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UNRESECTABLE HIGH-GRADE NON-INTESTINAL-TYPE SINONASAL ADENOCARCINOMA: CASE REPORT AND REVIEW OF EMERGING SYSTEMIC THERAPIES

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ABSTRACT

High-grade non-intestinal-type sinonasal adenocarcinoma (SNAC) is a rare and aggressive malignancy of the nasal cavity and paranasal sinuses. It typically presents with locally advanced disease and has a poor prognosis, with limited data guiding therapy. We describe a 70-year-old male who presented with progressive nasal obstruction and a right cervical lymph node mass. Imaging revealed an extensive sinonasal tumor with cervical nodal metastasis. Histopathological examination confirmed a high-grade non-intestinal-type adenocarcinoma lacking intestinal differentiation. Immunohistochemistry showed strong cytokeratin 7 positivity and absence of CDX2/CK20 staining, consistent with a non-intestinal phenotype; no salivary gland tumor markers were expressed. Given the advanced stage and unresectability, the patient received palliative systemic chemotherapy with weekly carboplatin and paclitaxel. Treatment was well tolerated, and after 8 weeks a partial clinical and radiologic response was achieved, with significant reduction of the tumor burden and improvement of symptoms. This case illustrates that platinum-taxane chemotherapy can induce meaningful tumor regression in high-grade sinonasal adenocarcinoma, suggesting a role for systemic therapy in metastatic or unresectable cases. We discuss the differential diagnosis (including intestinal-type adenocarcinoma and other sinonasal malignancies), the pathologic and molecular features (such as EGFR and TP53 mutations), and emerging treatment strategies for this rare tumor based on a review of the literature. Multimodal therapy and molecular profiling may improve outcomes in the future. This case underscores the importance of recognizing non-intestinal-type SNAC and the potential benefit of palliative chemotherapy in improving disease control and patient quality of life.

KEYWORDS: Paranasal Sinus Neoplasms; Sinonasal adenocarcinoma; Non-intestinal type adenocarcinoma; Carboplatin; Paclitaxel; Palliative chemotherapy.

INTRODUCTION

Sinonasal adenocarcinomas (SNACs) are rare malignancies representing approximately 12% of cancers of the nasal cavity and paranasal sinuses. Overall, tumors in this region are uncommon (<3% of all upper respiratory tract cancers) and predominantly affect males.[1] According to the World Health Organization (5th edition), SNACs are categorized into intestinal-type adenocarcinomas (ITAC) and non-intestinal-type adenocarcinomas (non-ITAC). ITACs resemble colorectal adenocarcinomas and are strongly linked to occupational exposure to wood dust, whereas non-ITACs lack intestinal differentiation and are unrelated to salivary tissue origin.[2] High-grade non-intestinal-type

adenocarcinomas (HG-NITACs) are exceedingly rare and aggressive tumors with poor prognosis, often presenting at an advanced stage. Advances in immunohistochemistry and genomics have refined their classification, identifying molecular subtypes such as SMARCB1-deficient sinonasal carcinoma.[3-4] This article presents a case of metastatic HG-NITAC, emphasizing diagnostic challenges and therapeutic outcomes with platinum-taxane chemotherapy.

CASE PRESENTATION

A 70-year-old man with no prior medical conditions presented with a 4-month history of progressive right nasal obstruction and a painless swelling in the right upper neck. He denied epistaxis, visual disturbances, or systemic symptoms. There was no exposure to wood or leather dust, and no family history of malignancy. Examination revealed obstruction of the right nasal cavity by a fleshy mass extending toward the nasopharynx, with a 2 cm mobile lymph node in the right level II region. MRI showed an enhancing mass occupying the right nasal cavity and ethmoid sinus with bony destruction and extension into the maxillary sinus and septum, as well as nodal involvement. computed tomography scan showed an enhancing sinonasal mass with cervical lymphadenopathy and distant metastases, consistent with stage IV (T4b N3 M1) disease **Figure 1 and 2**.

Histopathology of an endoscopic biopsy demonstrated a poorly differentiated adenocarcinoma forming irregular glands and solid nests with marked atypia, necrosis, and angiolymphatic invasion. Immunohistochemistry showed CK7 positivity, but CK20 and CDX2 negativity, excluding ITAC. S100, SOX10, and DOG1 were negative or only weakly expressed, excluding seromucinous carcinoma. Myoepithelial markers (p63, SMA) were absent, and INI1 expression was retained, ruling out SMARCB1-deficient carcinoma. p53 showed diffuse strong positivity, and the Ki-67 index was approximately 40%, confirming a high-grade non-intestinal-type adenocarcinoma **Figure 3**.

Given the extent and nodal spread, curative surgery was deemed infeasible. The patient received palliative systemic chemotherapy with weekly **paclitaxel (80 mg/m²)** and **carboplatin (AUC 2)** administered intravenously once per week for 3 weeks, followed by a 1-week rest, in 4-week cycles. This regimen was selected for its tolerability and suitability in older patients. After 8 weeks, the patient experienced marked improvement in nasal airflow and regression of the cervical node, with imaging showing 50% tumor reduction. Chemotherapy was well tolerated aside from mild fatigue and peripheral neuropathy. After 24 weeks of treatment, therapy was paused; the patient remains in good clinical condition with stable disease after 12 months of follow-up.

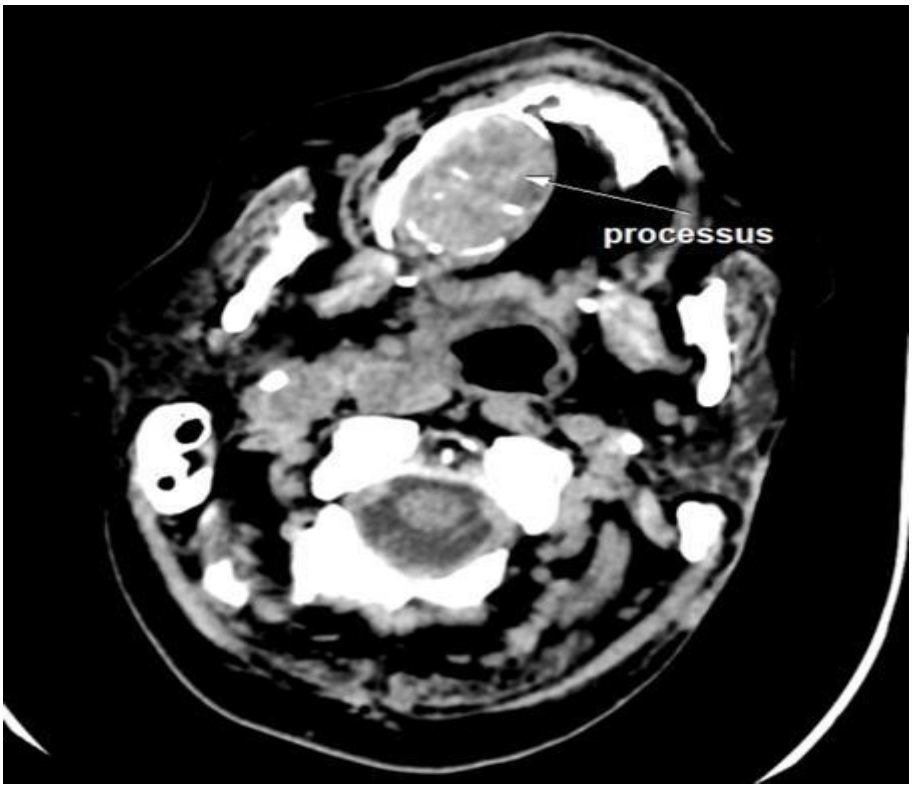

Figure 1 Axial CT scan of the paranasal sinuses demonstrating extension of a tumor mass into adjacent structures.

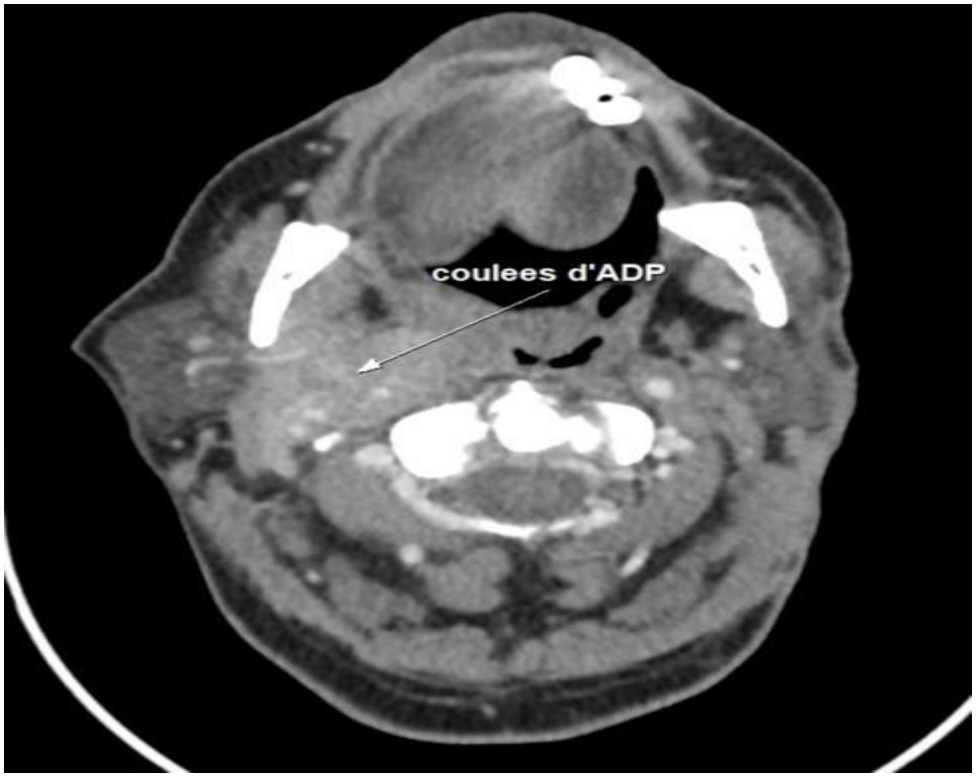

Figure 2: Axial contrast-enhanced CT scan demonstrating multiple cervical lymph node enlargements consistent with metastatic lymphadenopathy.

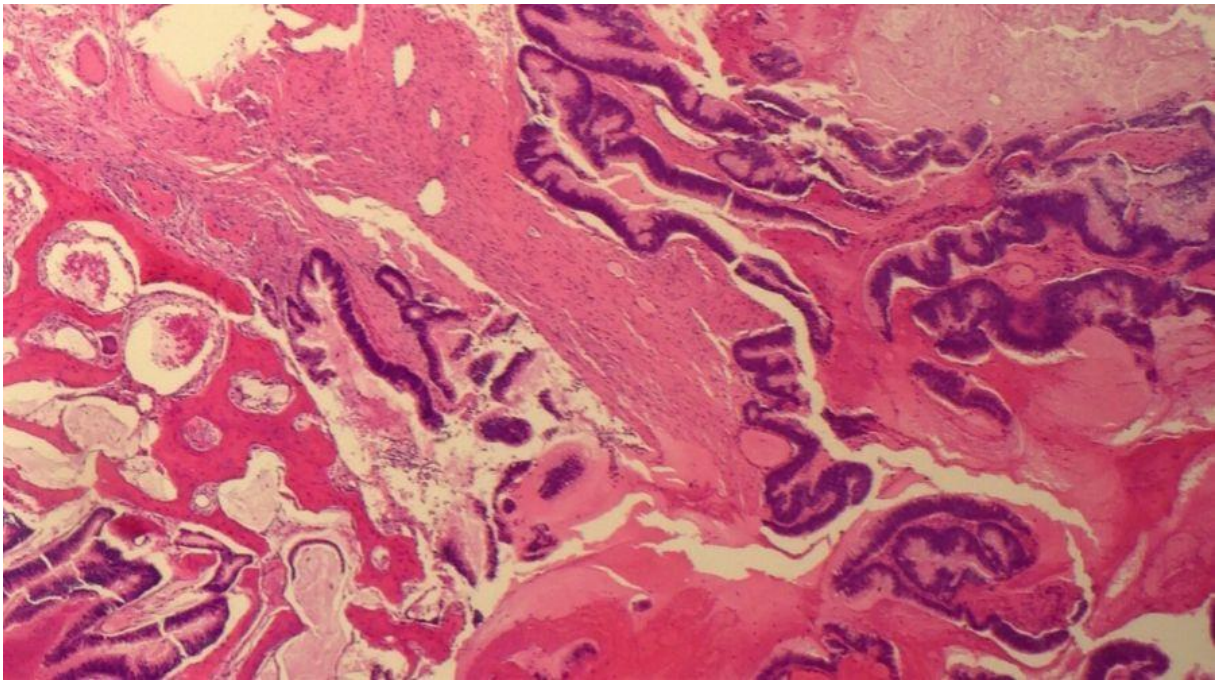

Figure 3: Sino-nasal infiltration by an adenocarcinomatous tumor proliferation showing intestinal differentiation (HE ×100).

DISCUSSION

Non-intestinal-type sinonasal adenocarcinomas (non-ITACs) are rare, heterogeneous malignancies with limited evidence guiding optimal management, mostly derived from small series and case reports. Our case highlights a metastatic high-grade NITAC successfully managed with chemotherapy alone, an approach infrequently documented in the literature. Typically, surgical resection with or without radiotherapy remains the mainstay of treatment when feasible.[2] For example, Alfadley et al. (2024) reported a low-grade non-ITAC treated with endoscopic resection and disease-free survival at 6 months.[1] High-grade NITACs, however, generally exhibit aggressive behavior and poorer

outcomes, often requiring multimodal therapy. Due to the tumor's rarity, standardized chemotherapy protocols are lacking. The use of platinum-based regimens, such as paclitaxel–carboplatin in our case, draws from experience with ITAC and other head and neck carcinomas. Our patient's marked partial response supports the notion that high-grade sinonasal adenocarcinomas retain some chemosensitivity, consistent with sporadic reports of favorable outcomes following systemic therapy or induction chemoradiation in advanced cases.[3]

Accurate pathological assessment is essential to differentiate non-intestinal-type adenocarcinoma (NITAC) from other sinonasal malignancies. By definition, NITAC lacks goblet cells, dirty necrosis, and the intestinal-type glandular architecture typical of ITAC. Immunohistochemistry is key: ITACs coexpress CK7, CK20, and CDX2, whereas non-ITACs are CK7-positive and CK20/CDX2-negative.[3] Our case matched this pattern. NITACs display variable histology (papillary, tubular, or solid)[4]; low-grade tumors show seromucinous features with S100, SOX10, and DOG1 expression , while high-grade forms, like ours, lose these markers. Differential diagnoses include high-grade salivary-type carcinomas, which were excluded by the absence of myoepithelial markers, and sinonasal undifferentiated carcinoma, ruled out due to evident glandular differentiation. Metastatic adenocarcinomas from lung or kidney were excluded through negative TTF-1 and PAX8 staining. INI1 (SMARCB1) expression was retained, excluding SMARCB1-deficient carcinoma. Recognition of such molecularly defined variants, including SMARCA4-deficient, NUT, and IDH-mutant carcinomas, is crucial, as they carry prognostic and potential therapeutic implications.[4]

The molecular profile of sinonasal adenocarcinomas (SNACs) is still being elucidated. In intestinal-type adenocarcinomas (ITACs), frequent TP53 mutations present in up to 50% of cases along with alterations in KRAS, BRAF, and EGFR have been documented.[5] TP53 mutations correlate with poorer prognosis, and our patient's diffuse p53 positivity suggests such an alteration, possibly explaining the tumor's aggressive behavior and partial chemotherapeutic response.[6] EGFR mutations are rare but occasionally actionable; Yang et al. (2024) described a high-grade NITAC harboring concurrent EGFR and TP53 mutations that responded dramatically to gefitinib after multiple prior therapies.[3] This highlights the potential role of molecular testing in advanced cases. Other markers, including HER2/neu overexpression and VEGF or MUC1 expression, have been linked to adverse outcomes but lack therapeutic validation.[6] Overall, the evolving molecular landscape, including entities like IDH-mutant sinonasal carcinomas, underscores the biological diversity within high-grade NITAC.[7]

Management of high-grade sinonasal adenocarcinoma (SNAC) demands a multidisciplinary, individualized approach integrating surgery, radiotherapy, and systemic therapy depending on tumor stage and patient factors. When feasible, complete surgical excision with negative margins remains the standard of care and offers the best chance for long-term control. Adjuvant radiotherapy significantly improves local disease control and survival outcomes in high-grade or margin-positive tumors.[2] However, in unresectable or metastatic cases, palliative systemic therapy becomes the mainstay. There is no universally accepted chemotherapy regimen for SNAC, and treatment is often extrapolated from other head and neck adenocarcinomas.

Our patient received weekly **paclitaxel (80 mg/m²)** plus **carboplatin (AUC 2)**, an outpatient regimen balancing efficacy and tolerability in elderly patients. Alternative regimens include **cisplatin–5-fluorouracil**, as used for intestinal-type adenocarcinomas[2], or **FOLFOX/FOLFIRI** for intestinal-type variants. While partial responses are achievable, durability remains limited. Re-irradiation or stereotactic radiotherapy may be considered for local control in recurrent disease.

Emerging therapies particularly immune checkpoint inhibitors (nivolumab, pembrolizumab) show promise, as a subset of SNACs express PD-L1.[2] Clinical trial **NCT02834013** is evaluating nivolumab and ipilimumab in rare sinonasal cancers.[3] Targeted therapy represents another frontier: EGFR-mutant cases may benefit from tyrosine kinase inhibitors such as gefitinib, while rare NTRK fusions or DNA repair mutations could guide future personalized treatment strategie.[8]

The prognosis of high-grade non-intestinal-type sinonasal adenocarcinoma (NITAC) is generally poor. Outcomes depend on tumor grade, stage, intracranial or distant spread, and completeness of surgical resection when feasible.[2] High-grade tumors show markedly lower survival than low-grade lesions.[1] Cervical lymph node metastasis, as in our patient, is uncommon but signifies advanced disease and worsened prognosis. Although our patient achieved an initial partial response to chemotherapy, progression occurred soon after, reflecting the tumor's aggressive biology. Long-term survival in metastatic SNAC is exceptional, and current management focuses on palliation and quality of life while research continues to refine systemic therapies.[9]

CONCLUSION

High-grade non-intestinal-type sinonasal adenocarcinoma (NITAC) is a rare and aggressive tumor that presents important diagnostic and therapeutic challenges. Accurate diagnosis relies on thorough pathological and immunohistochemical assessment, while systemic chemotherapy particularly platinum–taxane combinations may offer symptomatic improvement in cases that are unresectable or metastatic. Molecular profiling can help identify actionable

alterations such as EGFR mutations and guide personalized treatment approaches. Optimal care requires close collaboration within a multidisciplinary team, with consideration for inclusion in immunotherapy trials when appropriate. Although the prognosis remains poor, individualized multimodal management can achieve meaningful disease control, underscoring the importance of further research and continued reporting of such cases.

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