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Case Report

NUTM1-BRD4 fusion mutation-positive salivary gland myoepithelial carcinoma: A diagnostic conundrum

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ABSTRACT

Nuclear protein of the testis (NUT) carcinoma is an extremely rare and aggressive malignancy characterized by *NUTM1* gene rearrangements, often presenting as poorly differentiated tumors in midline structures. This case describes a 27-year-old male with a rapidly progressive nasal mass extending into adjacent structures, ultimately diagnosed as NUT carcinoma of salivary gland origin through molecular confirmation of the BRD4-NUT fusion. Despite surgery, radiotherapy, and systemic chemotherapy, the disease exhibited poor response and aggressive progression, consistent with its known high mortality and resistance to conventional treatment. This case underscores the importance of molecular diagnostics in diagnosing rare cancers and highlights the urgent need for targeted therapies such as bromodomain and extraterminal inhibitors to improve outcomes.

Keywords: Aggressive malignancy, Molecular diagnostics, Myoepithelial carcinoma, NUTM1-BRD4 mutation, Salivary gland

INTRODUCTION

Nuclear protein of the testis (NUT) carcinoma, a rare and poorly differentiated carcinoma, is defined by a genomic rearrangement involving the *NUT* gene, most commonly resulting in the BRD4-NUT fusion variant.[1] NUT carcinoma most commonly arises in the mediastinum; however, there have also been documented cases involving the head-and-neck region, with the sinonasal area being the primary site of occurrence in such instances.[2] Affected patients are predominantly young adults, though the age range spans widely, from newborns to the elderly.[3] NUT carcinoma has poor prognosis, with a mean survival of <12 months from diagnosis.[4] Patients generally present with advanced lesions, often characterized by a rapidly expanding mass at the affected site. Without effective treatment regimens, the overall outcome for patients remains poor.

CASE REPORT

A 27-year-old male presented to Head and Neck Surgery Department in May 2023 with complaints of right nasal stuffiness, gradually increasing swelling over the right side of the nose for 15–20 days. It is associated with mild discomfort and occasional serosanguineous discharge. The patient had no complaints of visual difficulty, neck mass, weight loss, or loss of appetite. The patient had no history of smoking, tobacco chewing, or environmental exposure to known

carcinogens. He had no significant family history, including malignancy.

On examination, the patient was fairly built, nourished, body mass index - 29.6, and eastern cooperative oncology group (ECOG) Performance Status-I. There was ill-defined swelling over the later nasal wall on the right side. There was no palpable cervical lymphadenopathy. Nasal endoscopy examination revealed erosion in the right inferior meatus. Punch biopsy from the lesion suggested a malignant round-to-spindle cell tumor [Figure 1]. His magnetic resonance imaging (MRI) base of skull and neck with contrast revealed large lobulated soft-tissue intensity heterogeneously enhancing mass lesion in the right side of nasal cavity, right ethmoid, and maxillary sinuses. Size of the lesion was ap-5.2 × ts-4.0 cm and cc-5.3 cm. Superomedially, it was extending into the right orbit with the destruction of medial wall. Superiorly, it caused erosion of the cribriform plate without intracranial extension. Inferolaterally, it was causing destruction of medial wall of the right maxillary sinuses and extending into the right maxillary sinus. It was eroding

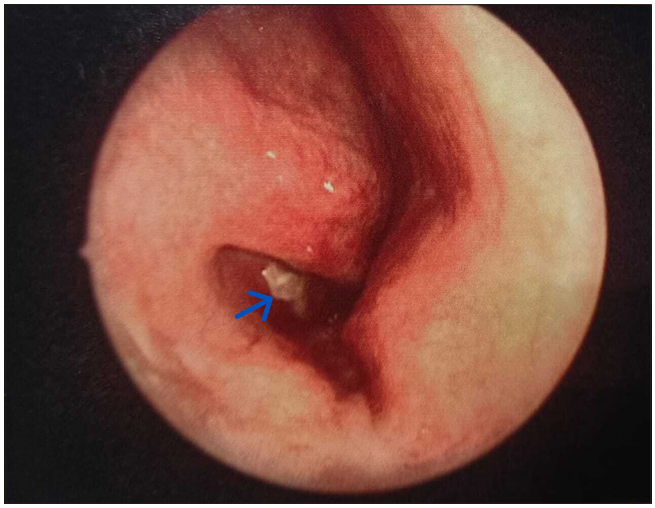

Figure 1: Endoscopy of nose: Erosion in right inferior meatus (blue arrow).

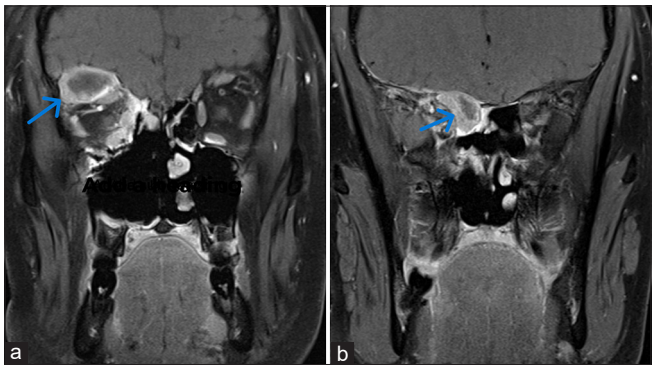

Figure 2: (a-b) Post-contrast T1-weighted coronal image showing heterogeneously enhancing mass lesion, the blue arrow shows invasion of (a) intraorbital extraconal compartment of right orbit and (b) right posterior ethmoidal air cells.

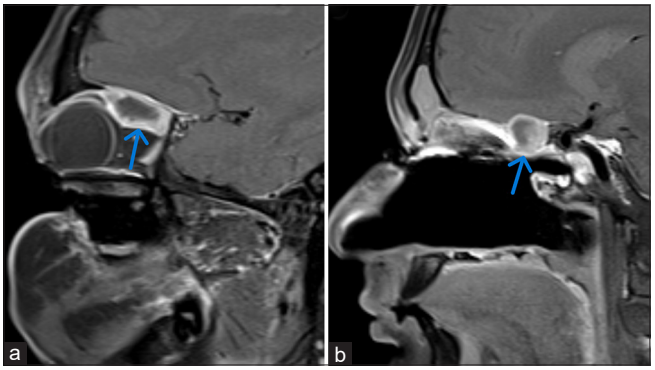

Figure 3: (a-b) Post-contrast T1-weighted sagittal image showing heterogeneously enhancing mass lesion, the blue arrow shows invasion of (a) intraorbital extraconal compartment of right orbit and (b) right posterior ethmoidal air cells.

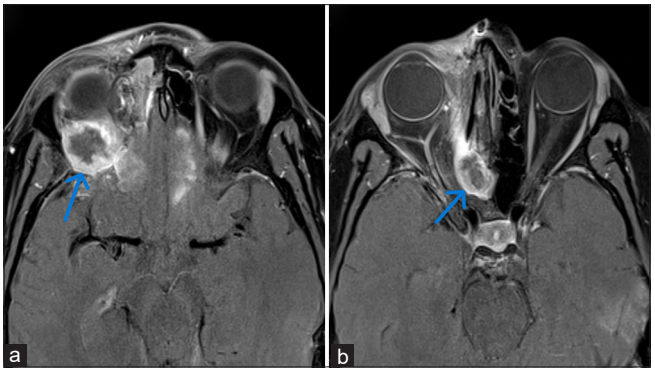

Figure 4: (a-b) Post-contrast T1-weighted axial image showing heterogeneously enhancing mass lesion, the blue arrow shows invasion of (a) intraorbital extraconal compartment of right orbit and (b) right posterior ethmoidal air cells.

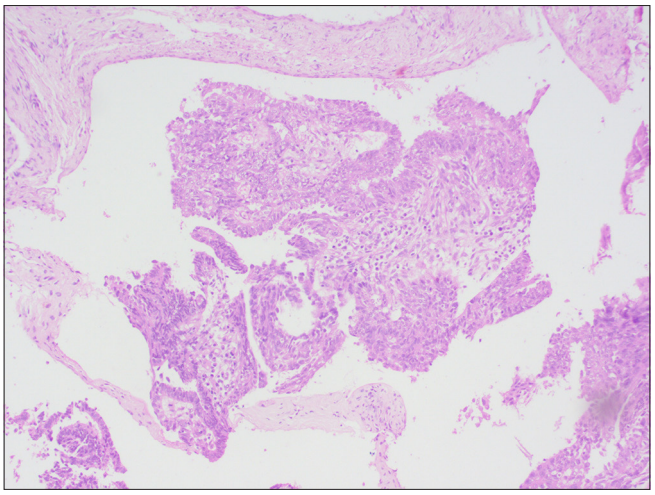

Figure 5: Hematoxylin and eosin staining showing squamous differentiated cells mixed with poorly differentiated tumor cells with a high nuclear–cytoplasmic ratio (magnification × 40).

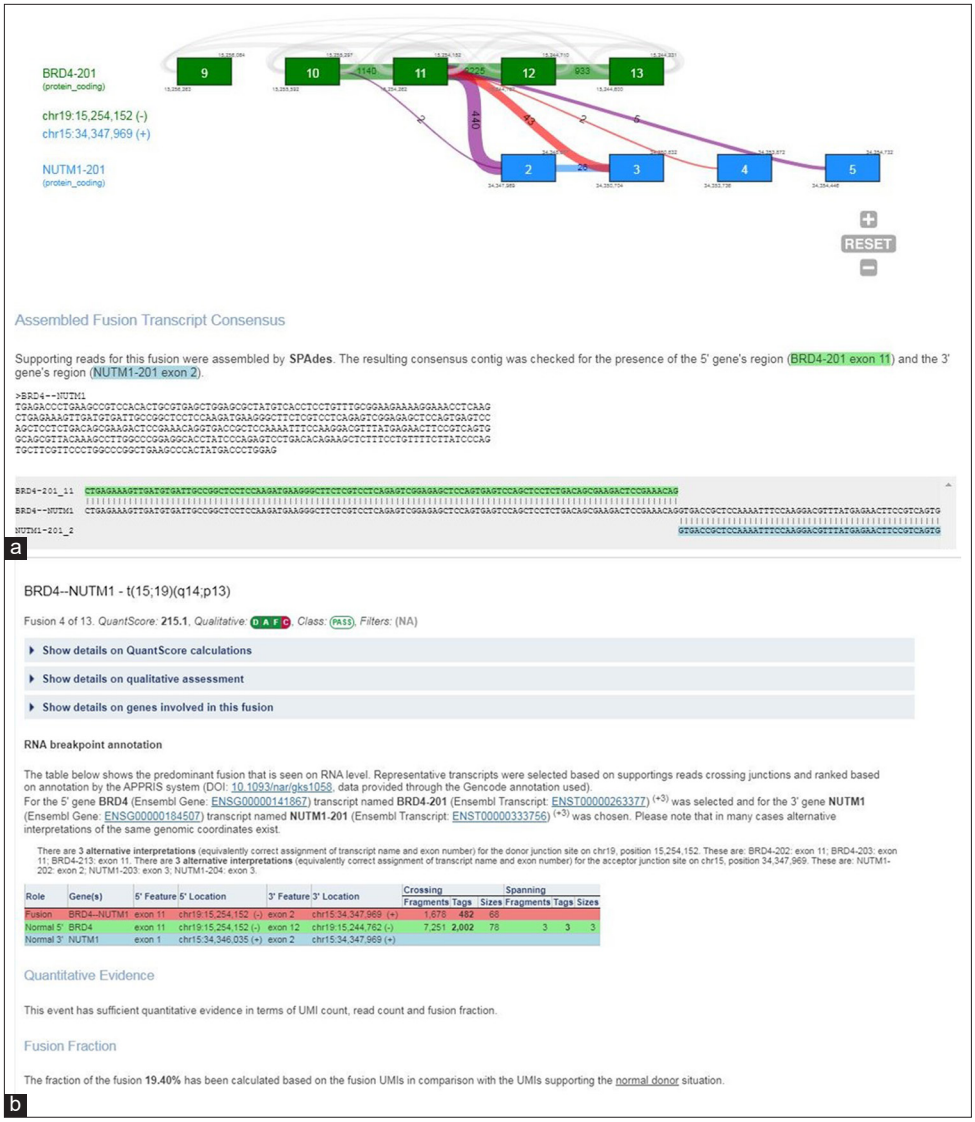

Figure 6: (a and b) Next-generation sequence report showing NUTM1-BRD4 mutation.

anterior wall of the right maxillary sinus and infiltrating into the adjacent muscle with erosion of frontal process of maxilla. Right nasolacrimal duct was involved by lesion [Figures 2-4]. On positron emission tomography-computed tomography (PET-CT) scan, there was no evidence of cervical lymphadenopathy or distant metastasis.

The patient underwent wide local excision full-thickness skin just lateral to nose, right maxillectomy with orbital floor reconstruction + left paramedian forehead flap on May 26, 2023. Histopathological examination was suggestive of poorly differentiated malignant round blue cell tumor in fibro myxoid stroma [Figure 5]. On immunohistochemistry (IHC), tumor cells were positive for pan-cytokeratin, EMA, p63, GATA3, p40, and GFAP and negative for synaptophysin, chromogranin A, MyoD1, desmin, SS13, EBERs, and LCA, consistent with the diagnosis of high-grade myoepithelial carcinoma possibly arising from a minor salivary gland.

Postoperatively, the patient received radiotherapy of 60 Gray in 30 fractions, 2 Gray per fraction.

After 5 months, the patient developed complaints of local pain, right orbital swelling, and diplopia. On PET-CT, there was 2.1 × 1.1 cm FDG-avid lesion in the right ethmoid sinus eroding the cribriform plate and another 2.1 × 1.5 cm FDG-avid lesion in the right orbit eroding the roof of the orbit. Findings were consistent with recurrent metastatic disease. Repeat biopsy was done for further molecular studies. Programmed death-ligand 1 IHC was done using the DAKO PT link platform. Tumor proportion score and combined proportion score both were 4%. Molecular study

(next-generation sequence [NGS]) was done using the Ion Torrent next-generation sequencing platform. NGS report was consistent with NUTM1-BRD4 fusion [Figure 6].

The patient was deemed inoperable and repeat radiation was also not feasible. The patient was started on palliative chemotherapy with cisplatin and doxorubicin. Post 3 cycles chemotherapy, MRI was suggestive of progressive disease. The patient received second-line chemotherapy docetaxel and gemcitabine, and re-evaluation MRI revealed no clinical benefit. At this time point, the patient and family opted for no further chemotherapy and for supportive care only.

DISCUSSION

NUT carcinoma, characterized by the NUTM1-BRD4 fusion, is a rare and aggressive malignancy, typically arising in midline structures such as the mediastinum and nasopharynx. Its occurrence in the salivary gland, as in this case, is exceptionally uncommon and presents a diagnostic conundrum. The initial biopsy findings of a poorly differentiated malignant round blue cell tumor lacked specificity, necessitating further immunohistochemical analyses for definitive diagnosis. The tumor's immune profile, coupled with NGS revealing the NUTM1-BRD4 fusion, confirmed the diagnosis. This case underscores the importance of considering NUT carcinoma in undifferentiated salivary gland neoplasms and highlights the critical role of advanced molecular diagnostics in accurate identification.

This case aligns with prior reports in demonstrating the tumor's aggressive behavior, including rapid local invasion and early recurrence despite multimodal treatment.[5] The primary presentation of nasal stuffiness and localized swelling, with subsequent orbital and sinus invasion in this case mirrors the patterns seen in previously published cases of head and neck NUT carcinoma. Similar cases of salivary gland origin have also shown the diagnostic difficulty due to overlapping features with other high-grade carcinomas, such as neuroendocrine or myoepithelial carcinomas.[6] However, the definitive identification of NUT carcinoma requires IHC for NUT protein or molecular tests, as evidenced here.

Management of NUT carcinoma remains challenging due to its aggressive course and poor response to conventional therapies. In this case, extensive surgical resection, followed by adjuvant radiotherapy, was initially employed. However, early recurrence in the orbit and ethmoid sinus necessitated palliative chemotherapy. Multiple regimens, including cisplatin-doxorubicin and docetaxel-gemcitabine, were ineffective, leading to disease progression. These findings align with the literature, which indicates limited success with traditional chemoradiotherapy and highlights the urgent need for targeted treatments.[7]

The prognosis for NUT carcinoma remains dismal, with mean survival rarely exceeding 1 year from diagnosis. Emerging therapies, such as bromodomain and extraterminal inhibitors targeting the BRD4-NUT fusion protein, offer potential but are not yet widely available.[8] The low PD-L1 expression in this case also limits the feasibility of immunotherapy. Early molecular testing may provide opportunities for personalized approaches or inclusion in clinical trials.

This case emphasizes the importance of maintaining a high index of suspicion for NUT carcinoma in undifferentiated or poorly differentiated tumors of the head and neck. Early and comprehensive diagnostic workups, incorporating IHC and molecular testing, are critical for timely diagnosis and management. Furthermore, it highlights the need for continued research into targeted therapies and innovative treatment strategies to improve outcomes for this rare and devastating malignancy.

By documenting this rare presentation and its treatment course, this report adds valuable insights to the limited knowledge base on NUT carcinoma, potentially aiding clinicians in managing future cases.

CONCLUSION

We encountered a case of primary NUT carcinoma originating from the salivary gland. It is a diagnostic challenge as it is very rare. The importance of considering NUT carcinoma in the provisional diagnosis of undifferentiated or poorly differentiated salivary gland neoplasms is highlighted in this case. IHC and molecular testing for NUT carcinoma can assist in diagnosis; however, limited accessibility to these tests may pose a significant barrier to diagnosis and management. Although effective treatments have not yet been established, early testing may offer insights and broaden treatment options to improve patient outcomes. The details of this case's progression and treatment may inform clinical decisions for future cases and aid in identifying effective therapies.

Ethical approval: The research/study was approved by the Institutional Review Board at IEC-2, Bhaikaka University, number IEC/BU/2025/Cr.01/07/2025 dated 07th January, 2025.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
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