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A RARE CASE OF NUT MIDLINE CARCINOMA OF MAXILLA

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INTRODUCTION

Nuclear protein in Testis (NUT) Midline carcinoma (NMC) is highly aggressive, lethal, uncommonly encountered variant of squamous cell carcinoma, caused by genetic re-arrangement of NUT gene with a gene from BRD family[1]. 143 patients were registered to International NMC Registry between 1990 to 2017[2].Similarly data of 119 patients from 64 literatures published between 1950 to 2017 were retrieved on PUBMED and Google search[3]. Diagnosis of NMC has increased annually since 2007[4, 10] (Figure 1).Median age of onset is 24 years[1]with equal incidence in male and female.[2]Most common site of occurrence is thoracic (54%) followed by Head and Neck. (40%) [2] Among Head and Neck NMC sinonasal origin is commonest.[1,2,3,5,6,11].Median Overall Survival quoted by various literatures is about 6.8 months[2].We report a case of a boy who presented to us with typical features of NMC.

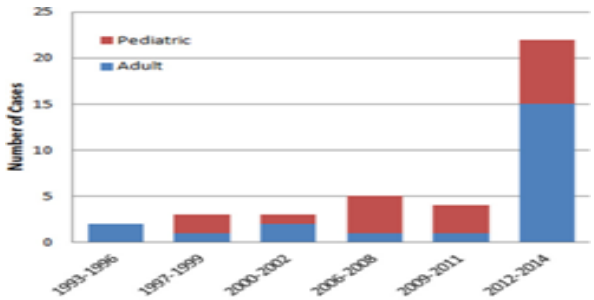

Figure 1.Diagram depicting increase in number of NMC diagnosis in recent past. [10]

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CASE REPORT

A 19-year-old boy presented with complaints of bloodstained secretion from his right nostril associated with painful right cheek swelling and loosening of a right upper second molar tooth in early January 2016. On tooth extraction, a growth protruding from the empty tooth socket was seen. Computed tomography scan head and neck demonstrated heterogeneously enhancing soft tissue mass in the right maxillary sinus eroding all its bony walls and infiltrating the surrounding structures.

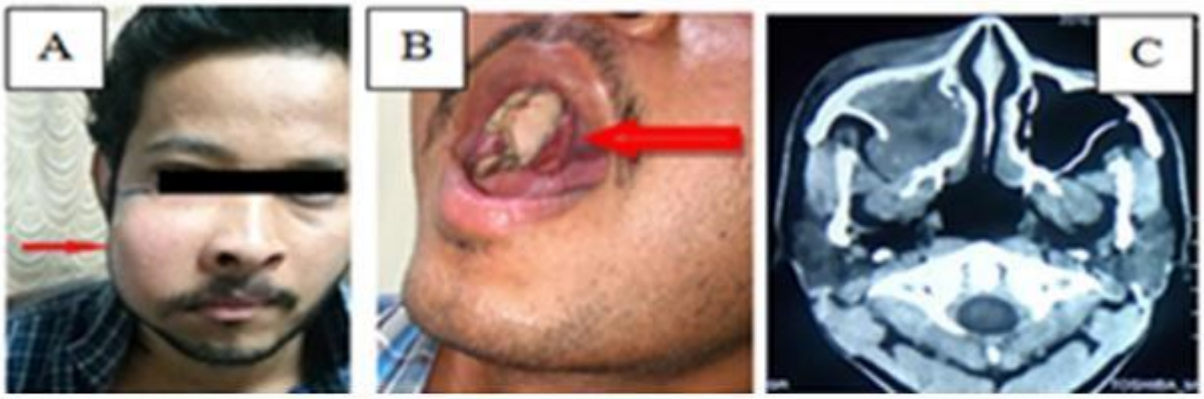

Figure 2.A and B: Picture of the patient at presentation showing right cheek swelling and right upper alveolar growth. C:Computed tomography Scan demonstrating a right Maxillary enhancing mass,infiltrating surrounding structures.

Biopsy from the growth in early February 2016 revealed malignant small round cell tumor with undifferentiated epithelioid morphology. The tumor cells were large, having vesicular nuclear chromatin with prominent eosinophilic nucleoli and a moderate amount of cytoplasm. Based on the morphology possibilities of Undifferentiated Carcinoma, Esthesioneuroblastoma, Ewing Sarcoma and Embryonal Rhabdomyosarcoma were considered. Preliminary Immunohistochemistry [IHC] assay with three markers showed patchy positivity to pan CK and negativity to Desmin with background lymphocytes expressing CD-45 supporting squamous cell lineage with an unclear diagnosis.

To check the rapidly progressive disease palliative radiotherapy with 12 Gy in 3 fractions was started. Meanwhile a Whole body 18 FDG PET CT Scan was done, which demonstrated localized, metabolically avid right Maxillary mass with SUV of 18.7 and an enlarged right level IB lymph node with SUV of 3.3. In light of aggressive disease with focal

squamous cells differentiation, the pathologists were compelled to test further for rare tumor markers.It was only in early March that immunohistochemistry test with wide array of markers confirmed the diagnosis of NMC based on its expression of Cytokeratin (focally) and NUT oncoprotein. Cells were immunonegative for EMA, p63, MUM-1, HMB-45, s100 protein, Desmin, Synaptophysin and Mic-2.In situ hybridization for EBERs was negative and Nuclear INI-1 expression was intact.

Looking at an impressive clinical response to radiation, a radical dose of 70 Gy was delivered. PET CT Scan repeated in May 2016 demonstrated a non-metastatic disease with a significant decrease in SUV from 18.7 to 4.7.

He subsequently underwent Near total Maxillectomy, Supraomohyoidal neck dissection and excision of orbital, nasal and palatal bones (Figure 3). The histopathological examination revealed residual viable foci of poorly differentiated carcinoma with keratin pearls amidst extensive areas of fibrosis and necrosis with focally positive posterior margins. Early in June 2016, revision surgery was done to the clear posterior margin.

Figure 3.Pictures of the patient during Near total Maxillectomy, Supra Omohyoid Neck Dissection.

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Within a few weeks, the patient developed skin nodules on the right cheek, anemia, sepsis at surgical site on face and bilateral lower limb weakness. A repeat PET CT scan showed multiple metastases in bone, liver, and lungs. Finally, palliative radiation with 30 Gy in 10 fractions was given to alleviate pain and impending cord compression. He died due to progressive disease on 9th of September 2016.

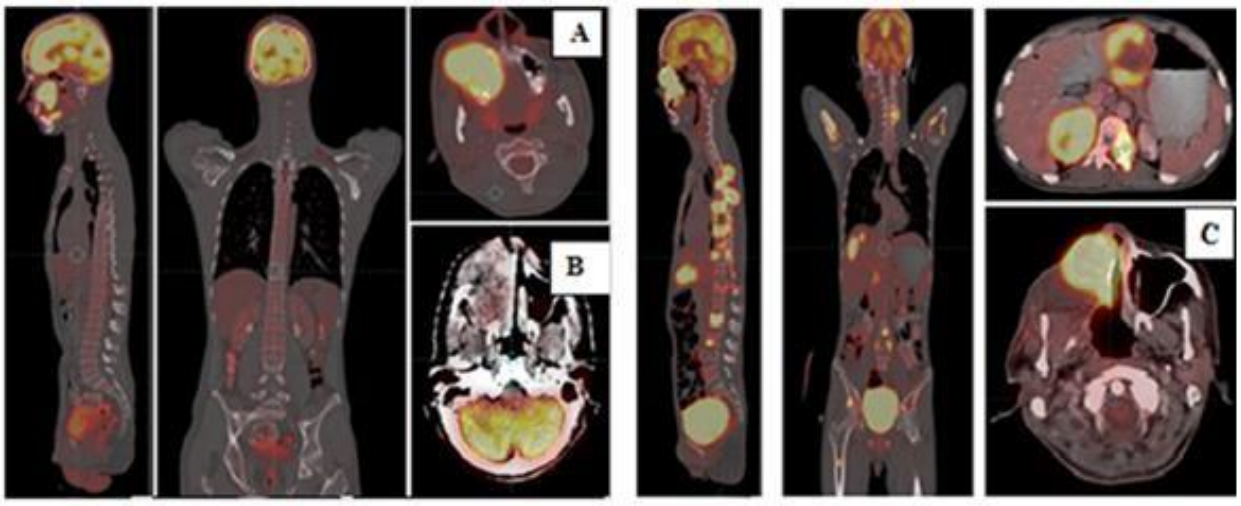

Figure 4.

A.18 FDG PET CT Scan before Radiation showing mass in right Maxilla with SUV 18.7.

B.PET CT Scan after Radiation with decreased SUV from18.7 to 4.7.

C.PET CT Scan after surgery when patient presented with bilateral lower limb weakness.

DISCUSSION

Single Translocation abnormality t(15,19),(q14;p13.1) causes NMC.In 75% of cases, NUT gene present on q arm of Chromosome15 is fused to BRD4 gene on p arm of chromosome 19 resulting in BRD4-NUT fusion gene. In rest of the cases NUT gene fuses to either BRD3 orother uncharacterized genes resulting in NUT variants[5,6,7,9] (Figure 5)

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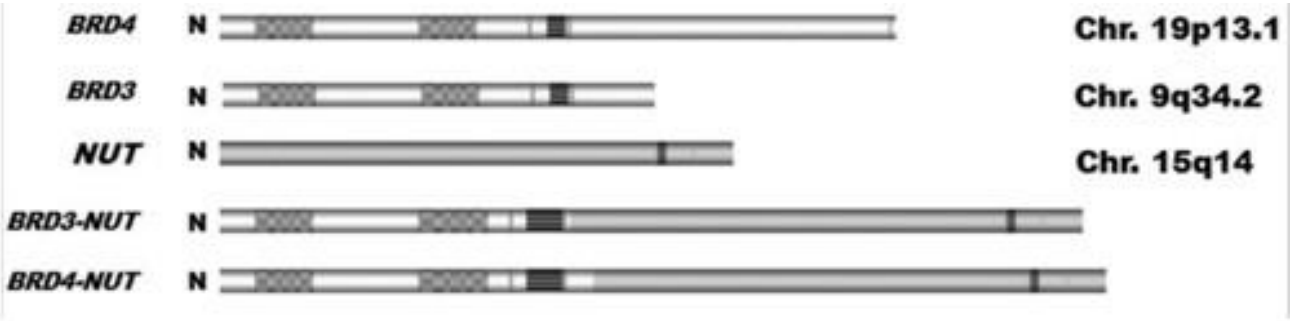

Figure 5. In 75% of cases NUT gene translocates with BDR 4 gene. In rest of the cases NUT gene fuses with either BRD3 or other uncharacterized genes resulting in NUT variants

BRD4-NUT gene protein suppresses differentiation of NMC precursor cells and allows their continuous proliferation. This is evidenced by the fact that when siRNA of BRD4-NUT oncoprotein is knocked down, rapid squamous differentiation occurs. (Figure 6) [5, 6, 7, 9.]

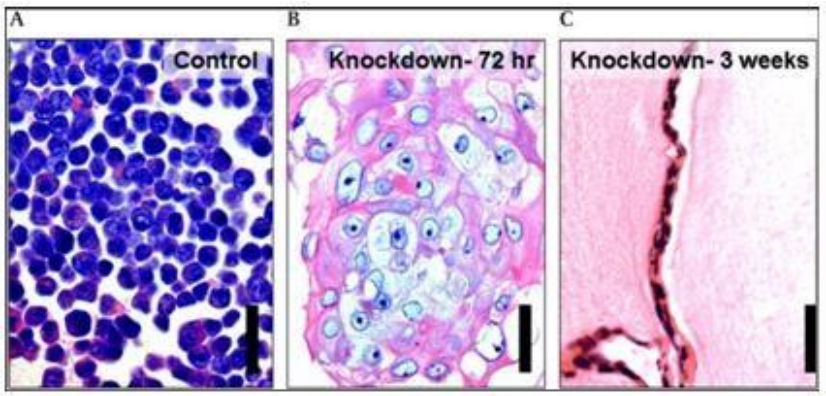

Figure 6.

Knocking down BRD4-NUT expression causes well defined squamous cell differentiation in 3 weeks.This is the basis for using BRD4-NUT inhibitor to treat NMC[5].

Pathologically it consists of undifferentiated monomorphic small round cells with abrupt focal squamous keratinization unlike other tumors where cells are pleomorphic.[5, 6, 7, 9] (Figure 7).

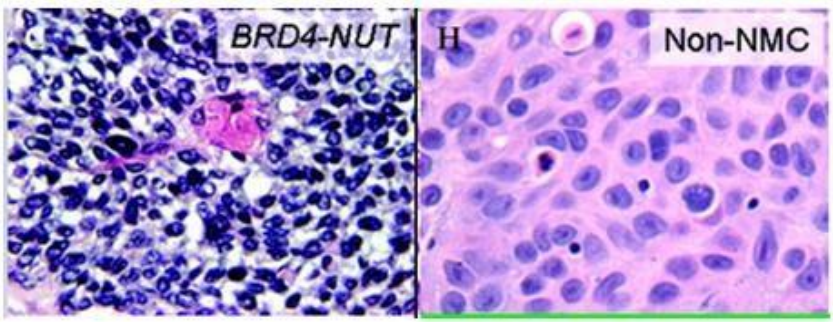

Figure 7

Monomorphic cells in NMC and pleomorphic cells in NON NMC.[5]

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Patients are commonly referred to higher centers for treatment of symptoms related to mass lesion or metastasis. NMC rapidly spreads by local invasion, through lymphatics and hematogeneously. Hence Whole body 18 FDG PET CT Scan is recommended tool for metastatic assessment and response evaluation.[5, 6, 7] Typically patients with head and neck NMC are nonsmokers and are not associated with Epstein Bar virus and Human Papilloma virusinfection[2,6,10].

Diagnosis based on cell morphology is less reliable due to its resemblance to various tumors like germ cell tumor, Ewing sarcoma and lymphoma. NUT specific monoclonal antibody is commercially available to confirm diagnosis by Immunohistochemical(IHC) assay. Normal NUT is exclusively expressed in the testis. Thus, positive nuclear IHC staining for NUT in tissue outside the testis is indicative of aberrant expression, such as in NMC (Figure 7).NUT-BRD translocation can be demonstrated by FluorescentIn Situ Hybridization (FISH) or by Reverse transcriptase Polymerase Chain Reaction (RT-PCR).[5,6,7]

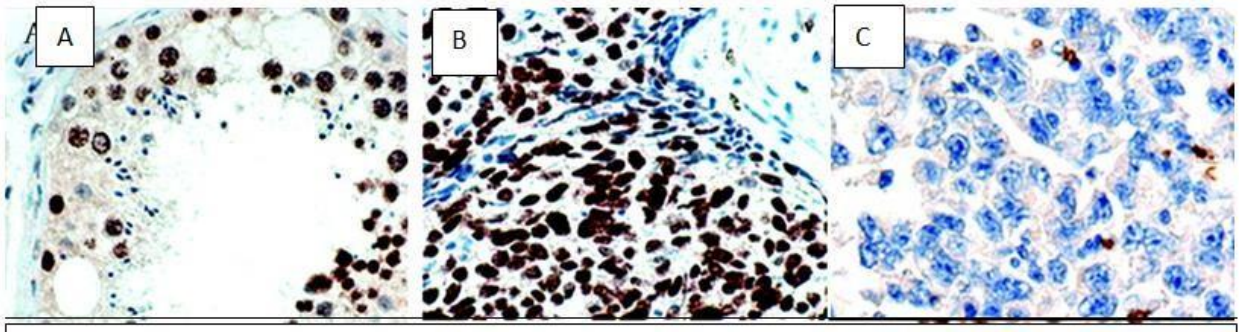

Figure 8. A] Nut stains positive In Spermatogonial Cells in Testis.

B]NUT stains positive in NMC. C] NUT stains negative in non NMC cells.[5]

When feasible surgery should be considered although ironically the disease is large[>5cm] and inoperable at diagnosis[4,6,7,8,9,10,11]. Initial excellent response is observed to Radiotherapy and Chemotherapy followed by vigorous progression and dissemination. Chemotherapy tried so far were combination of drugs used for various sarcomas, carcinoma and germ cell tumors .[4, 5, 6, 7, 10].

At least 5 phase 1 clinical trials in the United States (NCT01587703, NCT01987362, and NCT02431260) and Europe (NCT02259114 and NCT01587703) are currently evaluating bromodomain inhibitors in patients with NMC.[3, 6]

A new drug PhosphoInositide 3 kinase[PI-3 and Histone deacetylase inhibitor [HDAC] under the code name of CUDC-907 is being evaluated in an phase I multicentric trial (NCT02307240) for its use in NUT Midline cancer[6].

CONCLUSION

NMC should be suspected if a midline cancer in a non smoker patient not infected with Epstein Bar virus or Human Papilloma virus shows primary histology of poorly or undifferentiated, monomorphic cells, that does not stain for lineage-specific markers[2 3, 5, 9, 10, 11]. Best attempt should be made to diagnose it,as it aids in counselling the patients, prepares caregivers to act quickly and rightly and finally identifies candidates for BRD4 inhibitor drugs.As awareness increases it is likely that hundreds of diagnosis of NMC could be made per year with the help of simple IHC and simple suspicion[4,10].

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11) Bishop JA, Westra WH. NUT Midline Carcinomas of the Sino nasal Tract. The American Journal of Surgical Pathology. 2012; 36 (8):1216–21. Table 1 .Battery of tumor markers performed on the index case and was Negative.

Table 1.Battery of tumor markers tested in the index case and found negative

Sl No. -	Tumor marker	Description	Cancers with positive markers
1	Pan CK	Cytokeratin (CK) are intermediate filaments found in epithelial cells of all types and have subtypes 1through 20	• Squamous cell carcinoma • Endometrial adenocarcinoma • Gastric adenocarcinoma
2	Desmin	Muscle-specific protein suggesting mesenchymal origin	• Rhabdomyoma • Rhabdomyosarcoma • Leiomyosarcoma
3	MUM 1	MUltiple Myeloma associated protein, Is a lymphocyte-specifictranscriptional factor helping in B- cell differentiation.	• DLBCL • Plasmacytoma, • Classical Hodgkin lymphoma
4	HMB-45	Human Melanoma Black-45 is a monoclonal antibody that binds to antigen present in melanocytic tumors.	• Melanomas
5	S-100 protein	Normally present in cells derivedfrom the neural crest (Schwanncells and melanocytes, chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells and keratinocytes.	• Melanomas, • Schwannomas • Neurofibromas • Malignant peripheral nerve sheath tumors • Histiocytoma • Clear cell sarcomas

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6	Synaptophysin	Integral membrane glycoprotein of neuronal synaptic vesicles normally present in all synapses and neoplastic neuroendocrine cells in the nervous system.	• Ganglioneuromas • Ganglioneuroblastomas • Neuroblastomas • Paragangliomas • Primitive neuroectodermal tumors
7	Mic-2	CD99 antigen, also known as MIC2	• Ewing's sarcoma • Peripheral primitive neuroectodermal tumor
8	EBER	Epstein Bar Virus-Encoded small RNAs (EBER)	EBV related • Nasopharyngeal cancer • Gastric cancer, • Subset of Hodgkin's lymphoma and DLBCL..
9	Nuclear-INI-1	Is a Tumor suppressor gene on Chromosome 22.	• Malignant rhabdoid tumor of infancy, • renal medullary carcinomas, epithelioid sarcomas

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