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Case Series

Pathology Section

NUT Carcinoma: A Diagnostically Challenging Rare Entity with an Aggressive Course: A Case Series

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ABSTRACT

Nuclear Protein in Testis (NUT) carcinomas are rare, extremely aggressive, poorly differentiated squamous carcinoma, characterised by the presence of NUT gene (NUTM1) rearrangement. NUT carcinoma most commonly arises in head and neck region and thorax however, they can occur in other parts of the body also. Here, we are presenting a case series of three cases of NUT carcinoma. All patients were females with disease involving head and neck region. The first case was an eight-year-old girl. The second case was a 36-year-old woman. The third case was a 61-year-old woman. Histopathology of all cases showed poorly differentiated neoplasm, comprising of sheets of monotonous cells with minimal indistinct, clear cytoplasm, round to oval nuclei with prominent nucleoli. High mitotic rate with areas of tumour necrosis were also present. Areas of abrupt keratinisation classically described in this entity were seen in two of the cases. Speckled nuclear positivity for NUT1 monoclonal antibody by immunohistochemistry, which is sensitive and specific for diagnosis was observed in all three cases. There is no definite treatment for this disease, and most patients respond poorly to conventional chemotherapy and radiation. Targeted therapy targeting the BRD4 portion of BRD4-NUT, termed BET bromodomain inhibitors, are in clinical trials. Two of our patients succumbed to disease within one year of diagnosis. Third patient is on follow-up for eleven months after diagnosis.

Keywords: Abrupt keratinisation, Carcinoma, Midline, Sinonasal

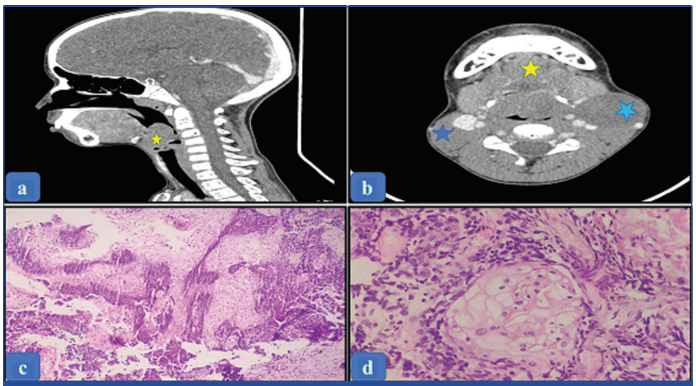
INTRODUCTION

The Nuclear Protein in Testis (NUT) carcinomas are highly aggressive carcinomas showing propensity for involving midline structures, mediastinum, thymus, thorax and head and neck, although they can occur in other sites also [1]. In head and neck region the most common site is the sinonasal region [2]. Histology is usually that of a poorly differentiated neoplasm with round cells with high mitotic rate and necrosis. Areas of abrupt keratinisation, when present help in diagnosis. Because of the rarity, lack of awareness and non specific histomorphology, this entity can be diagnosed as undifferentiated or poorly differentiated carcinomas. It is important for the pathologist to diagnose this entity because of prognostic and therapeutic reasons. The median survival is less than one year and requires aggressive management. Speckled diffuse nuclear positivity (>50%) for NUT monoclonal antibody C52, by immunohistochemistry is diagnostic [3]. Molecular study characteristically shows translocations involving the NUT gene (15q14), most commonly with BRD4 (19p13) [4]. The cases included in this study presented to the Regional Cancer Centre, Thiruvananthapuram, Kerala, India and were diagnosed in the Department of Pathology of this centre during a four-year period from January 2018 to December 2021.

CASE SERIES

Case 1

First case was of an eight-year-old girl, who presented with noisy breathing and enlarged left cervical lymph node of six months duration. Computed Tomography (CT) scan of the neck showed homogeneous lobulated midline mass in vallecula measuring 3.4×3.3×2.4 cm and enlarged bilateral cervical lymph nodes [Table/Fig-1a,b]. Fine Needle Aspiration Cytology (FNAC) from left cervical node was reported as malignant round cell neoplasm. Open incision biopsy of left cervical lymph node was done. Histopathology showed a poorly differentiated neoplasm, comprising of sheets of monotonous cells with minimal indistinct, clear cytoplasm, round to oval nuclei with prominent nucleoli. High mitotic rate with areas of tumour necrosis were also present. Considering the morphology and age of the patient immunopanel for round cell neoplasm was done. Desmin, Leukocyte Common Antigen (LCA), synaptophysin, chromogranin, CD20, CD5, CD3, Terminal deoxynucleotidyl Transferase (TdT) was negative. Serial sections studied however showed areas of squamous differentiation with abrupt keratinisation, which was easily appreciable and not a focal feature [Table/Fig-1c,d]. With this additional finding in histopathology and the immunoprofile ruling out the possibility of malignant round cell neoplasm, we considered the possibility of NUT carcinoma. Further, immunostaining done showed tumour cells to be positive for cytokeratin (CK AE1/AE3) and p63. Staining with NUT antibody showed the characteristic speckled nuclear positivity in more than 50% of cells, confirming the diagnosis of NUT carcinoma. She was given chemotherapy, however, she succumbed to the disease within one year of diagnosis.



[Table/Fig-1]: a,b) CT scan of neck showing homogeneous lobulated midline mass in vallecula measuring 3.4×3.3×2.4 cm and enlarged bilateral cervical lymph nodes; c) Areas of squamous differentiation along with poorly differentiated areas (H&E x200); d) Higher magnification showing area of abrupt keratinisation along with poorly differentiated cells (H&E x400).

Case 2

Second case was of a 36-year-old lady, who presented with nasal obstruction, anosmia and epistaxis of one month duration. CT

showed heterogeneously enhancing mass measuring 7.9×5.5×2.9 cm in right nasal cavity and right fronto-ethmoidal sinus extending to nasopharynx and orbit. The patient developed epistaxis and during nasal packing she expelled a mass which was submitted for histopathological examination. Microscopy showed poorly differentiated malignant neoplasm with sheets of monotonous round cells with scanty to moderate cytoplasm and nucleus with prominent nucleoli [Table/Fig-2a]. Broad immunopanel covering carcinoma, lymphoma, rhabdomyosarcoma, melanoma and neuroendocrine neoplasms was done. The neoplastic cells were positive for CK (AE1/AE3) and was negative for all other markers. Correlating histomorphology, immunoprofile and location we proceeded with p63 and NUT antibody immunostains. The cells were positive for p63 [Table/Fig-2b]. Immunostaining with NUT monoclonal antibody showed diffuse nuclear positivity [Table/Fig-2c]. She was given chemotherapy, however, she also succumbed to the disease within two months of diagnosis.

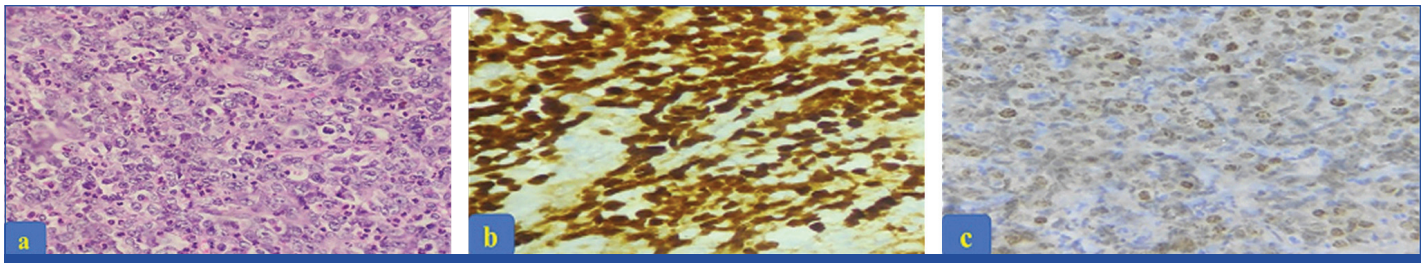
Case 3

Third case was of a 61-year-old lady who presented with right nasal obstruction of five months duration. CT scan of head and neck showed an enhancing soft tissue lesion obliterating right nasal aperture, measuring 2.5×2.2×1.9 cm, extending to vestibule and subcutaneous tissue of nose on right-side with erosion of maxilla [Table/Fig-3a]. She was taken up for surgery. Wide excision with nasolabial reconstruction was done. Histopathology showed a carcinoma with focal squamous differentiation, along with poorly differentiated areas showing sheets of neoplastic cells with round nucleus and prominent nucleoli [Table/Fig-3b,c]. Areas of necrosis and brisk mitotic activity were noted. Immunoprofile showed positivity for CK and p63. Considering the sinonasal location we proceeded with synaptophysin, chromogranin and NUT antibody immunostains. Tumour cells were positive for NUT antibody and negative for neuroendocrine markers. She was given radiotherapy and is currently on follow-up for 11 months after the diagnosis. The clinicopathological features of the three cases are presented in [Table/Fig-4].

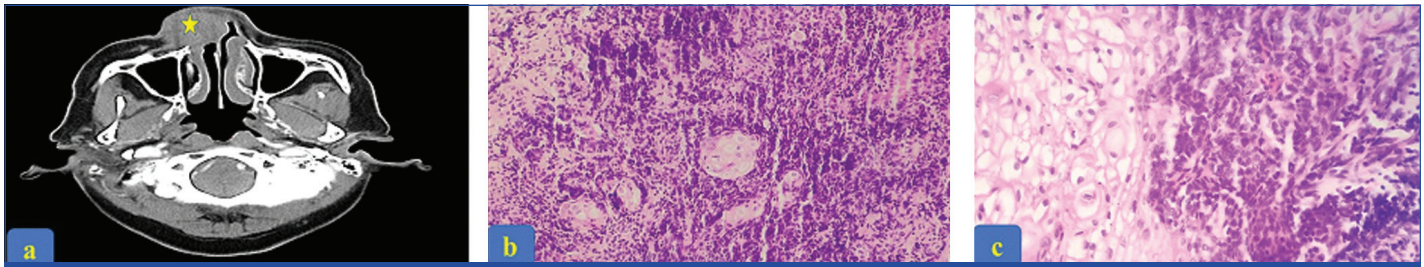
DISCUSSION

The NUT carcinoma is a rare, aggressive subtype of squamous cell carcinoma, which is characterised by rearrangement of the NUTM1 gene. Most common rearrangement is due to chromosomal translocation, BRD4-NUT resulting in formation of NUT-fusion oncoproteins. Molecular analysis to demonstrate NUTM1 fusion gene is diagnostic. Molecular tests are however not essential now for confirming the diagnosis as immunohistochemical staining with NUT monoclonal antibody, C52 showing speckled nuclear staining in more than 50% of neoplastic cells is also considered to be highly sensitive and specific for diagnosis. Lack of awareness, unavailability of specific NUT monoclonal antibody and sophisticated molecular techniques along with non specific histomorphology are reasons for under reporting of this entity [5].

In our case series, we have reported three cases of NUT carcinoma diagnosed in our centre. All three of our patients were females with involvement of head and neck region, two cases involving sinonasal region and one patient with involvement of epiglottis. The age range was wide, eight years, 36 years and 61 years. The available studies in the literature also support the head and neck region to be a common site for this rare carcinoma [6]. Previously, it was thought



[Table/Fig-2]: a) Poorly differentiated neoplasm with sheets of monotonous round cells with scanty to moderate cytoplasm and nucleus with prominent nucleoli (H&E x400); b) Neoplastic cells are showing diffuse strong nuclear positivity for p63 (IHC x400); c) Neoplastic cells are showing diffuse speckled nuclear positivity for NUT monoclonal antibody (IHC x400).



[Table/Fig-3]: a) CT scan of head and neck showed an enhancing soft tissue lesion obliterating right nasal aperture, measuring 2.5×2.2×1.9 cm, extending to vestibule and subcutaneous tissue of nose on right-side with erosion of maxilla; b) Sheets of poorly differentiated neoplastic cells along with foci of abrupt keratinisation (H&E x200); c) Higher magnification showing poorly differentiated cells with hyperchromatic nucleus and scant to moderate eosinophilic cytoplasm along with area of abrupt keratinisation.

Case no.	Age	Gender	Chief complaint	Differential diagnosis	IHC findings	Histopathology diagnosis	Follow-up
1	8 years	Female	Noisy breathing, enlarged left cervical node of six months duration	Malignant round cell neoplasm, poorly differentiated carcinoma with areas of squamous differentiation	Desmin, LCA, synaptophysin, chromogranin, CD20, CD5, CD3, TdT negative and CK, p63, NUT positive	NUT carcinoma	Succumbed to disease within one year of diagnosis
2	36 years	Female	Nasal obstruction, anosmia, epistaxis of one month duration	Poorly differentiated malignant neoplasm ?carcinoma, ?lymphoma, ?melanoma, ?rhabdomyosarcoma	LCA, desmin S100, synaptophysin, chromogranin negative and positive for CK, p63, NUT	NUT carcinoma	Succumbed to disease within two months of diagnosis
3	61 years	Female	Right nasal obstruction of five months duration	Poorly differentiated carcinoma with squamous differentiation	CK, p63, NUT positive, synaptophysin, chromogranin negative	NUT carcinoma	Currently on follow-up 11 months after diagnosis

[Table/Fig-4]: Clinicopathological features of the three cases.

that NUT carcinoma was a disease affecting children and young adults. However, now it is known that any age group can be affected. Studies in the literature have shown cases affecting patients as young as three years to as old as 78 years [7]. Our youngest patient was an eight-year-old child and oldest patient was 61 years. All our patients were females; the other studies in the literature with larger series of patients have also shown a slight female predominance [8]. In all the previous studies, the clinical outcome was fatal with median survival of less than one year [9]. We also lost two of our patients, within one year. The third patient is currently on follow-up 11 months after initial diagnosis.

Because of the non specific histological features, this entity is a diagnostic challenge for pathologists and is often misdiagnosed as poorly differentiated carcinoma based on cytokeratin positivity. Monotonous round to oval nuclei with variably prominent nucleoli, high mitotic rate along with prominent tumour necrosis is the usual finding. Based on this histopathology a whole lot of differentials can be considered. All small blue round cell neoplasms, lymphoma, rhabdomyosarcoma, Ewing sarcoma and also entities like germ cell tumours, malignant melanoma, undifferentiated carcinoma are entities which form differentials. Hence, a broad immunopanel is often required including CK, LCA, desmin, myogenin, S100, SALL4, and p63. Foci of abrupt keratinisation if present are helpful in making a diagnosis. However, rarely the squamous areas may be extensive as in one of our cases [10]. In classical locations like sinonasal, thorax etc., when patients present with aggressive clinical course, NUT carcinoma should always be considered in the differential.

Although NUT carcinoma is a sub-type of squamous cell carcinoma, it has a highly aggressive behaviour when compared to other high-grade carcinomas of the head and neck or mediastinum. Most of the patients succumb to their illness within one year of diagnosis and hence, it is important to diagnose this entity for prognostic and therapeutic reasons. The translocations of NUT carcinoma are targetable, and there are on-going trials. Targeted therapy using histone deacetylase inhibitors as well as Bromodomain and Extra-Terminal (BET) inhibitors are now in clinical trials [11].

CONCLUSION(S)

The NUT carcinoma is an aggressive and fatal disease with most of the patients succumbing to disease within a year of diagnosis. The non specific histomorphology features makes it a diagnostic challenge for pathologists. A high degree of suspicion in case of clinically aggressive disease in classical locations like head and neck and thorax is needed. Usually, a large immunopanel is required to rule out other entities, as we observed in our series of cases. Positivity for NUT antibody by immunohistochemistry is diagnostic. This aggressive disease is currently managed by chemotherapy and radiotherapy, however, the response is limited. Building up data on this rare entity will help in better understanding and characterisation and better clinical management. Individual case reports and case series will go a long way in contributing to better understanding of this underdiagnosed entity.

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