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NUT Midline Carcinoma in a Pregnant Woman

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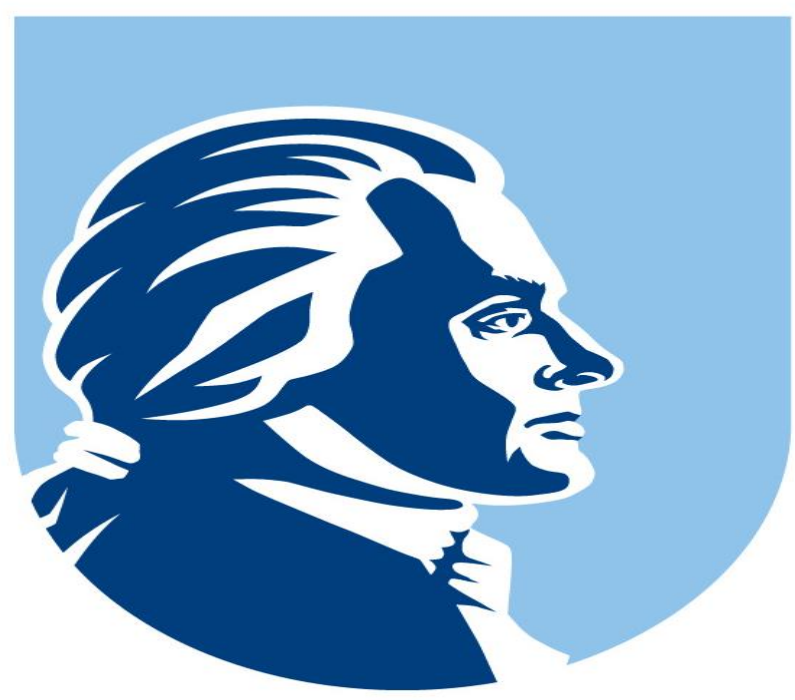
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NUT Midline Carcinoma in a Pregnant Woman

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ABSTRACT

NUT midline carcinoma is a rare, highly aggressive tumor that involves midline structures, particularly in the head, neck and mediastinum. It is characterized by NUT gene translocations on chromosome 15. It typically impacts teenagers or young adults, and has a fulminant course leading to death in less than a year in most cases despite aggressive chemoradiotherapy. Due to its location, this tumor is frequently considered inoperable. We present a case of a sinonasal NUT midline carcinoma with orbital invasion discovered during the workup of sinusitis in a young, pregnant woman. The tumor was managed with definitive excision to negative margins followed by aggressive chemoradiation, with no evidence of recurrence for 12 months. We propose that diagnosis of NUT midline carcinoma should prompt recognition of the limitations of current medical therapy and rapid surgical intervention should be undertaken when possible.

CASE REPORT

A 32 year old, 27 week pregnant female presented to her primary care doctor for evaluation of a two month history of worsening nasal congestion, facial pressure, and rhinorrhea refractory to antibiotics. Her symptoms also included right periorbital edema without vision changes. Her medical history was significant for hypothyroidism, but no history of immunosuppression or malignancy. There was no history of prior tobacco use. Given her worsening symptoms despite maximal medical therapy, a CT of the midface (Fig 1) was obtained, demonstrating a large right-sided nasal mass involving the adjacent paranasal sinuses and right orbit. MRI of the orbits, face, and neck (Fig 2) was obtained for soft tissue characterization, and further demonstrated right orbital extension inferiorly and medially, with tumor adjacent to optic nerve. Pre-operative imaging also revealed the presence of an enlarged right level II node.

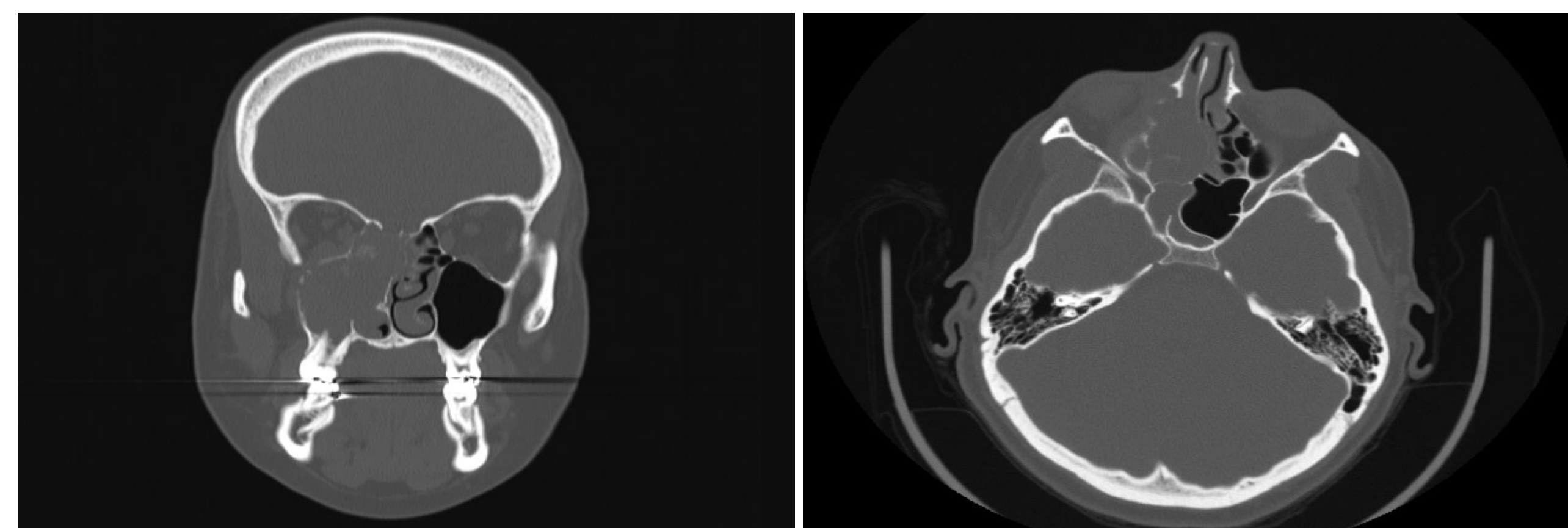


Fig 1 CT maxillofacial coronal (left) and axial (right) views. A large mass is causing panopacification of right sided sinuses and bone erosion. A small dehiscence of the right skull base is seen on coronal view.

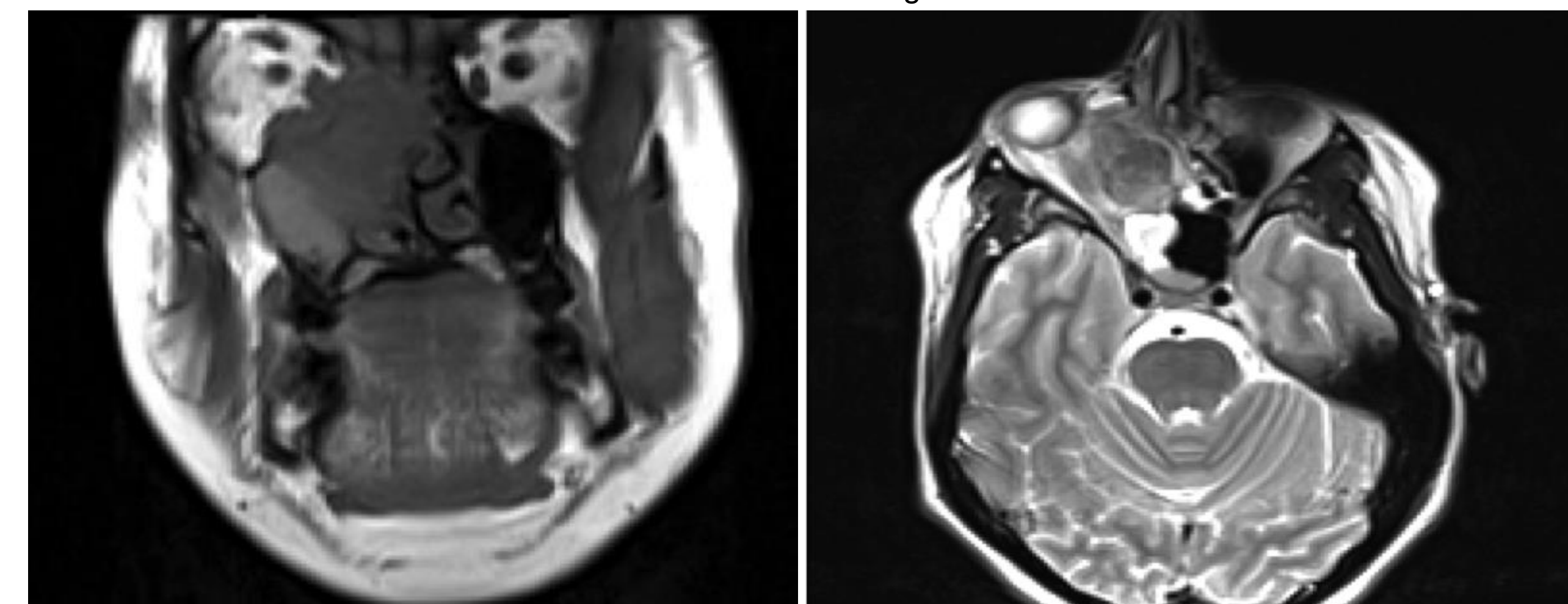


Fig 2. T1-weighted MRI orbits, face and neck, coronal (left) and T2-weighted axial image (right) demonstrating orbital extension of the tumor.

PATHOLOGY

Biopsy of the mass showed a malignant epithelial neoplasm with squamous features. Immunoprofiling was carried out, with positive staining for the markers of squamous differentiation, p16, and NUT antibody markers. Both histologic features (Fig 3A) and immunochemical profile (Fig 3B) confirmed the diagnosis of NUT midline carcinoma.

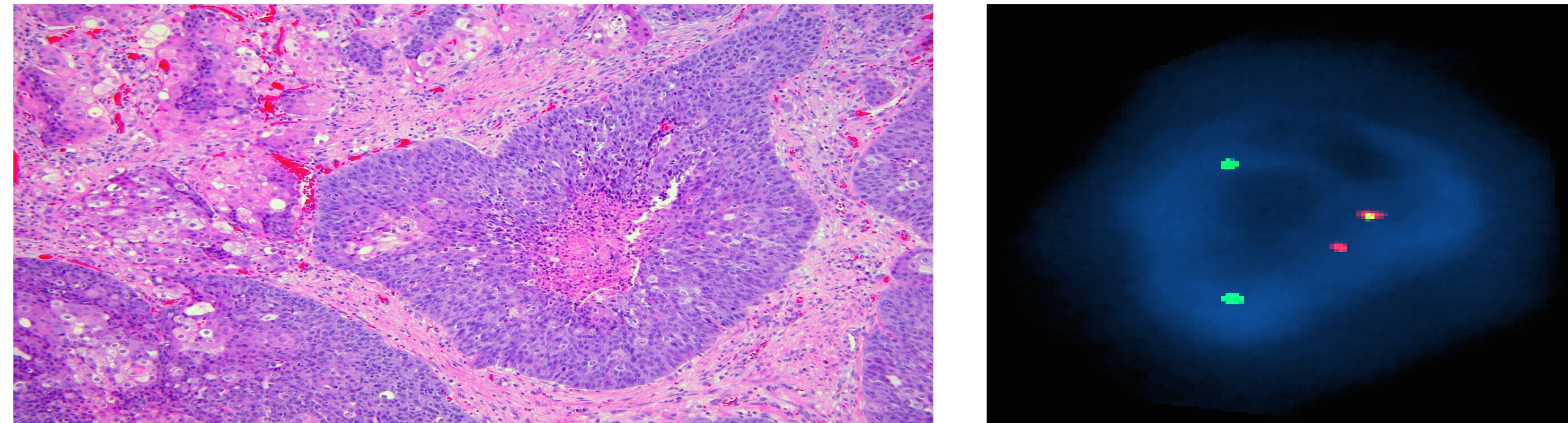


Fig 3. A. Infiltrative, high grade squamous carcinoma showing abrupt transition from undifferentiated cells to well differentiated, mature appearing squamous cells. Tumor necrosis, nuclear atypia and mitotic activity are present (hematoxylin eosin, original magnification 40x). B. FISH analysis performed in Dr. Christopher French's laboratory at the Brigham and Women's Hospital, Boston, Massachusetts demonstrated the presence of NUT-BRD4 translocation. Split probes to the NUT and BRD4 genes have been used to demonstrate NUT rearrangement.

TREATMENT

Given the complexity of the diagnosis in a young, pregnant patient, this case was reviewed extensively at a Multidisciplinary Tumor Board Conference. The lack of standardized treatment and history of poor response to traditional chemoradiation in association with the typically fulminant course of NUT midline carcinoma led to a consensus recommendation for aggressive surgical extirpation. Right orbital exenteration was carried out after intraoperative frozen section samples confirmed intraorbital invasion into both inferior oblique and inferior rectus muscles. Extensive sinonasal resection was carried out, with removal of involved skull base structures, including the cribriform plate, fovea ethmoidalis, and underlying dura. Bilateral modified radical neck dissection of levels I-IV was carried out. Given the extent of the resection, harvest of an anterolateral thigh free flap was undertaken for reconstructive purposes. A maternal fetal medicine team was present in the operating suite for continuous fetal monitoring. Both the patient and the fetus remained stable throughout the case and experienced no intraoperative or postoperative complications. All surgical margins were negative on final pathology and neck lymph nodes showed no evidence of local spread.

At 36 weeks gestation, birth was induced with uneventful delivery of a healthy infant. Postpartum PET/CT scan showed no evidence of metastatic disease. The patient underwent adjuvant therapy including three cycles of platinum-based chemotherapy and 60Gy of intensity-modulated radiation therapy to the primary site, as well as 54Gy to the right neck over 30 fractions. Surveillance PET/CT scans undertaken since surgery have so far shown no evidence of recurrent or metastatic disease. The patient remains disease-free at 12 months.

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DISCUSSION

NUT midline carcinoma (NMC) involves structures of the midline either in the thorax/mediastinum (57%) or within the head and neck (35%), with isolated cases of other organ involvement¹. NMC has been considered a disease of children and adolescents², though these tumors have been reported across a wide age range (0-78 years) with a mean of 23 years at age of diagnosis.

NMC is genetically defined by the presence of a translocation on the nuclear protein in the testis (NUT) gene on chromosome 5. In approximately two thirds of these cases, NUT is fused to BRD4 as a t(15;19) (q14;13.1) translocation. Head and neck lesions in particular demonstrate the BRD4-NUT translocation in 88% of cases^{3,4}.

The diagnosis of NMC is associated with a grim prognosis, with fewer than 20% of those diagnosed expected to survive to 1 year after diagnosis³. The median life expectancy is 6.7 months. Treatment options have focused on traditional chemoradiation. Surgical extirpation is often not considered due to the presence of metastatic disease or primary site involvement that is deemed unresectable because of involvement of critical structures. A 2012 review of 64 cases by Bauer et al suggests that it is likely this diagnosis is underreported in adults³: because NMC is considered a disease of the young, adult tissue is typically not sent for the cytogenetic and molecular testing needed to establish the diagnosis.

Recent research into targeted molecular therapy has opened new avenues for treatment of NMC. Bromodomain inhibitor therapy in a dose escalation phase is undergoing clinical trials, and is usually reserved for patients with recurrent or metastatic disease. Other promising therapies include acetyl-histone mimics (BETi) and histone deacetylase inhibitors (HDACi)^{1,6}.

In adults, NUT midline carcinoma is an underreported variant of poorly differentiated squamous cell carcinoma. With the increased clinical awareness of this diagnosis and wider availability of immunohistochemical staining, we anticipate increasing numbers of NMC cases in the future. Early aggressive therapy is warranted to provide the best chance of disease-free survival.

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