Case Report

Case report: NUT carcinoma in an elderly woman with unique morphology and immunophenotype highlights a diagnostic pitfall

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Background: NUT carcinoma (NC) is a rapidly progressing and rare neoplasm that primarily affects younger patients and has a survival time of about 1 year. Most of these neoplasms express epithelial markers with no neuroendocrine markers observed. Retrospective studies have shown that pathologists and clinicians do not have a sufficient understanding of the disease due to the lack of common clinical manifestations, imaging, and morphological features.

Case Description: A 60-year-old female presented at Beijing Friendship Hospital, showing repetitive epistaxis, nasal pain, and nasal congestion with obvious masses in the right nasal sinus and frontal sinus. Microscope analysis revealed two unique morphological changes which have not been previously reported in the existing literature: (I) small spindle cells with sparse cytoplasm and densely stained nuclei and (II) large tumor cells with abundant cytoplasm, some cells resembling plasma cells. The sudden appearance of keratinization was also a prominent feature. Immunohistochemical staining showed differences between the two cell morphologies. Small spindle cells simultaneously expressed CK5/6 and P40, and the Ki67 proliferation index was 40%. The large round cells did not express CK5/6 and P40 but were focal positive for synaptophysin and the Ki67 index was 10%. NUT and P63 were strongly expressed in both cell types and fluorescence in situ hybridization (FISH) revealed *BRD4-NUTM1* translocation. Following 20 rounds of postoperative radiation treatment, the patient was alive and no recurrence or metastasis was observed during a 5-month follow-up.

Conclusions: We present novel information from the oldest known and surviving patient of NC originating in the nasal cavity with unique morphological features and different immunohistochemical results. NUT antibody testing should be performed in undifferentiated or poorly differentiated malignancies, particularly those with either or both cytoplasmic vacuolation of medium-sized cells and abrupt keratinization, irrespective of patient age.

Keywords: NUT carcinoma (NC); sinonasal tract; BRD4-NUTM1; NUT; case report

Submitted Feb 20, 2022. Accepted for publication May 17, 2022.
doi: 10.21037/tcr-22-364
View this article at: https://dx.doi.org/10.21037/tcr-22-364

Introduction

NUT carcinoma (NC) is an extremely aggressive and rare neoplasm. At present, there are no more than 30 cases reported worldwide originating in the nasal cavity. This low number is attributed to an insufficient understanding of this type of tumor by clinicians and pathologists which can result in a missed diagnosis. In 2012, of the 151 cases of primary paranasal sinus carcinoma, only three cases (2%) of NC were identified (1). In 2014, Gökmen-Polar *et al.* (2) identified two cases of NC (1.8%) from 110 cases of thymic

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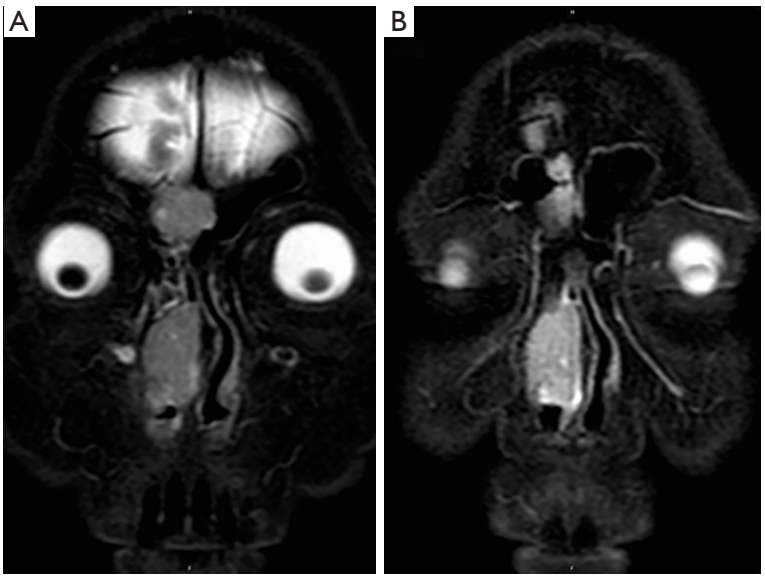

Figure 1 Magnetic resonance imaging showing irregular a heterogeneously enhanced soft tissue lesion. (A) T2 imaging, coronal plane. (B) T1 imaging, coronal plane.

carcinomas. Earlier NC study showed that NC tends to occur in the midline position of children and adolescents (3). However, here we present a unique case of NC in an elderly woman, who is the oldest known patient with NC in the nasal cavity. Additionally, 19 cases of NC primary occurring in the nasal cavity with typical clinical data are summarized and the clinical, pathological, and molecular characteristics along with current targeted therapies of the NC are provided. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-364/rc).

Case presentation

A 60-year-old woman was treated for epistaxis and nasal pain. The main complaint was a 4-year history of recurrent epistaxis and recent development of nasal congestion, nasal bleeding, paroxysmal sneezing, and a runny nose within the past 10 days. Allergic rhinitis was diagnosed at an initial visit to another hospital but the patients showed no significant improvement after treatment. When the patient was first examined at Beijing Friendship Hospital, there was no obvious cause of nasal pain. A nasal endoscopic examination revealed a significant mass blocking the nostril in the right sinonasal tract extending from the lateral wall of the nasal cavity to the nasal vestibule. The lesion was a soft ulcer on the surface with a light pink mucosa and left deviation of the nasal septum. Cranial computed tomography (CT) analysis revealed a CT density of about 40 HU and the bone around the lesion was compressed and thin. Magnetic resonance imaging showed an irregular heterogeneously enhancing the soft tissue lesion and blocking the right nasal cavity and frontal sinus (longest diameter of 2.5 cm × 1.3 cm, *Figure 1A*,*1B*). Both T2W1 and T1W1 fat suppression sequences showed moderately high signal intensity. The surrounding bone compression and thinning within the nasal septum bent to the left and the local boundary between the right inferior turbinate and the lesion was unclear. During operation, irregularly shaped masses with surface ulcers were found in the right nasal cavity and frontal sinus, and biopsies were performed. Exploration of the tumor boundary revealed the root at the lateral wall of the right sinonasal tract, the posterior end reached the middle turbinate, the lower part to the inferior turbinate, and the upper part to the olfactory fissure area. The lesion was ablated with low-temperature plasma up to the olfactory fissure area at the top of the nose and back to the middle turbinate.

Histopathology revealed poorly differentiated nest-like tumors comprised of a dense cell arrangement accompanied by extensive necrosis. Two types of tumor cells were observed, 20% of the cells were small fusiform cells with sparse cytoplasm and densely stained nuclei and the remaining 80% of cells were medium and large round cells

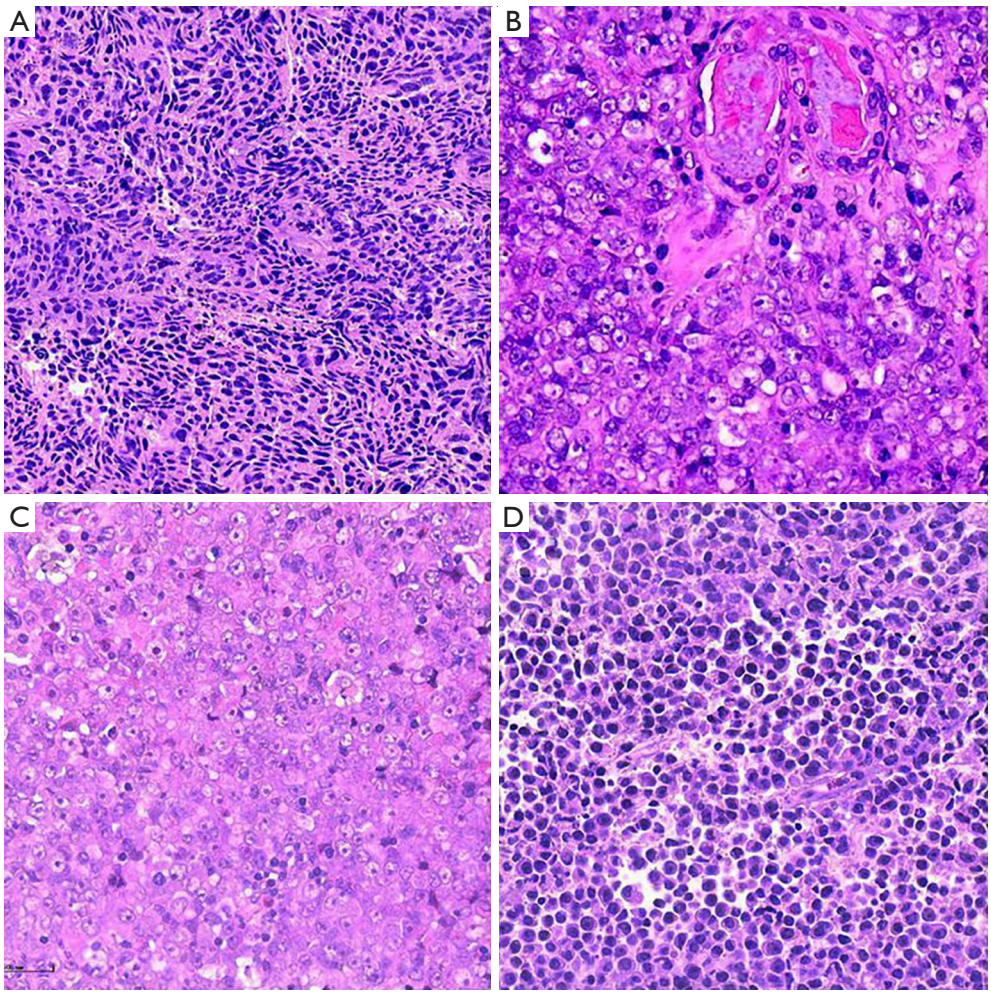

Figure 2 Morphological features of the NC. (A) Fusiform and irregular cells with sparse cytoplasm and densely stained nuclei (H&E stain, magnification ×200). (B) Sudden appearance of keratosis (H&E stain, magnification ×400). (C) High-power magnification reveals medium and large tumor cells with sparse cytoplasm a d round or oval nuclei with obvious nucleoli (H&E stain, magnification ×400). (D) Some cells with eosinophilic cytoplasm, like plasma cells were detected (H&E stain, magnification ×200). NC, NUT carcinoma.

with abundant cytoplasm, round or oval nuclei with obvious nucleoli and some cells showed eosinophilic cytoplasm resembling plasma cells. In addition, a phenomenon that cannot be ignored was the sudden appearance of keratosis in the poorly differentiated area (*Figure 2A-2D*).

The immunohistochemistry (IHC) results differed between the two cell morphologies. The small spindle cells expressed CK5/6 and P40, and the proliferation index of Ki67 was relatively high, about 40%. Whereas, the large round cells did not express CK5/6 and P40, were focal positive for synaptophysin, and the Ki67 index was 10%. Both cell types strongly expressed NUT (Clone C52B1, 1:200, Cell Signal Technology, Danvers, MA, USA) and P63 *(Figures 3-5*). The cytokeratin AE1/AE3 were punctate positive in limited areas. Chromogranin A, CD56, CD45RO, NKX2.2, P16, Vimentin, S-100 were all negative. The morphological and immunophenotypic features indicated NC. The *BRD4-NUTM1* rearrangement was identified via the fluorescence in situ hybridization (FISH) test and the patient was ultimately diagnosed with NC (*Figure 6*). Following twenty doses of postoperative radiotherapy, the patient remained alive five months postoperatively.

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

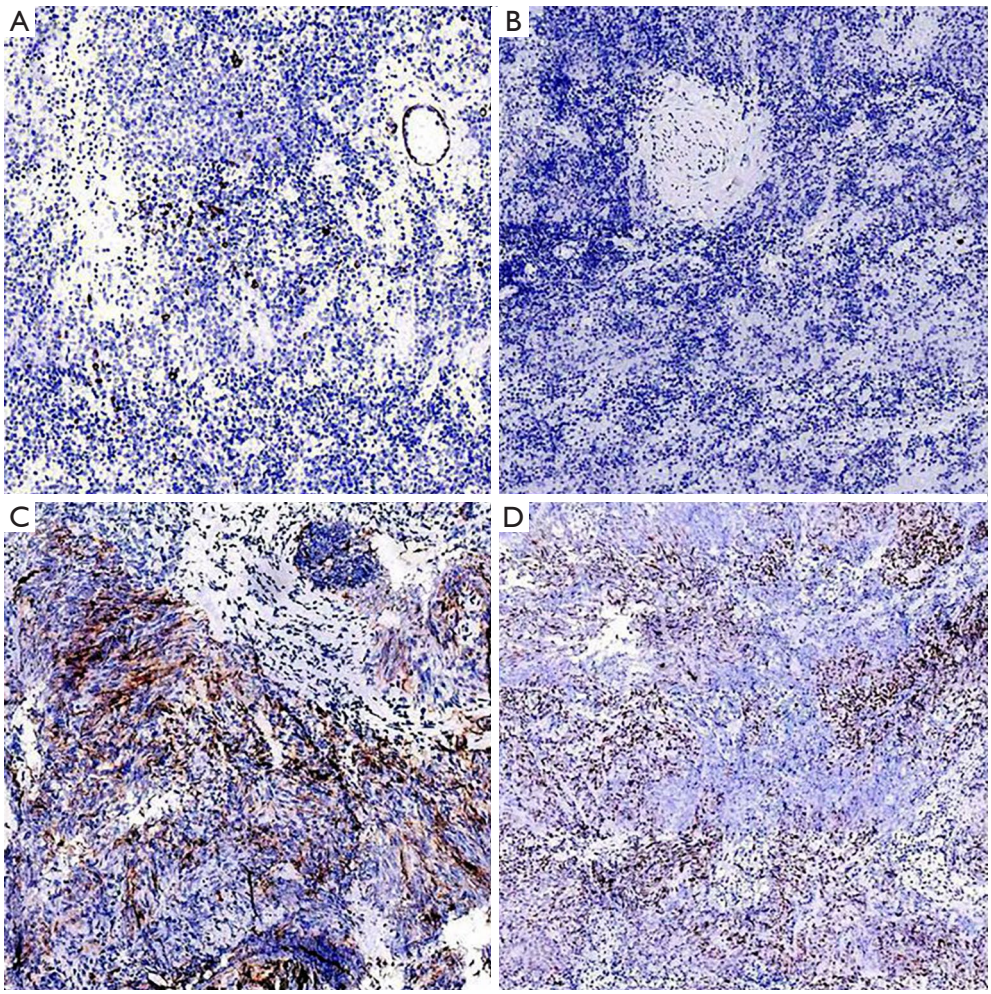

Figure 3 Immunohistochemical expression of two different cell morphologies for the NC. (A) CK5/6 and (B) P40 were negative in the round cell region (magnification ×200). However, (C) CK5/6 and (D) P40 were simultaneously positive in the small spindle cell region (magnification ×200). NC, NUT carcinoma.

Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

NC is an aggressive and rare carcinoma. The molecular feature most commonly observed is a *BRD4-NUTM1* translocation and, in a few cases, fusion of the *NUTM1* with *BRD3* and *NSD3* genes was observed (4).

The details for the clinical characteristics, IHC, and molecular testing of 19 primarily sinonasal tract NC patients are summarized in *Tables 1*,*2*. The median patient age was 42 years old, with the youngest patient being 10 years old and the oldest patient 60 years old (our reported case). The male to female ratio was 1.38:1. Five patients accepted chemotherapy and radiotherapy separately, three patients accepted chemoradiotherapy after surgery. The median survival time was 6 months (range, 1–16 months). IHC staining was observed for 89.4% NUT, 63.1% AE1/AE3, and 57.9% P63 expression and approximately 33% showed P40 and P16 expression. Only two cases expressed synaptophysin, including our reported case. *BRD4-NUTM1* fusion rearrangement was present in six patients and *NUTM1* gene rearrangement was present in one patient.

NC is likely underdiagnosed because it was originally

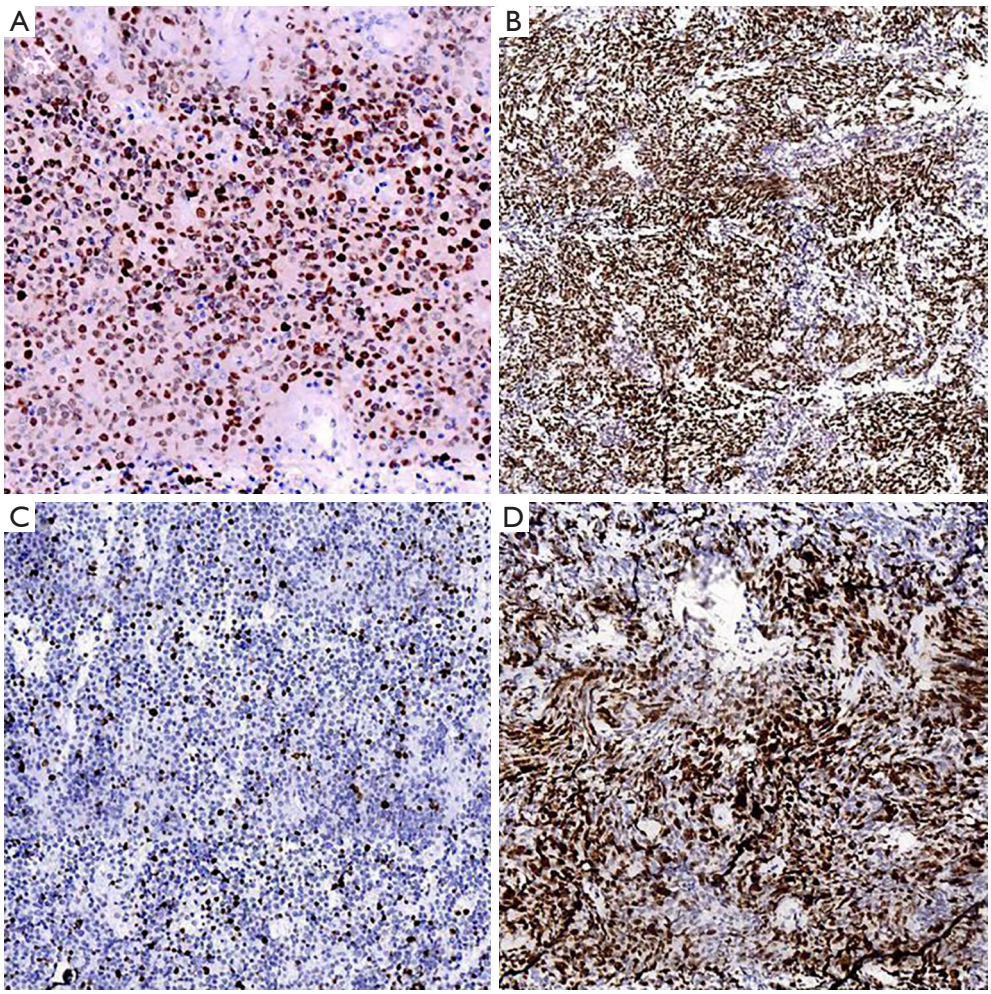

Figure 4 Immunohistochemical expression of two different cell morphologies of the NC. (A) P63 was positive in spindle cells (magnification ×400) and (B) round cells (magnification ×200). (C) The Ki67 proliferation index was 10% in the round cell region and (D) the Ki67 index is up to 40% in the spindle cell region (magnification ×200). NC, NUT carcinoma.

found in midline organs, often called "NUT midline cancer", and initial report indicated that NC occurs only in children and adolescents (3). However, according to recent studies, NC can occur at many sites and in patients of all ages (3,13,14). This is consistent with the information we have summarized in *Table 1*. Of the 19 NC patients evaluated, the median age was 42 years old, of which the youngest patient was 10 years old and the oldest patient was 60 years old (our reported case). Unexpectedly, the most common site of NC was not the head and neck (~33%) but the lung (~50%). The recent literature reports primarily on lung NC (15,16). Moreover, an increasing number of non-midline positions have been reported, including the pancreas (3), salivary glands (17), and lacrimal sac (9). Malignant tumors in the nasal cavity are more common in head and neck tumors, accounting for about 50% of cases; however, NC of the nasal cavity is highly invasive and often invades the surrounding areas, among which the frontal sinus and ethmoid sinus are the most common (18). This clinical feature can serve as a diagnostic hint of NC for clinicians. At present, no predisposing factors of NC have been identified, Epstein-Barr virus, human papillomavirus infection, and smoking were not found to be associated with NC (14,19).

Morphologically, the microscopic appearance of NC is not specific. Undifferentiated carcinoma or squamous cell carcinoma is often diagnosed for lack of typical morphological features (20). It is not necessarily difficult to diagnose NC; however, it is often not considered

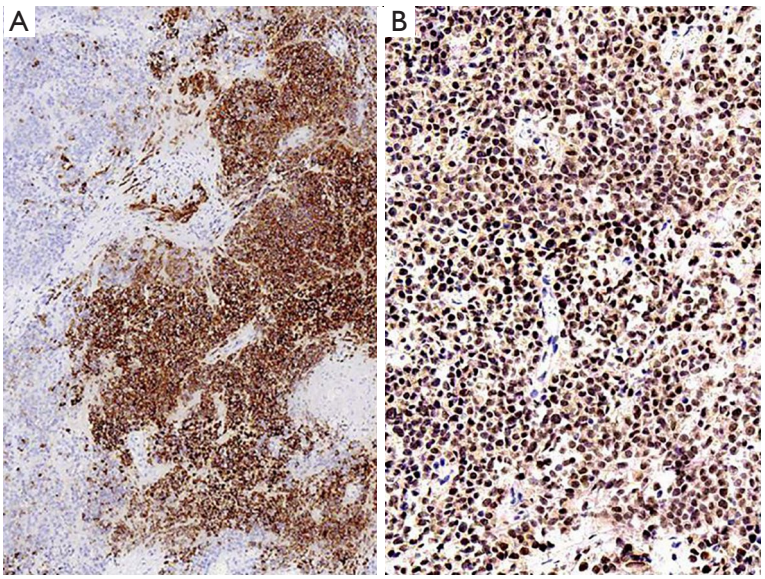

Figure 5 Immunohistochemical staining of the NC. (A) Synaptophysin with focal positive in the round cell region (magnification ×200) and (B) NUT nuclear immunostaining positive (magnification ×400). NC, NUT carcinoma.

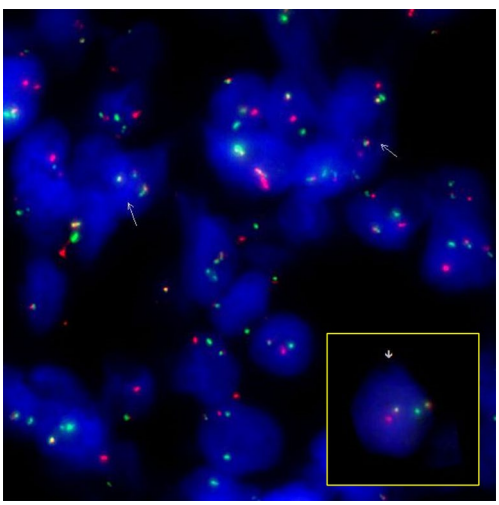

Figure 6 FISH results showing typical *BRD4-NUTM1* translocation: the red signal represents BRD4, the green signal represents *NUTM1*, and yellow signal indicate fusions (magnification ×400). Arrows show two yellow fusion signals. FISH, fluorescence in situ hybridization.

as a potential diagnosis. The appearance of sudden squamous differentiation within the lesion, especially in undifferentiated areas, was first reported as an indicator for an NC diagnosis via histopathology (21). Subsequent literature has concluded that the frequency of squamous cell differentiation in NC can be as high as 50% to 82%, which may be helpful in its diagnosis (1). We identified and summarized the coexistence of two types of cells based on shape and size for the first time. Small fusiform cells with sparse cytoplasm and densely stained nuclei and medium to large tumor cells with sparse cytoplasm, round or oval nuclei with obvious nucleoli were observed. Additionally, some cells with eosinophilic cytoplasm, with eccentric nuclei without nucleoli, resembling plasma cells were also noted. These traits distinguish NC from other poorly differentiated carcinomas or sarcomas, such as olfactory neuroblastoma, lymphoma, undifferentiated carcinoma, and Ewing sarcoma. Cytoplasmic vacuolation of medium-sized cells and abrupt keratinization are indicators that NUT antibody testing should be conducted to confirm NC. The case presented here serves as an important reminder to pathologists that the possibility of NC should be considered for round or spindle cells with or without sudden keratosis in the malignant neoplasm of the head and neck.

As an inexpensive and rapid method for NC diagnosis, NUT antibody is particularly important and has 100% specificity to diagnosis (22). Unfortunately, at present most Chinese hospitals do not consider this antibody due to the lack of knowledge about this kind of tumor and is, thus, a major reason for misdiagnosis. Since NC cannot be distinguished from other poorly differentiated or undifferentiated neoplasms, NUT antibody testing is encouraged for use in any undifferentiated malignancy

Table 1 Clinicopathological characteristics of sinonasal tract NC

Author, year	Sex/age	Site	Keratinization	IHC	FISH testing	Treatment	Prognosis
Fang (5), 2012	M/55	Nasal cavity	Y	CK, P63, NUT (+)	N	C	Alive (40 months after surgery)
	M/42	Nasal cavity	Y	CK, P63, NUT (+)	BRD4-NUTM1 rearrangement	CR	Dead (9 months after surgery)
	F/59	Nasal cavity	N	CK, P63, NUT (+)	N	C	Alive (12 months after surgery)
	M/50	Nasal cavity	N	CK, P63, NUT (+)	BRD4-NUTM1 rearrangement	N	Dead (1 months after surgery)
Bishop (1), 2012	M/26	Maxillary sinus	N	NUT, EMA, AE1/AE3 (+); P63 (–)	NA	C	Dead (8 months after surgery)
	M/33	Maxillary sinus	N	NUT, EMA, AE1/AE3, P63, CD34 (+)	NA	C	Dead (11 months after surgery)
	M/48	Ethmoidal sinus	Y	NUT, EMA, AE1/AE3, P63 (+)	NA	CR	Dead (16 months after surgery)
Suzuki (6), 2014	F/18	Right nasal cavity, and maxillary and ethmoidal sinus	N	Vimentin and NUT (+), CD138 and P63 (focal) AE1/AE3 (spotty)	BRD4-NUTM1 rearrangement	CR	Alive (12 months after surgery)
Stirnweiss (7), 2015	F/14	Right anterior ethmoid and maxilla	NA	NA	NUTM1 rearrangement	R	Dead (98 days after surgery)
Edgar (8), 2017	M/53	Left sinonasal	Y	CK5/6, P16, P40, P63 and NUT (+)	BRD4-NUTM1 rearrangement	CR	Dead (3 months after surgery)
Kakkar (9), 2018	M/30	Left sinonasal and orbital	Y	NUT and P40 (+); P16 and CD34 (focal)	NA	NA	NA
	F/31	Left nasal cavity, ethmoid, sphenoid, and maxillary sinuses	Y	NUT and P40 (+); P16 (focal)	NA	C	Dead (2 months after surgery)
	M/25	Right sinonasal	Y	CK, NUT, and P40 (+); P16 + (focal)	NA	NA	NA
	F/10	Nasolacrimal duct	Y	CK, NUT, and P40 (+); P16 + (focal)	NA	R	NA
	F/30	Left nasal cavity	N	NUT and P40 (+); P16 + (focal)	NA	NA	NA
Albrecht (10), 2019	M/48	Left sphenoid sinus	NA	NA	BRD4-NUTM1 rearrangement	CR	Dead (6 months after surgery)
Vakani (11), 2020	M/44	Right sinonasal	N	CK, P63, NUT (+); Syn (focal)	NA	NA	NA
Crocetta (12), 2021	F/56	Right sinonasal	Y	CK, NUT (+)	NA	CR	Dead (6 months after surgery)
The current case, 2022	F/60	Right sinonasal and frontal sinus	Y	P63 and NUT (+), P40 and Syn (focal) CK and CK5/6 (spotty)	BRD4-NUTM1 rearrangement	R	Alive (3 months after surgery)

NC, NUT carcinoma; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; M, male; Y, yes; N, no; C, chemotherapy; CR, chemoradiotherapy; F, female; NA, not available; R, radiotherapy; Syn, synaptophysin.

Table 2 Summary of clinical characteristics of sinonasal tract NC

Clinical characteristics	Number of patients (%)
Gender	
Male	11 (57.9)
Female	8 (42.1)
Keratinization	10 (52.6)
IHC	
NUT	17 (89.5)
AE1/AE3	13 (68.4)
P63	11 (57.9)
P40	7 (36.8)
P16	6 (31.6)
CK5/6	2 (10.5)
Syn	2 (10.5)
Treatment	
R	3 (15.8)
CR	5 (26.3)
C	5 (26.3)
Molecular testing	7 (36.8)
Median survival time (months)	6 (1–16)

NC, NUT carcinoma; IHC, immunohistochemistry; Syn, synaptophysin; R, radiotherapy; CR, chemoradiotherapy; C, chemotherapy.

as it provides an economical and rapid approach to aid in diagnosis.

Although NC shows no specific findings on general immunostaining, another recommended antibody to consider is P63, which is more sensitive to NC diagnosis than P40. Matsuda *et al.* (23) demonstrated that P40 was negative in 4 of 7 NC cases (57%), and was only focal or patchy positive in the other 3 cases. In our case, P63 was diffusely positive, whereas P40 showed only focal staining in the spindle cell region. However, it has also been reported that the expression of P40 and P63 is variable and both can be negative in cases of NC (24,25). Therefore, the use of P40 antibodies alone may lead to a missed diagnosis and is not suitable solely for the identification of NC. Neuroendocrine markers, mainly synaptophysin and chromogranin, can be locally expressed in NC (26). According to summary statistics (*Table 2*), only two cases expressed synaptophysin (including our case). This finding, although uncommon, demonstrates that small biopsies expressing both neuroendocrine and epithelial markers should not be misdiagnosed as neuroendocrine carcinoma. Meanwhile, an epithelial marker for NC was barely expressed in our case, which is different from most of the literature (*Table 2*). As was the case in our study, only spotty CK5/6 and cytokeratin AE1/AE3 staining were observed. This situation, in particular, should alert physicians of potential diagnostic pitfalls as it is possible to misdiagnose sarcomas or lymphomas without expression of individual epithelial markers, and, thus, it is best to combined use of epithelial markers. It is also an interesting phenomenon that the two types of cells have different immune expressions but both express NUT, particularly since the small spindle cells express CK5/6, P40 with a high KI67 proliferation index while the large round cells do not. This suggests that small spindle cells tended to differentiate into squamous cells. However, there is no obvious keratinization or appearance of keratinized beads in this area, therefore, further study is required. Rapid and accurate diagnosis is critical for NC patients due to the short survival time of this disease. NUT antibody is strongly recommended as a specific diagnostic marker for NC.

Diagnosis, in this case, was eventually made via the FISH test which detected *BRD4-NUTM1* fusion. At present, NC is molecularly characterized by the fusion between the *NUTM1* gene with bromodomain and extra terminal (BET) family members. Among them, *NUTM1* is most commonly rearranged with *BRD4* or *BRD3* and rare reports concerning *NSSD3-NUTM1*, *ZNF532-NUTM1*, *WHSC1L1-NUTM1*, and *NAP1L4-NUTM1* fused carcinomas have been documented (1,27-30). Studies examining the correlation between NUT IHC expression and *NUTM1* fusions have also been reported. For example, Fang *et al.* (5) reported that only two of four cases with positive NUT antibody expression were confirmed to have *NUTM1* gene rearrangement via the FISH test. It is speculated that the two cases without *NUTM1* gene rearrangement may have a latent *NUTM1* gene rearrangement or translocation with unknown partner genes. Similar situations have also been reported. In a study of 919 tumors, Haack *et al.* found that four cases resulted in a false negative for NUT, including one autopsy case, and speculated that weak staining could result in postmortem antigen degradation. In the other three false negative cases, there were two cases of *NUTM1* variant translocation detected using the FISH test. However, the FISH results for two patients with strong

positive NUT expression were negative for *NUTM1*. It is concluded that NUT sensitivity was 87% and the sensitivity of FISH analysis was 93% (22). In short, only through the combined analyses of FISH and IHC can 100% diagnostic sensitivity be achieved.

Surgical treatment is the main treatment for NC. Adjuvant therapy such as radiotherapy and chemotherapy benefit some patients, but the effect of long-term treatment is not satisfactory, and the disease progresses rapidly. Chau found that patients who went into remission were those who initially underwent surgery, emphasizing that the choice and sequence of initial treatment are critical to prognosis (13). Radiotherapy and complete tumor resection are critical for improving overall survival and chemotherapy had little effect on patient survival (13,31). Consistent with our reported case, the patient still survived twenty doses of radiotherapy after complete surgical excision of the lesion, in a 5-month observation period. Study has also shown that PD-L1 positive NC patients have better survival outcomes, even without immunotherapy; however, this conclusion needs to be validated through additional studies (16). The pathogenesis of NC is speculated to be through NUT-mediated histone modification of the whole gene suite which changes the expression of oncogene or tumor suppressor genes (32). Through an increased understanding of NC mechanisms, targeted therapies for BET/BRD4 bromine domain inhibitors have been gradually developed. Preliminary results from clinical trials have documented that many patients have benefitted from these treatments with prolonged survival and varying degrees of remission (33). Recently, a bivalent inhibitor of the BET protein BRD4 (AZD5153) was reported to be more effective than a monovalent inhibitor of the BET protein (34).

The prognosis of NC is poor, Bauer *et al.* (31) concluded the survival time averaged 6.7 months by summarizing the prognostic data from 54 cases of NC patients. Some scholars believe that the prognosis of patients with translocation of *NUTM1* and other genes is better than that of patients with *BRD4-NUTM1* gene rearrangement (35). A recent survival analysis of 124 NC patients showed that the site of disease and the type of gene fusion were directly related to patient prognosis. Among them, tumors arising in the chest had the worst prognostic outcome, with a survival time of 4.4 months. Patients with *BRD3-NUTM1* fusion and *NSD3-NUTM1* fusion had a longer survival time than those with *BRD4-NUTM1* fusion, with a median time of 36.5 and 10 months, respectively (15).

Conclusions

We report a case of NC, which is unique in the patient's age, cell morphology, and immunohistochemical staining. This is the first case of sinonasal tract NC to show focal positive for P40, synaptophysin, CK5/6, and only spotty positive for AE1/AE3 in an elderly patient, with unique morphological features compared to previous studies (1,23). The main objective of this report is to expand the understanding of NC and to strongly recommend that the possibility of NC should be considered for round undifferentiated cells or squamous differentiation tumors arising in the head and neck, regardless of patient age, clinical presentation, disease location. This case confirmed that the determination of immunohistochemical NUT antibody greatly facilitated the diagnosis of NC.

Acknowledgments

The authors thank AiMi Academic Services (https://www.aimieditor.com) for the English language editing and review services.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-364/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-364/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-364/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 obtained from the patient for publication of this case report and accompanying

images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Wei X, Teng X, Zhang Y, Cheng M, Chen G. Case report: NUT carcinoma in an elderly woman with unique morphology and immunophenotype highlights a diagnostic pitfall. Transl Cancer Res 2022;11(6):1850-1860. doi: 10.21037/tcr-22-364

