



Nut Midline Carcinoma-Nasal Cavity-A Case Report

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Abstract

NUT Midline carcinoma (NMC) is a very rare, poorly differentiated malignancy which is highly aggressive. Genetic hallmark is rearrangement in NUT gene located in chromosome 15. The median survival time of NMC patients is only 6.7 months despite of surgical resection or chemoradiotherapy, and most patients with NMC have been diagnosed with locally advanced or metastatic diseases. This is a case of a 36 year old lady with nasal cavity mass which turned out to be NUT Midline carcinoma.

Keywords: NUT gene, NMC, BETi.

Introduction

NMC is regarded as the clinically aggressive type of squamous cell carcinoma and majority of the patients will succumb to rapid disease progression¹. The actual incidence of NUT midline carcinoma is unclear. It is almost certainly under diagnosed.^{2,3} As the name indicates it typically occurs in the midline structures of head and neck, mediastinum. It is characterised by undifferentiated morphological features, immunoreactivity to NUT and defined by NUT rearrangement. Because of the poor prognosis (median survival 6.7 months)⁴ and poor response to conventional cytotoxic chemotherapy, new drugs such as BET inhibitor (BETi) and histone deacetylase inhibitor (HDACi) are now in clinical trials for patients with NMC. High clinical suspicion

and diagnosis of this rare entity is essential in a midline undifferentiated carcinoma

Case Report

A 36 Year old lady was evaluated for nasal obstruction, epistaxis and anosmia of one month duration. She was initially evaluated elsewhere and was found to have a polypoidal mass in right nasal cavity. She underwent Direct nasal endoscopy and biopsy from the mass which was reported as poorly differentiated carcinoma. CT done outside showed heterogeneously enhancing mass nasal cavity and right frontoethmoidal sinus extending to nasopharynx and orbit. She was referred to our institution. At presentation here, she had polypoidal mass protruding from the right nasal cavity with active bleeding, widening of nasal bridge, fullness

in the right nasolabial fold, proptosis of right eye and restricted elevation of right eye and anosmia. There was no other neurological deficits and systemic examination were within normal limits.

She was evaluated with an MRI head and Neck which showed a lobulated mass 7.9 x 5.5 x 2.9 cm in the right nasal cavity expanding it involving the cribriform plate of ethmoid and adjacent frontal bone and extending into the olfactory fossa and basifrontal region with thickening and enhancement of the dura, laterally the lesion is bulging into orbit with displacement of extra ocular muscles. Mass is T1, T2 hypointense with post contrast heterogeneous enhancement and restricted diffusion. No obvious cervical lymphadenopathy.

Histopathological examination showed fragments of cellular neoplasm composed of cells arranged diffusely and in perivascular pattern. Individual cells were large with round to ovoid nuclei with irregular nuclear membrane. Brisk mitotic activity (MIB 75-90%), areas of haemorrhage and necrosis were present. IHC showed positivity with cytokeratin, EMA, CD 138 and negative for LCA, KP1, MUM 1, CD56, CD 5, CD20, CD30, CD31, Myogenin, suggestive of high grade malignant neoplasm-undifferentiated carcinoma.

An outside pathology opinion was sought for further IHC typing. NUT immunostaining was performed which showed speckled nuclear positivity and diagnosis of midline NUT carcinoma was obtained. As surgical resection was not possible in view of extensive intracranial extension, she was initiated on platinum based chemotherapy. She received first cycle of chemotherapy with Cisplatin and 5 Fluorouracil (CDDP 100 mg/m², 5 FU 1g/m² iv 24 hour infusion D1-D4). She improved symptomatically and there was also visible reduction in the protruding nasal mass, proptosis of right eye. She was discharged in a stable condition. She got admitted in another centre on 10th day of chemotherapy with grade IV neutropenia and she succumbed to death.

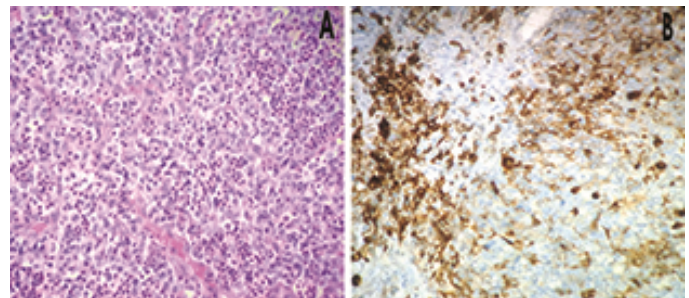


Figure 1 A.: H&E (400 X): Tumour cells with round vesicular nuclei and prominent nucleoli admixed with neutrophils. B.: IHC: Patchy expression for pancytokeratin.

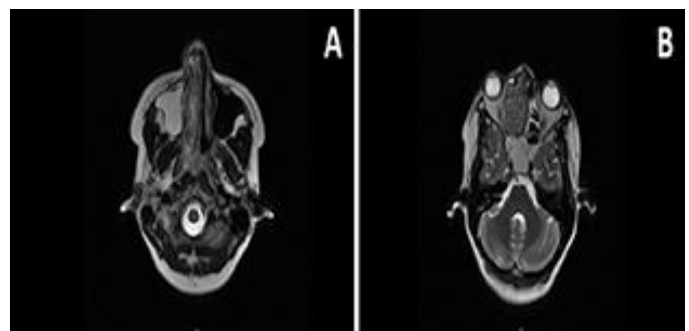


Figure 2 Axial T2 weighted images of MRI Head and neck showing lobulated mass lesion filling entire right nasal cavity extending to ethmoid sinus, frontal recess, Cribriform plate of ethmoid, olfactory fossa and orbits

Discussion

NUT midline carcinoma (NMC) is a rare and aggressive genetically defined subtype of squamous cell carcinoma characterized by chromosomal rearrangements of the gene NUT, at 15q14. The bromodomain protein family member 4 (BRD4) gene on 19q13 is the most common translocation partner forming a fusion oncogene, BRD4-NUT. NMC was originally considered as a disease of children and young adults, but recent publications have shown that NMC can affect individuals at any age (0-78 years, median 16) and both genders are affected equally⁴.

The majority of cases occur in the midline of the body, including the head, neck, and the mediastinum.^{5,6} There is no proven association between environmental agents, smoking or oncogenic viruses. Most common symptoms are local mass and pain caused by tumor cells infiltrating oppression and diffusion. Some patients

remain asymptomatic for extended periods of time, and diagnosis is made when tumor burden is significant.⁷

Histologically the tumor cells were largely poorly differentiated and most pathology specimens typically show abrupt squamous differentiation. Nests and sheets of primitive cells with high nuclear/cytoplasmic ratios imparting a blue, low-power appearance. The tumor nuclei were round to oval with even chromatin, a single delicate nucleolus, and little variability in size and shape⁸.

NMC is morphologically categorized as a variant of squamous cell carcinoma. NMCs are mostly immunoreactive with antibodies to p63, cytokeratin, CK20, CD34⁹. Tumors have reportedly been nonreactive with antibodies to desmin, myoglobin, smooth muscle actin, muscle actin, chromogranin, synaptophysin, leukocyte common antigen, placental alkaline phosphatase, S100 protein, alpha-fetoprotein, neuron specific enolase, CD57, CD99, and HMB45⁹

Recently, a highly sensitive and specific monoclonal immunohistochemical test for NUT (C52 monoclonal antibody) was introduced, which greatly simplified the diagnosis. Positivity was defined as strong, speckled nuclear staining in greater than 50% of nuclei. FISH, RT-PCR, or cytogenetic analysis is no longer required for this diagnosis as the specificity of the NUT immunostaining is 100 % and the sensitivity is excellent at 87 %¹⁰

In a recent study by Chau et al. on head and neck NMC, Unlike most HN cancers, HNNMC appears to affect women more than men for unclear reasons. Survival outcomes are poor with a median survival of 9.7 months, although this appears to be better than thoracic NMC by historical comparison. Survival appears to be impacted by treatment selection and initial therapeutic sequencing strategy. Initial surgical resection, and the extent of surgical resection (negative margins), was significantly associated with progression free and overall survival. No specific treatment protocol exists for NMC. Multimodality approaches using surgery, radiotherapy, chemotherapy were tried with limited

clinical benefits. Chemotherapy regimens used were mainly anthracyclines, platinum compounds, taxanes. Recently targeted agents like histone deacetylase inhibitors and BET inhibitors have shown promising results

Conclusions

Midline NUT carcinoma is a rare, genetically defined and aggressive neoplasm. It should be considered as a differential in midline poorly differentiated carcinoma. Survival is very poor even with aggressive multimodality approach. Characteristic molecular rearrangement is paving way to novel targeted strategies to tackle this aggressive neoplasm.

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