

NUT Carcinoma, a Rare and Aggressive Disease: A Case Report

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Abstract

Introduction: NUT carcinoma is a highly aggressive subtype of squamous cell carcinoma characterized by rearrangements and translocations involving the NUTM1 gene on chromosome 15q14. It primarily occurs along the midline structures of the body, such as the head, neck, and thorax. The disease carries a poor prognosis, with a median survival of approximately nine months. To date, no specific treatment protocol has demonstrated consistent efficacy in the management of NUT carcinoma. **Case Presentation:** We report the case of an adolescent patient presenting with a partially resected lesion in the nasal cavity. Histopathological examination confirmed the diagnosis of NUT carcinoma. The patient underwent a rhinectomy with supraomohyoid lymph node dissection and simultaneous nasal reconstruction. Postoperatively, the patient received cisplatin-based chemotherapy and adjuvant radiotherapy targeting the surgical bed and cervical region. **Conclusion:** This case emphasizes the critical need to recognize and understand this rare and highly aggressive malignancy, for which surgical resection remains the preferred treatment when feasible. It also underscores the importance of ongoing research to establish standardized treatment approaches.

Keywords

Squamous Cell Carcinoma, NUT Carcinoma, Nose, Lymph Node Dissection, Radiotherapy

1. Introduction

Squamous cell carcinoma of the head and neck encompasses several types of malignant tumors that develop in the oral cavity, pharynx, hypopharynx, larynx, nasal cavity, and salivary glands. Collectively, this type of cancer represents the seventh most common oncological diagnosis worldwide, with 890,000 new cases and

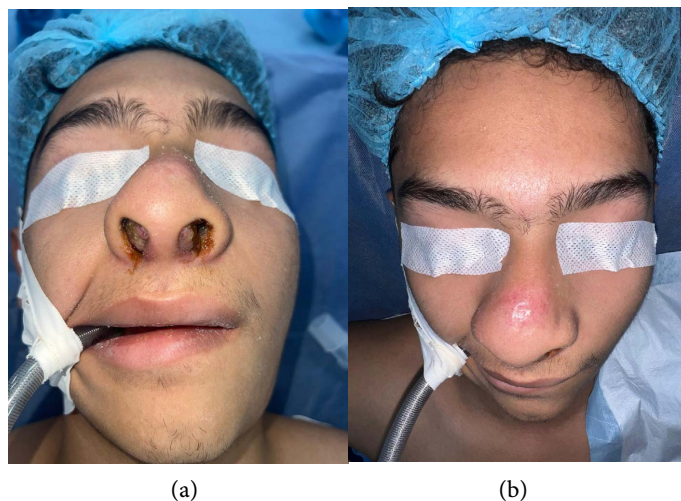
450,000 deaths annually, according to GLOBOCAN estimates.

NUT carcinoma is a highly aggressive subtype of squamous cell carcinoma characterized by rearrangements and translocations in the NUTM1 gene located on chromosome 15q14. It was first described in 1991 in association with two cases originating in the thymus of young patients. Subsequently, it has been reported in patients of various ages and in different anatomical sites, primarily presenting along the midline of the body, such as the head, neck, and thorax. Despite its typical features, diagnosis is very challenging. It has a median survival of 9 months. No specific treatment protocol has proven effective in treating NUT carcinoma.

2. Case Report

We present the case of a 15-year-old male patient who initially sought medical attention for a lesion in the left nasal fossa, clinically suspected to be a pyogenic granuloma. He underwent lesion resection and bilateral turbinectomy with no intraoperative complications. Histopathological examination revealed a high-grade nasopharyngeal carcinoma with positive resection margins, lymphovascular invasion, no perineural involvement, and a Ki-67 proliferation index of 90%. Immunohistochemical analysis showed positivity for CK AE1/AE3, CAM 5.2, p63, and p40, confirming the epithelial origin of the neoplasm. Additionally, strong nuclear expression (>90%) of the NUT marker was observed, indicating a high proliferative index.

On physical examination, bilateral anterior rhinoscopy revealed bulging of the septum in area II, pale mucosa, and partially obstructive septal thickening encroaching on the right nasal cavity. Over the course of approximately two months, the lesion demonstrated rapid growth, resulting in 80% nasal obstruction (**Figure 1**), with oral breathing and significant dysphagia. A 3 × 4 cm hard, immobile, non-tender left submandibular mass was also detected, associated with restricted mouth opening.

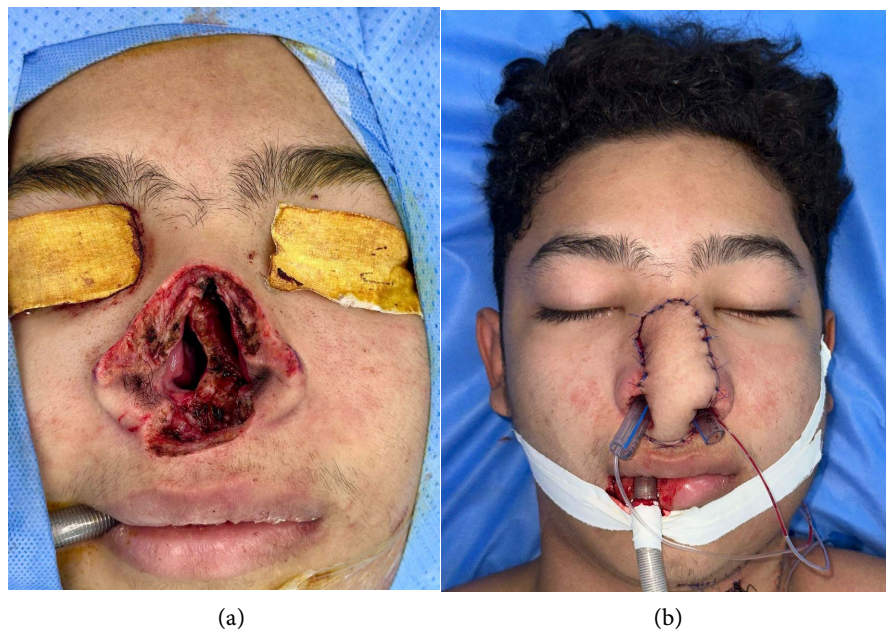


Source: Authors.

Figure 1. (a) 80% nasal obstruction. (b) Skin involvement.

For staging purposes, further imaging studies were performed. Thoracoabdominal computed tomography (CT) and positron emission tomography-CT (PET-CT) ruled out distant metastatic disease. Facial magnetic resonance imaging (MRI) demonstrated a persistent, well-defined solid component along the anteroinferior nasal septum, isointense on T1- and T2-weighted sequences, with contrast enhancement and dimensions of $19 \times 45 \times 25$ mm, resulting in decreased patency of the right nasal cavity. Adjacent to the left submandibular gland, an oval lesion measuring $30 \times 42 \times 19$ mm was identified, containing cystic areas, heterogeneous multilobular enhancement, and restricted diffusion of free water, indicating progressive growth. Based on these findings, anterior rhinectomy and left supraomohyoid neck dissection with simultaneous nasal reconstruction were planned.

The patient underwent surgery four weeks after the initial intervention. Intraoperatively, mucosal infiltration of the midline and distal nasal septum was observed, with a 5×5 cm lesion and no apparent bone involvement (**Figure 2(a)**). A metastatic nodal conglomerate was identified in left neck levels I and II, consisting of multiple lymph nodes ranging from 5 mm to 50 mm in size, some showing abscess-like changes. An anterior rhinectomy and functional supraomohyoid lymphadenectomy were performed, preserving the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. A left radial forearm free flap was used for internal and external nasal lining, along with a costal cartilage graft for nasal support and skin grafts at the donor site (**Figure 2(b)**). The postoperative course was favorable, and the patient was discharged six days after the procedure.



Source: Authors.

Figure 2. (a) Anterior rhinectomy; (b) Nasal reconstruction.

The patient is currently receiving a treatment protocol consisting of cisplatin

(CDDP 100 mg/m² on days 1, 21, and 42) and adjuvant radiotherapy with a total dose of 70 Gy, administered in 30 sessions to the surgical bed and cervical region. A radiation boost of up to 64 Gy is being delivered to levels II and III.

3. Discussion

Squamous cell carcinoma (SCC) is the most common malignant tumor of the nasal cavity and paranasal sinuses, accounting for the majority of sinonasal malignancies, with a reported prevalence ranging from 41.9% to 80% in different series [1]. Other relevant histological subtypes include adenocarcinoma, malignant melanoma, adenoid cystic carcinoma, and various sarcomas.

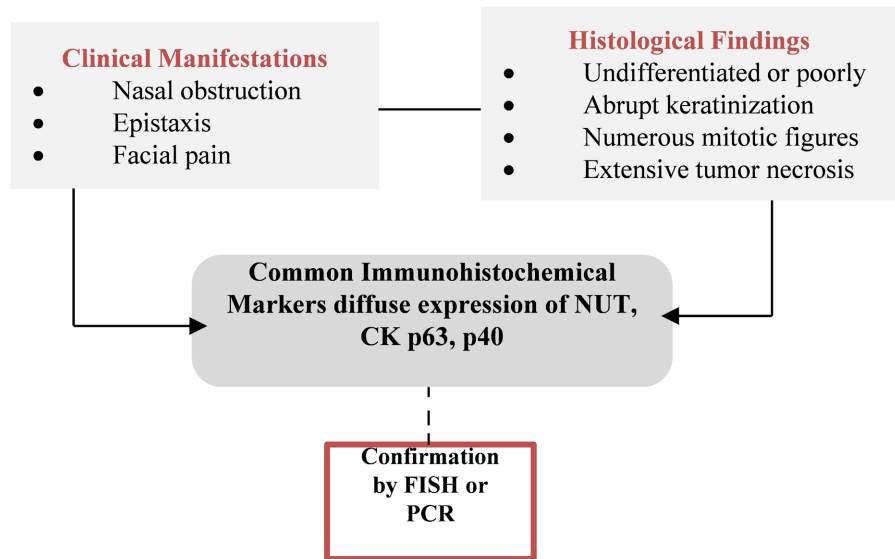
The predominance of SCC is attributed to its origin in the epithelial lining of the nasal cavity and paranasal sinuses. Although less frequent, adenocarcinomas are clinically significant, particularly among individuals with occupational exposure to wood dust. Additionally, strong associations have been established between sinonasal malignancies and risk factors such as tobacco and alcohol use, as well as infection with human papillomavirus (HPV) and Epstein-Barr virus (EBV), particularly in the case of nasopharyngeal carcinomas [1]. Despite their rarity, malignant melanoma and esthesioneuroblastoma are of notable clinical concern due to their aggressive biological behavior and tendency to invade adjacent structures.

NUT carcinoma, also known as NUT midline carcinoma, is a recently characterized, rare, and highly aggressive variant of squamous cell carcinoma. It is defined by chromosomal rearrangements involving the NUTM1 gene located on chromosome 15q14. In 2003, French *et al.* first identified the BRD4–NUT fusion oncogene [2] [3]. Approximately two-thirds of cases involve (15; 19) (q14; p13.1) translocation, resulting in the BRD4–NUT fusion. The remaining cases may involve fusion with BRD3 (t (9; 15) (q34.2; q14), BRD3–NUT) or with other, yet uncharacterized, partner genes (NUT variants).

According to GLOBOCAN 2022, the incidence of nasopharyngeal carcinoma in Colombia is approximately 0.28%. However, the true incidence and prevalence of NUT carcinoma remain uncertain due to underdiagnosis and limited awareness. A 2004 study by French *et al.* estimated that NUT carcinoma accounts for approximately 7% of poorly differentiated carcinomas in patients under 40 years of age [4].

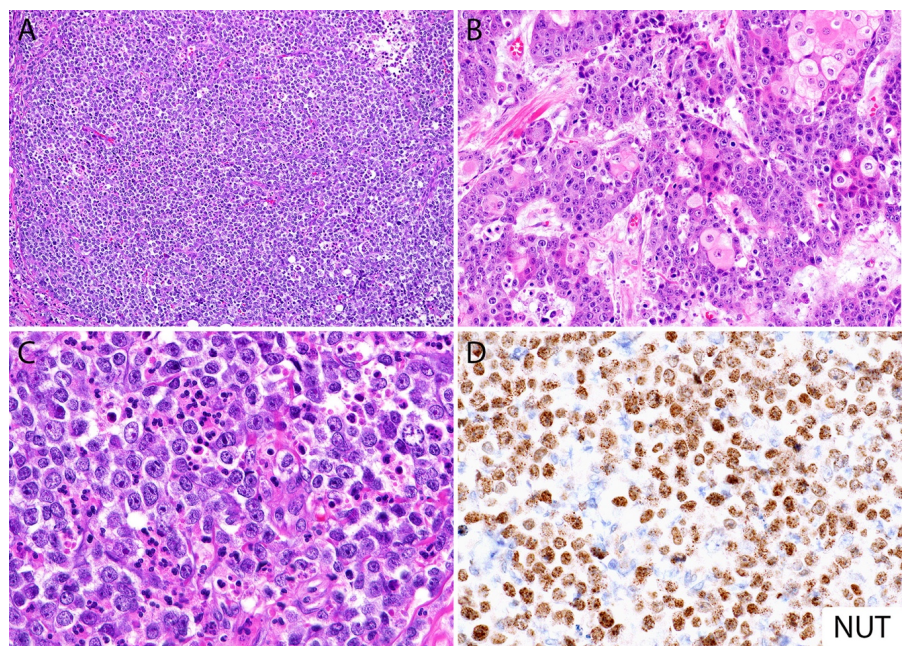
Diagnosis is primarily based on the demonstration of nuclear NUT protein expression via immunohistochemistry or the identification of NUTM1 rearrangements using fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR). Histologically, these tumors typically present as poorly differentiated or undifferentiated carcinomas with occasional evidence of squamous differentiation (**Figure 3, Figure 4**).

In the head and neck region, NUT carcinoma may arise in various anatomical sites, including the nasopharynx, though it more commonly involves the sinonasal tract and major salivary glands. The disease is characterized by an aggressive clinical course and poor disease-specific survival.



Source: Authors.

Figure 3. Diagnostic aspects.



Source: Image used under Creative Commons Attribution 4.0 international (CC BY 4.0) license. [5]

Figure 4. Histomorphology of NUT carcinoma and diagnosis by immunohistochemistry. (A) Diffuse sheets of poorly differentiated monotonous round cells with focal necrosis (top right). (B) Areas with abrupt keratinization in NC can be seen in up to 30% of cases. (C) Focal cytoplasmic clearing and intratumoral neutrophilic inflammatory infiltrate. (D) NUT immunohistochemical stain (mono-clonal antibody, clone C52) shows diffuse nuclear labeling, often with a speckled pattern. Same case from panel (B).

The prognosis of patients with NUT carcinoma is generally dismal, with median overall survival ranging from 6 to 9 months, primarily due to the tumor's

rapid progression and limited response to conventional therapies [4]. Currently, there is no established standard of care for this entity. However, novel therapeutic strategies targeting its unique molecular pathogenesis—such as bromodomain and extra terminal (BET) inhibitors and histone deacetylase inhibitors—are under investigation. Initial aggressive surgical resection, with or without adjuvant chemoradiotherapy, has been associated with improved survival outcomes in selected cases [4].

In the present case, anterior rhinectomy combined with a functional supraomohyoid neck dissection was proposed with palliative intent, along with an attempt at nasal reconstruction by the plastic surgery team. Total rhinectomy is an uncommon and disfiguring surgical procedure, generally reserved for advanced nasal malignancies or severe traumatic injuries when the preservation of life is not otherwise feasible.

The nose, as the central and most prominent feature of the face, is critical both for respiratory function and facial aesthetics. It is estimated that approximately 25% of cutaneous head and neck neoplasms affect this region. In most cases, conservative surgical excision and reconstruction or radiotherapy suffice. However, in tumors with aggressive biological behavior, radical procedures such as rhinectomy may be required to achieve adequate oncologic control [5].

Rhinectomy is associated with significant functional, psychosocial, and aesthetic consequences. Nonetheless, it may be the only viable treatment for extensive or recurrent malignancies. High recurrence rates are commonly reported, and surgical approach and extent depend on intraoperative findings and surgeon expertise [6]. Notably, the lesion's location does not always dictate the need for an extensive rhinectomy. According to the literature, squamous cell carcinoma is the most frequently reported histologic type in such cases, typically involving the nasal ala and dorsum [7].

In NUT carcinoma specifically, the most frequent translocation in head and neck cases is BRD4-NUT, present in approximately 72% of cases. This subtype is associated with particularly poor outcomes, especially when metastatic at diagnosis since surgical resection is generally not feasible. Conversely, patients with localized disease may benefit significantly from complete oncologic resection performed at an early stage.

There are no standardized treatment protocols for NUT carcinoma. Current management typically involves a combination of surgery, radiotherapy, and chemotherapy. Surgical resection is often attempted, but the tumor's aggressive nature and propensity for early metastasis limit its efficacy. Radiotherapy and chemotherapy can improve short-term survival but do not typically result in long-term remission. Current research efforts are focused on gaining a deeper understanding of the molecular mechanisms underlying NUT carcinoma and on developing targeted therapies. Among these, BET inhibitors such as RO6870810 have shown promising results in preclinical models by interfering with BRD4-NUT fusion-mediated oncogenic transcription. However, the emergence of resistance mecha-

nisms—such as activation of compensatory pathways and involvement of chromatin remodeling complexes—limits their clinical effectiveness. As a result, combination therapeutic strategies are being explored, particularly the use of BET inhibitors in conjunction with histone deacetylase inhibitors, which have demonstrated synergistic effects by modulating chromatin accessibility and transcriptional regulation. Additionally, immunotherapy has emerged as a promising approach and is currently being evaluated in clinical trials, both as monotherapy and in combination with targeted agents. [8]

In this case, anterior rhinectomy was performed. The procedure began with preoperative surgical planning and cutaneous marking. A cold blade incision was made, followed by meticulous dissection along anatomical planes. A bulky midline mass was identified, involving the nasal septal cartilage, the floor of the nasal cavity, and extending into the superior meatus. Based on these findings, complete resection of the cartilaginous nasal framework was carried out up to its insertion into the nasal bones, with bilateral preservation of the minor alar cartilages. The patient is currently receiving treatment with adjuvant chemotherapy and radiotherapy.

4. Conclusions

NUT carcinoma is a highly aggressive malignancy with a median survival of approximately 9 months, ranging from 28 to 96 weeks. To date, no consistent association has been established between survival and patient- or treatment-related variables. Furthermore, there is currently no standardized therapeutic protocol for its management. Platinum-based chemotherapy regimens remain the most employed systemic treatment. In the present case, the patient underwent surgical resection and is currently receiving adjuvant platinum-based chemoradiotherapy.

This case underscores the critical importance of recognizing NUT carcinoma as a rare but highly lethal entity for which early diagnosis and complete surgical excision, when feasible, represent the most effective therapeutic approach. It also highlights the urgent need to promote research efforts aimed at improving our understanding of molecular biology and facilitating the development of standardized, evidence-based treatment strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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