I trial of ODM-207 showed very little activity of the compound (20). Lastly, a subcutaneous drug R06870810 at a dose of 0.65 mg/kg daily had 2 participants with NUT carcinoma demonstrating a partial response (21). The first international NUT carcinoma symposium in 2021 highlights the additional therapies being investigated as well as future directions for therapy and to raise awareness and support patients with NUT carcinoma (22).

Our case highlights the challenge in diagnosis and treatment of NUT carcinoma as well as the importance of considering NUT carcinoma as a possible diagnosis of undifferentiated, aggressive, thyroid malignancy and brings attention to this rare disease.

Learning Points

- NUT carcinoma is a rare and aggressive subtype of squamous cell carcinoma, affecting young adults, typically arising from midline structures.
- NUT carcinoma is defined by rearrangement of the *NUTM1* (Nuclear Protein in Testis) gene on chromosome 15, involving fusion with the *BRD4* gene in most cases, but also with *BRD3* and *NSD3*.
- The histologic appearance of NUT carcinoma is distinctive but not diagnostic; immunohistochemical staining and molecular analysis can help to establish the diagnosis.
- Identifying the fusion partner to *NUTM1* is helpful as *NSD3-NUTM1* and *BRD3-NUTM1* fusions are associated with a significantly improved survival compared to *BRD4-NUTM1* fusions.
- Currently, there is no standard treatment for NUT carcinoma, but local surgical resection and radiotherapy should be attempted as they are both associated with improved 2-year overall survival.

Contributors

A. Cadesky: updated the literature as well as edited, revised, and submitted the manuscript. R.S.R.: edited and provided guidance in writing the manuscript. A. Carter: created the original draft of the manuscript and did the initial research. E.P.: edited the initial draft. S.J.: edited and provided guidance in writing the manuscript.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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