Case Report

Primary thyroid nuclear protein in testis carcinoma: a case report and literature review

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Background: Nuclear protein in testis (NUT) carcinoma (NC) is a rare, highly aggressive neoplasm, usually accompanying with *NUTM1* (NUT midline carcinoma family member 1) gene fusions. Primary thyroid NC is clinically rare and to date there is no established treatment guideline available for NC. We report a case of histopathologically confirmed thyroid NC and provide reference for diagnosis and treatment.

Case Description: We presented a 32-year-old female admitted to hospital with "painful neck swelling and progressive dysphagia". Preoperative ultrasound-guided core needle aspiration biopsy suggested a poorly differentiated tumor. Considering the tumor was totally unresected on computed tomography (CT) scan, a partial thyroidectomy was performed to obtain sufficient tissue for a clear diagnosis. Histopathological specimens showed features of sudden keratosis. Strong immunoreactivity with NUT was detected by immunohistochemistry (IHC) and thus confirmed the diagnosis of NC. CK5/6, P40 and P63 were partially positive exclusively in keratosis area. Next-generation sequencing (NGS) and RNA sequencing results revealed a *NSD3-NUTM1* fusion. The patient was treated with a combined regimen of radiotherapy of 70 Gy, chemotherapy with paclitaxel (albumin-bound), immunotherapy with nivolumab, targeted therapy with anlotinib and BET inhibitor NHWD-870, but the patient died 7 months after diagnosis.

Conclusions: Thyroid NC is a rare and distinct pathological subset of NUT carcinoma with a higher rate of *NSD3-NUTM1* fusion. In the clinical diagnosis process, we recommended performing NUT IHC for poorly differentiated thyroid tumors. Gene rearrangement detection is also helpful for diagnosis and treatment. At present, surgery and radiation are still first choices for NC, and advances in targeted immunotherapy such as bromodomain and end motif inhibitors (BETi) may bring better treatment options to patients.

Keywords: Nuclear protein in testis carcinoma (NUT carcinoma); thyroid gland; head and neck; case report

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Introduction

Nuclear protein in testis (NUT) carcinoma (NC) is a rare and aggressive malignancy. The tumors are mostly found in the midline and usually accompanied by chromosomal translocation t(15;19) (1). NC can occur at any age, but is more common in children and adolescents (2,3). NC originating in the thyroid is even rarer. By reviewing the literature, we found a few clinically reported cases, mainly focused on pathological studies (4-8). At present, there is no established treatment guideline for the disease, and the prognosis is poor (9). Here, we report the diagnostic and therapeutic course of a patient with NC originating in the thyroid gland with a *NSD3-NUTM1* fusion gene and review the literature with the aim of providing a reference for clinical diagnosis and treatment. We present this article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-77/rc).

Case presentation

A 32-year-old female patient presented in April 2022 with a painful anterior neck swelling and progressive dysphagia for 1 month. The patient's past history included a cesarean section 1 year ago and laser surgery for myopia 11 years ago, with no history of radiation exposure and no family history of tumors. The patient underwent thyroid ultrasound examination and found diffuse thyroid lesions with hypoechoic area in the right lobe (*Figure 1*). An ultrasound-guided fine-needle aspiration biopsy (US-FNAB) was recommended and the puncture smear of hypoechoic area showed medium-sized primitive cells with round to oval nuclei and sparse eosinophilic cytoplasm. Mitoses were common and atypical mitoses were seen. The pathology department considered it to be a specific type of malignancy and recommended obtaining more tissue for diagnosis. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was given by the patient's authorized attorney (her husband) to publish this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Over the next 10 days, the patient's neck swelling accelerated and developed hoarseness and shortness of breath, showing extremely rapid tumor growth rate. The patient was subsequently admitted to the Department of Otolaryngology-Head and Neck Surgery. On examination, the right lobe of thyroid gland was seen to be enlarged, hard, with indistinct borders, and the trachea was left deviated. An ultrasound-guided core-needle biopsy (US-CNB) was performed. Two small strips of the right lobe nodule punctured showed large necrotic areas and a few lamellar structures with atypical cells. Additional immunohistochemical findings did not support neuroendocrine tumor nor medullary thyroid carcinoma, and was considered as a poorly differentiated tumor. Serologic tests revealed decreased thyroid stimulating hormone (TSH) (0.03 μIU/mL) and the rest indicators (T3, T4, FT3, FT4, TG, TGAb, TPOAb) were in the normal range. Laryngoscopy showed right vocal cord immobility. Cervical computed tomography (CT) scan revealed a high possibility of thyroid malignant tumor, reaching the level of the upper edge of the aortic arch, possible invasion of trachea, esophagus, thyroid cartilage plate and cricoid cartilage, and multiple lymph nodes in the bilateral cervical region, and some of which were considered metastasis (*Figure 2*).

Since the type of tumor was still unclear and the patient had already developed dyspnea, we performed a partial thyroidectomy and tracheostomy under general anesthesia in order to remove sufficient tissue for a clear pathological diagnosis and to prevent the growth of the

Highlight box

Key findings

- We report an extremely rare case of primary thyroid nuclear protein in testis (NUT) carcinoma.

What is known and what is new?

- Thyroid NUT carcinoma (NC) is a rare and distinct pathological subset of NUT carcinoma with a higher rate of *NSD3-NUTM1* fusion, and its prognosis is mainly affected by the fusion partner, tumor extent and metastasis, thoroughness of surgical resection, and sensitivity to targeted immunotherapy.
- Uniform treatment guidelines for thyroid NC are lacking, so we recommend individualized treatment including complete surgery and supplemental radiation to remove the tumor as well as metastatic lymph nodes and targeted immunotherapy such as bromodomain and end motif inhibitors at an early stage.

What is the implication, and what should change now?

- The possibility of NC should be highly suspected when investigating patients with poorly differentiated thyroid tumors. NUT immunohistochemistry, next-generation sequencing, RNA sequencing and fluorescence in situ hybridization are all helpful methods for further definite diagnosis.

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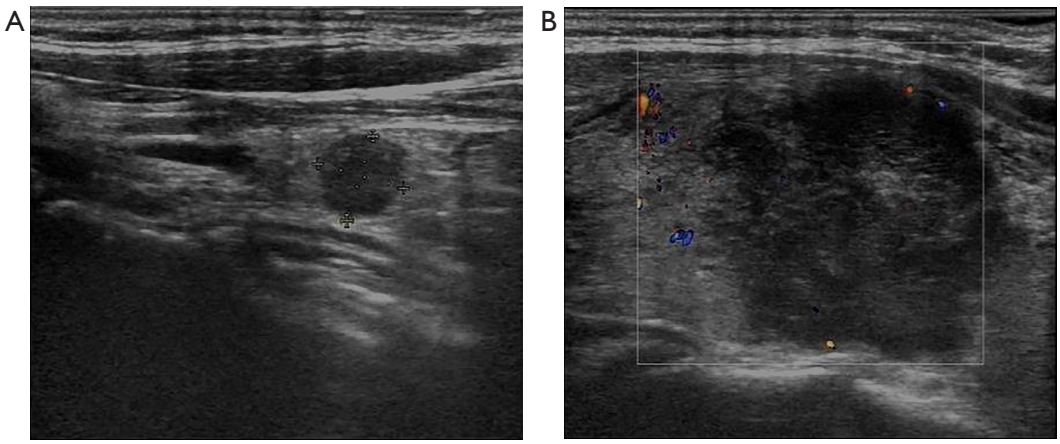

Figure 1 Ultrasound images of the patient's thyroid gland. (A,B) The right lobe of the thyroid was enlarged and the echogenicity of the gland was diffusely unevenly reduced. Hypoechoic area was seen in the right lobe, ranging from 3.45 cm × 2.50 cm, with unclear and irregular boundary, and blood flow signal was seen inside.

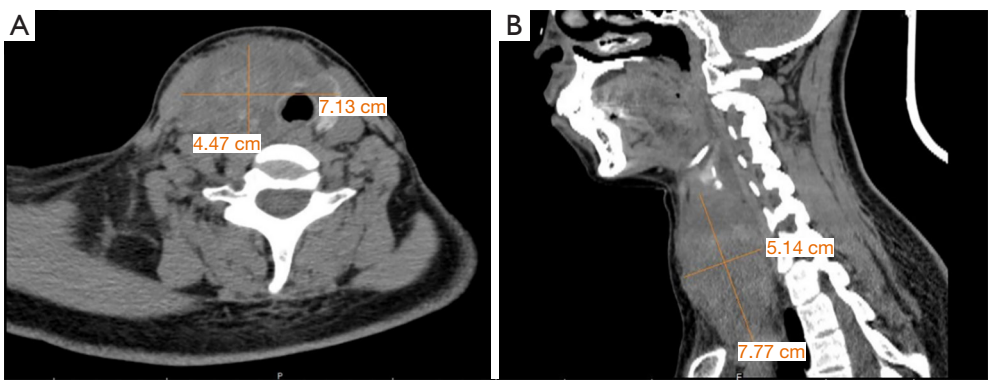

Figure 2 Axial (A) and sagittal (B) CT images of the mass preoperatively. CT, computed tomography.

mass in the trachea from causing asphyxia. During surgery, the thyroid cartilage plate, cricoid cartilage, 1–5 tracheal lumen and the esophageal lumen were found to be invaded by the tumor. Besides, the tumor had obliterated the right common carotid artery and the aortic arch, and these above structures were fused with the tumor and it was difficult to perform a radical *en bloc* resection of involved tissues. Postoperative pathology revealed the mass was consistent with NUT carcinoma, invading blood vessels, fat, muscles and thyroid tissue. Histologically, the tumor cells were large, with abundant eosinophilic cytoplasm and macronucleoli, and infiltrated the gland in the form of nests and cords with sudden keratosis observed (*Figure 3*). Additional immunohistochemical findings are as following: BRAF (–), CD56 (–), Syn (–), Ki-67 (about 70% +), TTF-1 (–), PAX-8 (–), CK5/6 (patchy +), P63 (patchy +), P40 (patchy +), CD5 (–), CD117 (–), CK (patchy +), BCL-2 (–), P53 (wild type), NUT (+, repeated), Vimentin (–), INI-1 (not deficient), BRG-1 (not deficient), EMA (–), CD34 (–), CD30 (–), LCA (–), CD3 (–), CD20 (–), ALK (–), CD38 (–), MUM-1 (–), CK-H (patchy +), CK-L (equivocal), ERG (–), p16 (about 20% +), EVG + HE (showing vascular invasion), EBER (–, *in situ* hybridization).

Postoperative staging positron emission tomography-CT (PET-CT) and enhanced magnetic resonance imaging (MRI) scan were performed on the patient, which showed residual mess of NC in the right neck with multiple invasions of surrounding structures (right sternocleidomastoid muscle, right common carotid artery, aortic arch, trachea, thyroid cartilage plate, cricoid cartilage, cervical esophagus, two lobes of the thyroid gland, right laryngeal recurrent nerve), with multiple regional lymph

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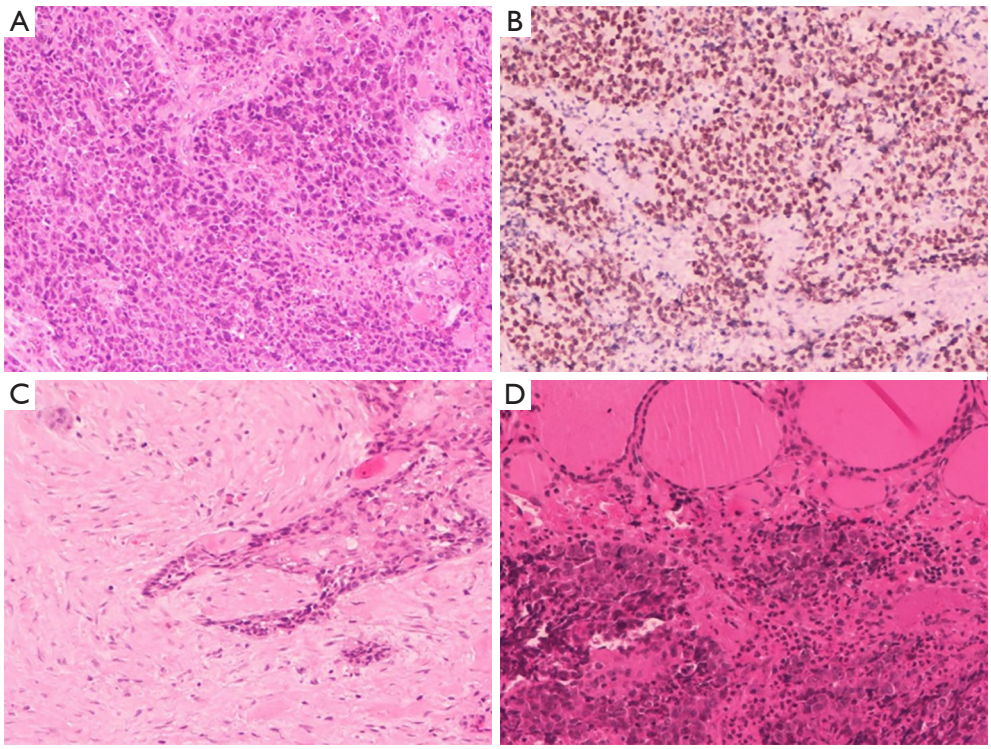

Figure 3 Histologic features of the tumor. (A) Tumor cells diffusely infiltrating thyroid gland tissues with eosinophilic cytoplasm and macronucleoli, with coagulative necrosis and sudden keratosis observed (hematoxylin and eosin, 200×). (B) Immunohistochemical NUT staining showing diffuse nuclear staining in tumor cells (staining >50% of tumor nuclei, 200×). (C) Invasion of muscle tissues (hematoxylin and eosin, 200×). (D) Nests and sheets of primitive cells infiltrate thyroid follicular tissues (hematoxylin and eosin, 200×). NUT, nuclear protein in testis.

node metastases (*Figure 4*). The imaging findings are consistent with those seen during the operation.

The patient was then advised to undergo genetic testing. The next-generation sequencing (NGS) and RNA sequencing results revealed an *NSD3-NUTM1* fusion. Moreover, two possibly pathogenic mutations in *ABL1* and *PPM1D* were also identified, with slightly increased tumor mutational burden (TMB) (1.86 Muts/Mb, 50.64%). However, the programmed cell death-ligand 1 (PD-L1) expression testing was negative. The human leukocyte antigen (HLA) Class I was heterozygous.

After multidisciplinary consultation with the Oncology Department, Radiotherapy Department, and Pathology Department, considering that the patient's tumor grew very fast and there were few opportunities for surgical resection, we formulated a comprehensive plan for the patient including radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Drug therapy was paclitaxel (albumin-bound) (260 mg/m^2, intravenous drip, once every 3 weeks), programmed death-1 (PD-1) inhibitor nivolumab (200 mg, intravenous drip, once every 2 weeks) and multi-target tyrosine kinase receptor inhibitor anlotinib (8 mg qd, orally every 2 weeks with 1 week off). One month later she started radiotherapy with a total dose of 70 Gy and divided into 7 weeks (5 times a week, 2.0 Gy each time). The patient's drug therapy continued for 2 months, with paclitaxel (albumin-bound) and nivolumab administered twice, and Anlotinib administered for a total of 4 weeks. During the treatment, the patient's repeated CT examination did not show any significant reduction nor enlargement of the tumor. After 3 months of combination therapy, follow-up evaluation of the patient revealed that although there was not particularly much growth in tumor volume, the TSH level spiked to 13.78 μIU/mL, and other indicators suggested severe hypothyroidism, suggesting that the tumor cells continued to proliferate, with very few normal thyroid cells remaining. Due to intolerance of side effects, the patient requested that the current regimen

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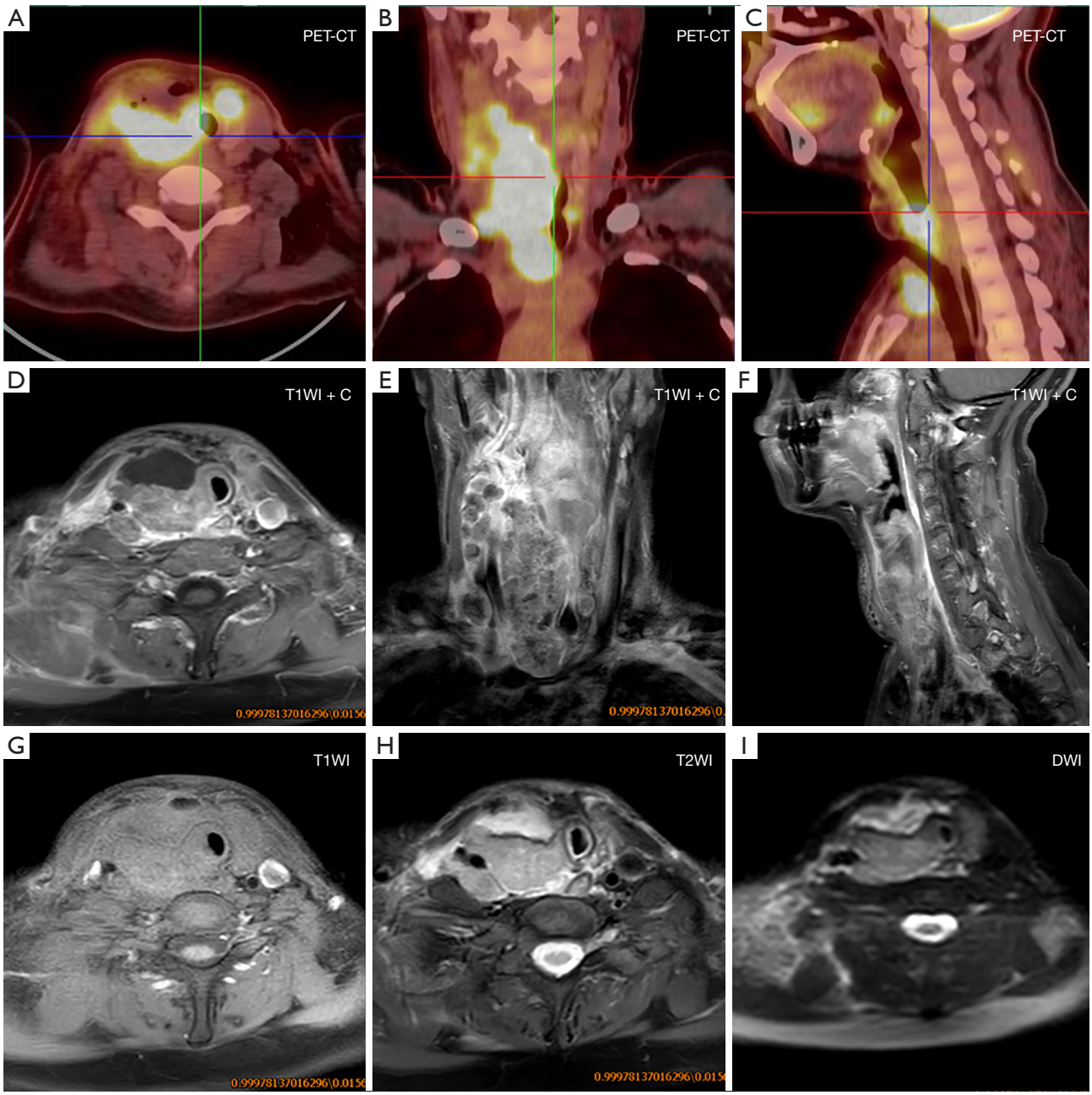

Figure 4 PET-CT and enhanced MRI of the thyroid tumor. (A-C) Axial, coronal and sagittal PET-CT images of the mass postoperatively. (D-F) Axial, coronal and sagittal MRI (T1WI + C) images of the mass postoperatively. (G-I) Axial MRI images of T1WI, T2WI and DWI sequences of the mass postoperatively. PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; T1WI + C, contrast-enhanced T1-weighted imaging; T2WI, T2 weighted image; DWI, diffusion-weighted imaging.

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be discontinued. Treatment with bromodomain and end motif inhibitors (BETi) NHWD-870 was initiated as a part of a "compassionate use" program. A follow-up CT scan 2 months later showed no significant tumor progression. Unfortunately, the patient developed more severe tracheoesophageal fistula and dysphagia seven months after diagnosis, and her pneumonia rapidly deteriorated, eventually leading to her death.

Discussion

NC is a rare malignant tumor which was originally found in midline organs, so it is also named "NUT midline carcinoma" (NMC) (1,3). However, many non-midline organs have also been diagnosed with NC (10). NUT is the protein product of *NUTM1* gene (located on the long arm of chromosome 15). Under physiological conditions, it is expressed in spermatogenic cells after meiosis of testis and is essential for male fertility. NUT has been shown to strongly enhance the activity of its downstream effector (histone acetyltransferase p300) through direct interaction in spermatogenic cells and NC cells (11). The NUT fusion proteins can also interact with chromatin to block cell differentiation and promote cell proliferation (12,13). In most cases of NC, *NUTM1* gene rearranges with bromodomain-containing protein 4 (*BRD4*) genes on chromosome 19 to form *BRD4-NUTM1* fusion genes, of which its possibility of happening is considered to be as high as 86% by some studies (14). Meanwhile, there are *BRD3-NUTM1*, *NSD3-NUTM1* (such as in our case), *ZNF532-NUTM1* and *ZNF592-NUTM1* fusion genes, which are collectively referred to as NUT variants (15-17). A recent study reviewing 12 cases of thyroid NC showed a higher rate of *NSD3-NUTM1* fusion (75%) compared to those nonthyroidal primary NCs (18). However, *NSD3* is not a unique fusion partner to thyroid, so whether thyroid NC is a distinct subset of NC remains to be investigated.

As a cancer associated with simple chromosomal translocations and few additional oncogenic mutations, *NUTM1* fusion may be the single trigger sufficient to cause carcinogenesis in NC (12,13), analogous to the role of the *BCR-ABL* fusion gene in chronic myelogenous leukemia. The absence of multiple molecular alterations in our patient confirms once again that NC development is not a process of accumulation of genetic alterations. However, we cannot conclude that the only two gene mutations detected in this case (*PPM1D* and *ABL1*) are completely unrelated to the development of NC. In addition, researchers have reported that mutations of protein PPM1D have oncogenic effects by influencing regulators of cell cycle, DNA damage response, and p53 pathways in the formation of diffuse midline glioma (19). *ABL1* gene encodes protein which exists in nucleus and cytoplasm and belongs to tyrosine kinase, mainly involved in cell differentiation, division and stress response. Specific mutations will make *ABL1* become a protooncogene, and ABL1 protein will continue to activate and lead to cell carcinogenesis (20). However, the relationship between the above genes and NC has not been reported, and it is difficult to investigate due to the rarity of the disease.

At present, the diagnosis of NC is mainly based on detection of *NUTM1* rearrangement [fluorescence in situ hybridization (FISH), NGS or RNA sequencing] or by positive NUT IHC (staining >50% of tumor nuclei) (18). Histologically, NCs are composed of relatively monotonous cuboidal cells with a high nuclear-to-cytoplasm (N/C) ratio that may be accompanied by focal keratinization (10), so sometimes it is difficult to distinguish NC from squamous cell carcinoma and undifferentiated carcinoma by cell morphology alone. One study showed that about 33% of NC can exhibit the histological characteristics of "focal abrupt keratinization", showing a tendency to mature squamous cell differentiation (21). In this case, the tumor did express squamous cell carcinoma markers (CK5/6, P40 and P63 are partially positive), consistent with this feature. Haack *et al.* in 2009 evaluated the accuracy of NUT monoclonal antibody (C52) in diagnosing NUT cancer patients, with sensitivity of 87% and specificity of 100% (22). Immunohistochemical detection of NUT showed diffuse nuclear staining in tumor cells of this patient, thus determined the diagnosis of NC and prompted additional genetic analysis. Although a positive PAX-8 or TTF-1 result is more supportive of a thyroid origin, a recent review of a small sample showed only 55% of cases were positive for PAX-8, and 54% for TTF-1 (18). Positive expression of both PAX8 and TTF-1 suggests that tumor cells may be derived from high-grade follicular cells. Some scholars estimate that about hundreds of NC cases are missed every year due to its rarity and lack of characteristic histological features (23). Therefore, NUT IHC is a necessary and relatively convenient method when poor differentiation is observed histologically. NGS, RNA

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sequencing and FISH are all helpful methods for further rearrangement analysis, but they have the disadvantage of being relatively time-consuming and expensive. Although NC also lacks specific manifestations on imaging (i.e., CT, MRI, and FDG-PET), these examinations are essential for assessing tumor extent and metastasis and for determining treatment options.

NC is highly malignant and usually has a dismal prognosis. Relevant literature has reported a median survival of 6 to 7 months and a 1-year survival rate of 30% for NC in different organs (24). The location of the primary tumor and fusion partners have been shown to be prognostic factors—the prognosis of non-thoracic primary NC patients is better than that of thoracic primary NC patients, and the median survival time of patients with *BRD3* or *NSD3* fusion partners is significantly better than that of patients with *BRD4* fusion partner among non-thoracic NC patients (21). Porocarcinoma is a malignant skin adnexal tumor harboring the *YAP1-NUTM1* gene fusion but can be cured by complete resection with a good prognosis (25). Many patients are treated when the tumor has metastasized, and the most common metastatic sites are the lymph nodes, bones, lungs, pleura, skin and subcutaneous soft tissues (9,26). Patients with multiple metastases at initial diagnosis have a worse prognosis (27). However, there are no standard treatment recommendations for NC to date. Giridhar *et al.* retrospectively analyzed 119 cases of lung NC and found that radiotherapy might benefit the patients (2). Bauer *et al.* conducted a retrospective analysis of 63 patients with NC, and concluded that extent of surgical resection and initial radiotherapy were the only predictors of improving the survival rate, while chemotherapy could not significantly improve the survival rate (9). In this article, a total of 7 cases were included (4-8), and their demographics, diagnosis, treatment, and outcome data are listed in *Table 1*. By reviewing these literatures, we can see that patients who underwent primary surgical resection of the tumor had an improved prognosis, and resection with negative margins might be associated with improved survival rates. In this case, at the time of diagnosis, the patient had multiple lymph nodes metastases, with trachea, esophagus and major vascular invasion, and had lost the opportunity for surgical radical removal. The oncologist still started nivolumab on her, considering that HLA Class I heterozygous type was more effective than homozygous type in receiving immune checkpoint inhibitors, including CTLA-4, PD-1 and PD-L1 monoclonal antibody (28). Our combination treatment regimen did significantly delay the progression of the tumor, compared with the tumor growth rate at the initial stage of the disease, which may be worthy of further study.

However, at the time of follow-up of this case, we also felt that patients with NC had limited benefit from conventional chemoradiotherapy. New treatment hopes lie in targeting fusion partners, including inhibition of DNA binding by BETi, or modification of downstream histones by histone deacetylase inhibitors (HDACi) (29,30), as Imatinib works in treating chronic myelogenous leukemia with BCR-ABL fusion gene. In this case, BETi NHWD-870 did show a significant inhibitory effect on tumor growth within 2 months. Unfortunately, the patient's condition deteriorated rapidly due to severe tracheoesophageal fistula, dysphagia, and pneumonia, otherwise we might have been able to observe her efficacy for a longer period of time. The overall survival time of the patient was 7.0 months, similar to that reported in the literature.

Based on the above case and literatures, we conclude that once sufficient evidence is obtained for the diagnosis of thyroid NC, aggressive surgery and targeted immunotherapy should be taken as soon as possible, such as complete tumor removal and early application of BETi. In the future, we still need to collect relevant cases to obtain a larger sample size to explore and summarize the best diagnosis and treatment strategies for primary thyroid NC.

Conclusions

In summary, NC is a solid tumor with high malignant degree, high misdiagnosis rate and high mortality rate. NC is characterized by recurring oncogenic translocations caused by defining fusion gene, which differs from classic accumulative mutational carcinogenesis. Patients often have regional lymph node or systemic metastasis when diagnosed. In the clinical diagnosis process, it is recommended to timely perform NUT immunohistochemical detection and gene rearrangement detection for undifferentiated or poorly differentiated tumors. At present, surgery and radiotherapy are still first choices for NUT carcinoma, and the in-depth research of targeted immunotherapy may bring better treatment options to patients.

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Table 1 Clinical features of 7 patients with thyroid NC

Case/author [year]	Age (years)/ gender	Diagnostic test	Treatment	Outcome
Agaimy *et al.* [2021] (4)	42/F	NUT IHC (positive); NGS and FISH (NSD3::NUTM1 fusion)	(I) Surgery (complete resection). (II) Local irradiation (70 Gy). (III) Chemotherapy (cisplatin and etoposide). (IV) BETi (molibresib, limited course due to adverse effects)	Alive with no evidence of disease 18 months after diagnosis
Scherman *et al.* [2022] (5)	38/M	NUT IHC (positive); NGS (ALK mutation); RNA sequencing (NSD3::NUTM1 fusion)	(I) Chemotherapy according to the Euro Ewing 2012 protocol (details unknown). (II) Local irradiation (details unknown). (III) BETi (molibresib, limited course due to adverse effects). (IV) Chemotherapy (carboplatin/ taxol)	Died 21 months after diagnosis
	37/F	NUT IHC (negative); NGS (CDKN2A mutation); RNA sequencing (NSD3::NUTM1 fusion; CDKN2A, SMARCA4, NOTCH2, KDM6A, SPOP mutations)	(I) Surgery (neck and axillary dissection for metastatic lymph nodes, with a history of total thyroidectomy for papillary thyroid carcinoma 4 years before). (II) No systemic treatment received	Alive with possible metastatic lymph nodes 18 months after diagnosis
Zhou *et al.* [2022] (6)	38/M	NUT IHC (positive); FISH and NGS (BRD4::NUTM1 fusion); qRT-PCR (BRD4::NUTM1 fusion); RNA sequencing (IGKV gene fusions)	(I) Surgery (details unknown). (II) Chemotherapy (epirubicin and paclitaxel liposome). (III) PD-1 inhibitor (camrelizumab)	Died 10 months after diagnosis
Allison *et al.* [2022] (7)	72/F	NUT IHC (equivocal: <10% staining); NGS (no pathogenic mutations detected); FISH (NSD3::NUTM1 fusion); RNA sequencing (NSD3::NUTM1 fusion)	(I) Surgery (complete resection). (II) Radioactive iodine ablation	Alive with no evidence of disease 3 months after diagnosis
Kuo *et al.* [2021] (8)	34/M	NUT IHC (equivocal); FISH (NSD3::NUTM1 fusion)	(I) Surgery (complete resection). (II) Chemotherapy (paclitaxel-carboplatin). (III) Local irradiation (66 Gy, with cisplatin as a radiation sensitizer). (IV) PD-1 inhibitor (pembrolizumab)	Alive with no evidence of disease 38 months after diagnosis
Current patient	32/F	NUT IHC (positive); NGS and RNA sequencing (NSD3::NUTM1 fusion; PPM1D and ABL1 mutations)	(I) Local irradiation (70 Gy). (II) Chemotherapy (paclitaxel). (III) Tyrosine kinase inhibitor (anlotinib). (IV) PD-1 inhibitor (nivolumab)	Died 7 months after diagnosis

NC, NUT carcinoma; F, female; M, male; NUT, nuclear protein in testis; IHC, immunohistochemistry; NGS, next-generation sequencing; FISH, fluorescence in situ hybridization; ALK, anaplastic lymphoma kinase; qRT-PCR, quantitative reverse transcription polymerase chain reaction; BETi, bromodomain and end motif inhibitors; PD-1, programmed death-1.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-77/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-77/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-77/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was given by the patient's authorized attorney (her husband) to publish this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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