http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i5.63

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Hard Nut to Crack: Case Report on Nut Midline Carcinoma- A Rare Sinonasal Malignancy

Author
Dr Aparna Rajan
Government Medical College, Gandhinagar P.O, Kottayam, Kerala
Corresponding Author
Dr Aparna Rajan
Padmaragam (H), West Desom P.O, Aluva, Ernakulam Dist, Kerala, INDIA

Abstract
NUT (Nuclear protein of testes) midline carcinoma of nasal cavity is a rare and aggressive tumour with rapid progression to adjacent sites. Diagnosis requires prompt clinical suspicion, confirmation of diagnosis and analysis of disease extend by radiology. Pathological diagnosis is by demonstration of NUT protein by Immunohistochemistry (IHC) or fusion oncogene detection by Fluorescent in situ hybridisation (FISH). Radical resection combined with chemotherapy and radiation is being tried for treatment but without much success. Newer targeted treatments are under trial. Here is a case report of a 35 year old patient with epistaxis and nasal block, diagnosed by IHC as NUT carcinoma. In spite of ongoing chemotherapy, patient expired 2 months after diagnosis which is less than the median survival period. Understanding about this rare malignancy and thinking about this rare entity among the differential diagnosis is important to prevent misdiagnosis. Successful treatment options and adequate treatment policies should be made at the earliest to prevent morbidity and mortality from this tumour.
Keywords: *NUT (nuclear protein of testes), Sinonasal malignancy, poorly differentiated carcinoma.*

Introduction

Sinonasal malignancies account for one percent of all malignancies and 3 to 5 % of head and neck cancers[(1)]. Squamous cell carcinoma is the most common subtype noted[(1)]. NUT MIDLINE CARCINOMA is a genetically defined uncommon malignant epithelial tumour occurring mainly in head and neck including nasal cavity and para nasal sinuses, mediastinum and upper aerodigestive tract including lungs. It is also reported in bone, bladder, abdomen, pancreas, retroperitoneum and salivary glands[(2)]. The exact incidence is largely unknown and needs high clinical suspicion, prompt pathological diagnosis and aggressive treatment options to improve the survival rates. In this article we describe a case of NUT midline carcinoma of Sinonasal origin.

Case Report

A 35 year old, previously asymptomatic healthy patient presented with complaints of bleeding from right nasal cavity and right sided nasal obstruction for three weeks. On examination she was moderately built and well nourished. Nasal

examination showed a smooth surfaced mass in the right nasal cavity which mimicked concha bullosa but it spotted on probing. Rest of the clinical examination was normal including vision and eye movements. To our surprise computed tomography of nose and paranasal sinuses showed an extensive lesion involving right frontoethmoid sinus and nasal cavity with extension into nasopharynx, erosion of skull base and medial wall of orbit causing extension to extraconal space of right orbit. Diagnostic Nasal endoscopy was done and biopsy taken from the mass lesion in the right nasal cavity.

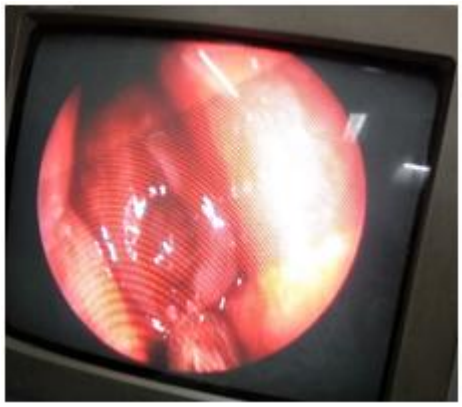

Figure 1 Diagnostic nasal endoscopic picture showing a smooth mass in the right nasal cavity, upon incising it a proliferative growth is seen.

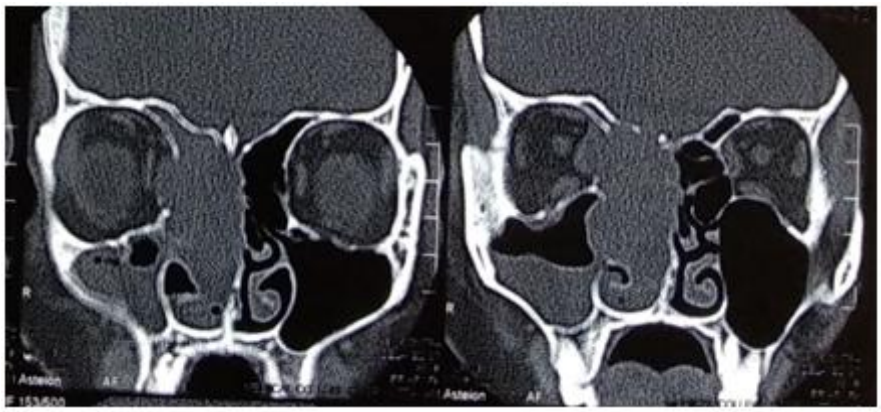

Figure 2 Computed tomography showing soft tissue density lesion right nasal cavity with intracranial and intraorbital extension

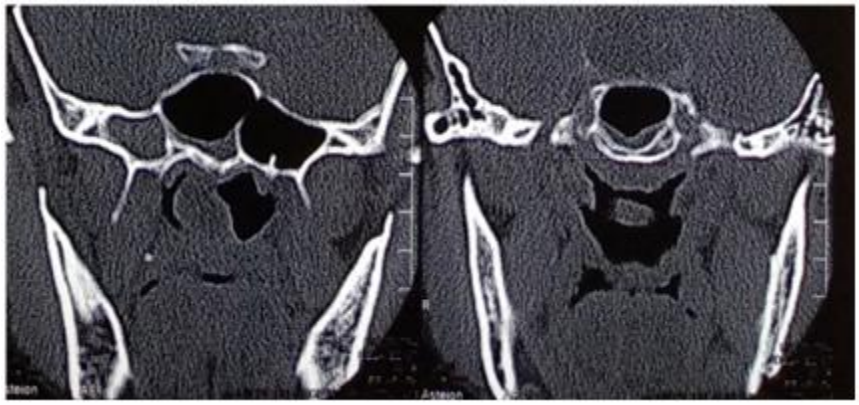

Figure 3 The mass is also seen extending to nasopharynx.

Clinically the diagnosis after radiologic evaluation was malignancy right nasal cavity with intra cranial and intraorbital extension with possible differential pathological diagnosis being Sinonasal squamous cell carcinoma, Haemangiopericytoma, Esthesio neuroblastoma, primitive neuro ectodermal tumour, mucosal melanoma and lymphoma. The histopathology report was that of a high grade poorly differentiated carcinoma adding Sinonasal undifferentiated carcinoma and NUT midline carcinoma into the differential diagnosis. Immunohistochemistry was sent in

which tumour cells expressed cytokeratin, MIB index 75 to 90%, EMM with strong variable expression all indicating a poorly differentiated aggressive carcinoma with squamous elements. Synaptophysin and chromogranin were negative. The final diagnosis was made by NUT immunostaining that showed speckled nuclear immunoreactivity.

Hence the final diagnosis of NUT midline carcinoma was made. Since there are no defined protocols for treatment, the patient was started on palliative chemotherapy with CDDP (cisplatin) and 5 Fluoro Uracil. She was not responding to treatment and reported expulsion of mass from nostril once and expired 2 months after diagnosis. Inspite of the early accurate diagnosis and aggressive chemotherapy patient survived less than the median survival period.

Discussion

NUT midline carcinoma is a genetically defined tumour. NUT is a protein normally expressed in human testes but also in ciliary ganglion which are of neural crest origin. Nut midline carcinoma is an aggressive solid tumor, affects teens, adolescents but also seen in adults(3). These arise from head and neck, mediastinum and upper aerodigestive tract including lungs(4). Origin of this rare tumour is attributed to genetic aberrations in the gene encoding the nuclear protein of the testes.

NUT carcinoma occurs as a result of a fusion oncogene NUT-BRD4 produced as a result of chromosomal translocation (15;19)[5]. BRD4 is bromodomain 4 protein expressed in chromosome 19. There are other variants with some showing rearrangement with BRD3 receptor[6]. The fusion oncogene blocks cellular differentiation and promote uncontrolled growth of carcinoma cells.

Differential diagnosis include Sinonasal carcinoma, Haemangiopericytoma, Lymphoma, Esthesioneuroblastoma, poorly differentiated squamous cell carcinoma, primitive neuroectodermal tumour, mucosal melanoma .But closely the differential diagnosis of this aggressive poorly differentiated carcinoma includes sinonasal undifferentiated carcinoma (SNUC). NUT carcinoma is frequently misdiagnosed as SNUC as they are histologically similar with elements of poor differentiation but the latter lacks squamous elements and genetically they are very distinct. These tumours are also similar to other poorly differentiated tumours but they can be differentiated by NUT antibody testing[3].

Diagnosis

Suspected lesion is confirmed to be a malignant lesion by radiological evaluation with computed tomography and supplemented by MRI which clearly delineates the aggressive nature of the disease and spread to sites adjacent to nose and paranasal sinuses like orbit and cranial cavity. Clinical findings are confirmed by diagnostic nasal endoscopy and biopsy of the mass. Many of the cases are undiagnosed and the actual prevalence is unknown since all laboratories donot have the expertise and equipment to detect the NUT protein or Fusion oncogene. In NUT immunohistochemistry, nuclear protein of testis can be detected. Diagnosis is also made by demonstration of the fusion oncogene BRD4 by fluorescent in situ hybridization.

Treatment

Even when diagnosed, treatment protocols are not defined. Treatment options include radical resection, radiation therapy and chemotherapy. Platinum or taxane based chemotherapy with or without radiotherapy is being tried without much success. There are isolated case reports of successful treatment with Docetaxel based chemotherapy and local radiotherapy[7]. This tumour is reported to have 80% likelihood of death within the first year after diagnosis for adult patients[8]. Irrespective of treatment given, the median survival period is only seven months[9].

Presently focus is on developing targeted therapy which could lead to better treatment options for this present day incurable cancer. Emerging treatment focuses on Histone deacetylase inhibitors like vorinostat that encourage

differentiation. Also trials are on using Bromodomain inhibitor as Bromodomain protein fuse with chromosome 19 and blocks formation of fusion oncogene. Tumour regression following this therapy is reported with only minor side effects like gastrointestinal irritability, fatigue and reversible thrombocytopenia[10].

Conclusion

Early clinical diagnosis should be supplemented by radiologic confirmation and accurate identification of this rare pathological entity by IHC and FISH. Clinicians should think of this differential diagnosis especially in children and young adults and should communicate to the pathologist regarding the same. In any such tumour with elements of poor differentiation steps to detect fusion oncogene by FISH or NUT protein testing by IHC should be taken to avoid misdiagnosis and under treatment. Newer research works that give promising results regarding treatment options are to be adopted and made available at every centre to improve survival rates and reduce the morbidity and mortality from this rare but aggressive tumour entity.

References

1. Lund VJ, Stammberger H, Nicolai P, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl 2010;22: 1-143
2. Den Bakker MD, Beverloo HB, van den Heuvel-Eibrink MM, Meeuwis CA, Tan ML, Johnson LA, French CA, van Leenders GJLH. NUT midline carcinoma of the parotid gland with mesenchymal differentiation. American Journal of Surgical Pathology. 2009:33(8),1253-1258
3. Stelow EB, Bellizzi AM, Taneja K, Mills SE, Legallo RD, Kutok JL, et al. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol 2008;32:828–34
4. French CA. Pathogenesis of NUT midline carcinoma. Annu Rev Pathol. 2012;7:247-65.
5. French CA et al BRD4-NUT fusion oncogene:a novel mechanism in aggressive carcinoma. Cancer Res. 2003;63:304-307
6. Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009;33(7): 984–991
7. Engleson et al Midline carcinoma with BRD4-NUT fusion oncogene in a 30 year old female with response to docetaxel and radiotherapy.BMC cancer.2006;6:69
8. Daniel E. Bauer, Chelsey M. Mitchell, Kelly M. Strait Clinicopathologic Features and Long-term Outcomes of NUT Midline Carcinoma Clinical cancer research 2012 18(20),5773-5779
9. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Lure SC, *et al*. Clinicopathologic features andlong-term outcomes of NUT midline carcinoma. Clin Cancer Res2012;18:5773-9.
10. Anastasios Stathis, Emanuele Zucca, Mohamed Bekradda. Clinical Response of Carcinomas Harboring the BRD4-NUT Oncoprotein to the Targeted Bromodomain Inhibitor OTX015/MK-8628. Cancer discovery 2016:6(5), 492-500.