Original Article

The Small Round Blue Cell Tumors of Sinonasal Tract: Pathologists Grey Zone

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Abstract

Background: One of the most challenging diagnostic categories in the sinonasal tract includes small-blue-round-cell tumors. These are malignant tumors which show many overlapping histomorphology and immunohistochemistry (IHC) findings. Limited, small biopsy of these not completely excisable tumors adds to the diagnostic confusion. **Materials and Methods:** A cross-sectional study was done for 2 years (January 2018–December 2020) in a tertiary care institute, which included 70 cases of tumors of which 49 cases were malignant. All paraffin-embedded blocks were subjected to hematoxylin and eosin stain and IHC followed by molecular study wherever needed. **Results:** Of the total cases, small-blue-round-cell tumor constituted the major category comprising 20 rare and interesting cases which included sinonasal undifferentiated carcinoma (4 cases), malignant lymphoma (2 cases of diffuse large B-cell lymphoma and 2 cases of extranodal natural killer/T-cell lymphoma), rhabdomyosarcoma (2 cases), olfactory neuroblastoma (2 cases), malignant melanoma (2 cases), plasmacytoma (2 cases), atypical Ewing's sarcoma (EWS) (1 case), EWS (1 case), nuclear protein in testis (NUT) carcinoma (1 case), and small-cell neuroendocrine carcinoma (1 case). **Conclusion:** Tumors of the sinonasal tract are very diverse, more so in small-round-cell tumor which present with a undifferentiated morphology. Thus, accurate diagnosis needs clinicoradiological parameters and special ancillary techniques such as IHC and molecular study in addition to histopathology for early diagnosis and therapy to prevent significant morbidity and mortality caused in these tumors.

Keywords: Ewing's sarcoma, extranodal natural killer/T-cell lymphoma, malignant melanoma, olfactory neuroblastoma, plasmacytoma, sinonasal undifferentiated carcinoma, small-round-blue-cell tumors

Introduction

The term "sinonasal tract" collectively refers to the nasal cavity and paranasal sinuses (PNS) which serves as a site for occurrence of 0.2%–0.8% of all malignancies.[1] Due to the close proximity to orbit and skull base, most of the malignancies extend to these structures.[1] In most of the regions, there is a lower incidence, accounting for <1.5/1 lakh cases and 1.0/1 lakh cases in males and females, respectively.[2] The most common location is maxillary sinus (60%), followed by the nasal cavity (20%–30%) and ethmoid sinus (10%–15%).[1,3] Small-round-blue-cell tumor (SRBCT) encompasses a diverse group of malignant tumors characterized by undifferentiated tumor cells having a small hyperchromatic nucleus and scant cytoplasm. The diagnostic classification of SRBCT of the sinonasal tract includes encloses malignancies of epithelial, hematolymphoid, neuroectodermal, and mesenchymal origin.[1] The epithelial SRBCTs include poorly differentiated nonkeratinizing squamous cell carcinomas which included nuclear protein in testis (NUT) carcinoma (4th edition, WHO 2017 classification) based on the identification of NUT gene by immunohistochemistry (IHC) or molecular/cytogenetics method, as well as sinonasal undifferentiated carcinoma (SNUC).[4] The neuroectodermal SRBCTs include olfactory neuroblastoma (ONB) and sinonasal mucosal malignant melanoma (MM). The mesenchymal SRBCTs of the sinonasal area encompass desmoplastic SRBCT, rhabdomyosarcoma (RMS), Ewing's sarcoma (EWS), and poorly differentiated synovial sarcoma. The hematolymphoid SRBCTs contain extranodal natural killer (NK)/T-cell

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lymphoma (nasal type) and extramedullary plasmacytoma.[3] These are rapidly growing tumors which yield smaller tissue in biopsies for diagnostic purposes. The diagnostic difficulty is compounded by the lack of architecture, crushing artifact, and overlapping histomorphology. The ancillary studies such as IHC and molecular study are mandatory for accurate diagnosis. The present study aims to differentiate the small-round-cell tumor which bears significant morphologic overlapping based on salient clinicoradiologic findings as well as ancillary techniques such as IHC and molecular markers.

Materials and Methods

A cross-sectional study was conducted in a tertiary care teaching hospital over 24 months (January 2018–December 2020) which caters as a referral center for oncology cases in the Eastern part of India. The present study was approved by the institutional ethical committee. The total number of biopsies from the sinonasal tract having small-blue-round-cell morphology accounted for 42 in number. For the study, all the cases with small-blue-round-cell histomorphology in the sinonasal tract were included irrespective of age and gender except those cases of high-grade cases, paraffin blocks of which were appended for referral to higher center even before IHC could be performed. Cases with inadequate material in biopsy and tumour other than small blue round cell tumors were also excluded. There are many drawbacks when small tissue samples are obtained in biopsy, such as a small amount of tumor cells, unclear architectural pattern, and a nonspecific gross information. The clinical, laboratory, and radiological details of all the cases were collected from the hospital information system and archives of the Department of pathology. All the paraffin blocks were subjected to routine hematoxylin and eosin stain and special stains (wherever required). Ancillary tests such as IHC (ready to use and polyclonal/monoclonal) and molecular study were also done for a definite diagnosis. The results obtained were analyzed by two pathologists in a blinded manner. The present study was approved by institutional ethical committee of IMS and SUM Hospital, Bhubaneswar, vide Ref.no/IEC/IMS.SH/SOA/2021/259 on dated 29th November 2021.

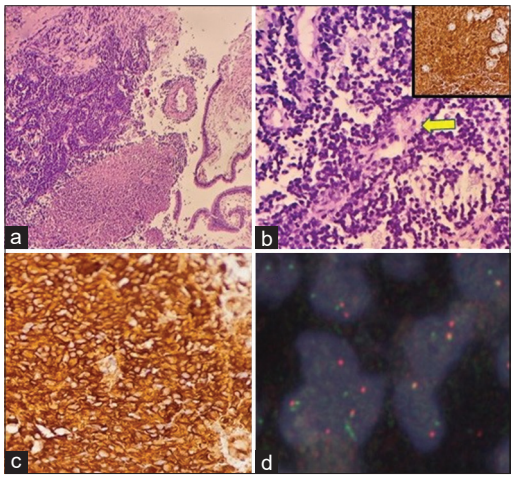

Figure 1: (a and b) Photomicrograph of Ewing's sarcoma/PNET showing respiratory epithelium and tumor in the subepithelium comprising small-round-blue cell in diffuse pattern and perivascular as well as Homer Wright rosettes (arrowed yellow) (hematoxylin and eosin, ×100) with strong and diffuse synaptophysin positivity (inset) (immunohistochemistry, ×400); (c) Immunohistochemistry for CD99 showing strong and diffuse positivity (immunohistochemistry, ×400); (d) Ewing's sarcoma R1-FLI1 fusion by fluorescent *in situ* hybridization

Results

Of 70 cases of sinonasal malignancies, 42 cases were small-round-cell tumors. However, 22 cases were not considered in the study as paraffin blocks of many cases of high-grade malignancies were appended for referral to higher center and those with inadequate material in biopsy. The rest 20 cases had SRBCT histomorphology, creating a diagnostic challenge during reporting and thereby concretizing the role of IHC and molecular studies in clinching the correct diagnosis. The age incidence was mostly in the fifth to seventh decade with a male: female ratio of 1.5:1. Majority of the patients had complaints of nasal obstruction, headache, and sinusitis, and grave symptoms such as epistaxis, visual disturbance, and facial palsy. According to the location, PNS constituted 42.8% of tumors, whereas the nasal cavity had 57.2% of tumors.

The SRBCT embraced majorly of SNUC (4 cases, 20%) and malignant lymphoma (ML) (4 cases, 20%) followed by ONB (2 cases, 10%), embryonal RMS (ERMS) (2 cases, 10%), EWS (1 case, 5%) [Figure 1], atypical EWS (1 case, 5%), malignant small-cell neuroendocrine tumor (1 case, 5%), mucosal MM (2 cases, 10%), NUT carcinoma (1 case, 5%) [Figure 2], and extramedullary plasmacytoma (2 cases, 10%) [Figure 3]. Age incidence was, however, variable, showing malignant melanoma, extramedullary plasmacytoma, small-cell neuroendocrine carcinoma, and malignant lymphomas occurring in the sixth to seventh decade of life,

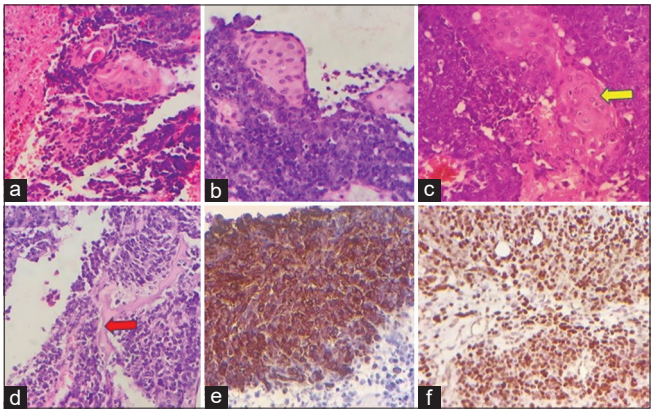

Figure 2: (a-d) Photomicrograph showing histomorphology of NUT carcinoma with characteristic squamous differentiation (arrowed yellow) (hematoxylin and eosin, ×400) and bone destruction (arrowed red) (d); (e) Photomicrograph showing pancytokeratin positivity for the tumor cells (immunohistochemistry, ×400); (f) Photomicrograph showing P63 positivity (immunohistochemistry, ×400)

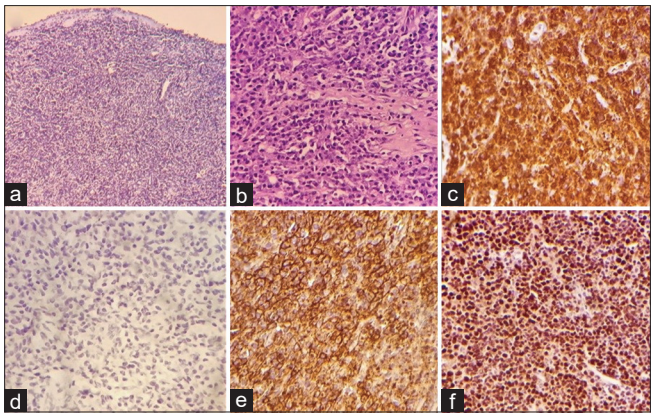

Figure 3: (a and b) Photomicrograph of extramedullary plasmacytoma, showing respiratory epithelium (a) (hematoxylin and eosin, ×100), with tumor beneath the epithelium comprising neoplastic plasma cells arranged diffusely nests, and cords (hematoxylin and eosin, ×400); (c) Photomicrograph showing immunohistochemistry for Kappa-light chain restriction (immunohistochemistry, ×400); (d) Immunohistochemistry for lambda light chain is negative; (e) Photomicrograph showing diffuse positivity for CD138 (immunohistochemistry, ×400); (f) Immunohistochemistry for MUM1 is strong and diffusely positive (immunohistochemistry, ×400)

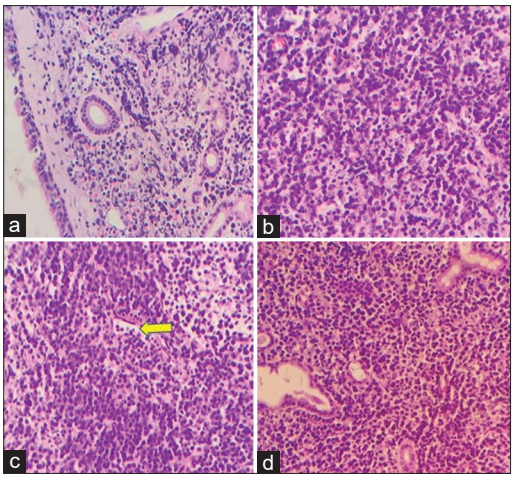

Figure 4: (a) Photomicrograph of extranodal natural killer/T-cell lymphoma showing respiratory epithelium with ducts beneath the epithelium along with tumor (hematoxylin and eosin, ×100). (b-d) The tumor comprised small round blue cells arranged diffusely and in angiocentric fashion (arrowed yellow) exhibiting moderate pleomorphism (hematoxylin and eosin, ×400)

whereas ONB and ERMS were encountered in the pediatric population. One case of NUT carcinoma was seen in a 42-year-old male. Among the two cases of EWS, one was found in older age at 60 years. Both the diffuse large B-cell lymphoma (DLBCL) were encountered in higher age, but it was found that among two cases of extranodal NK/T-cell lymphoma (ENK/TCL), one was Epstein–Barr virus (EBV) negative which was seen in older age, whereas the EBV positive one has been found in 40 years of age [Figures 4 and 5]. The patients with lymphomas, NUT carcinoma, and mucosal malignant melanoma presented with a polypoid lesion in the nasal cavity and hence diagnosed clinically as inverted papilloma. The SNUC and NUT carcinoma had extensive involvement of PNS, showing bony erosion. One SNUC had extension into orbital bone and skull base for which orbital exenteration was done. Cervical lymphadenopathy was associated in two cases. All SRBCT were subjected to a battery of IHC markers. Real-time polymerase chain reaction was done in EWS, showing EWSR1-FLI1 fusion. Extramedullary plasmacytomas showed monoclonality for IgM in serum protein electrophoresis. Epstein-Barr virus-encoded small RNA (EBER) was done in ENK/TCL, in which one showed latent membrane protein 1 (LMP1) positivity, whereas the other showed EBV (LMP1) negativity [Table 1].

Discussion

Sinonasal undifferentiated carcinoma and nuclear protein in testis carcinoma

It is a highly aggressive carcinoma with a high propensity for local extension, occurring in a broad age range.[1] The unique clinicopathologic characteristically permits its segregation for other SRBCT. Clinically, the patient has short duration of symptoms with radiologically large sinonasal lesions with the destruction of orbital and cranial bone.[5] Histologically, it has chances to grow along mucosal surface, showing ulceration with mucosal gland extension and lymphovascular invasion.[1,6] The cells are hyperchromatic to vesicular with conspicuous nucleoli. IHC shows positivity of cytokeratin (CK) 7 and CK 19 and isocitrate dehydrogenase-1 positivity.[7] It has to be differentiated from NUT carcinoma which has high mortality, usually within 1 year.[8] Histologically, NUT carcinoma shows focal squamous differentiation with pearl formation, and IHC shows NUT, P63, and CK 5/6 positivity. We encountered two cases of SNUC who presented with cervical lymphadenopathy and underwent radical excision with orbital exenteration. The NUT carcinoma occurred in a 42-year-old male with polypoidal mass in the middle turbinate of the right nose involving right maxillary, ethmoid, and bilateral sphenoid sinuses, clinically diagnosed as invasive fungal sinusitis. The tumor shows brisk mitosis, necrosis, and bone destruction in addition to undifferentiated cells arranged in nests and trabeculae.

Small-cell neuroendocrine carcinoma

Small-cell neuroendocrine tumor generally occurs in aged population, with male predominance having a strong association of history of heavy smoking. Microscopically, it shows a rosettoid pattern of small cells with Azzopardi effect and crushing artifact. The tumor is extremely aggressive, showing median survival of 18 months.[9]

Olfactory neuroblastoma

ONBs are relatively uncommon, accounting for 1%–5% of malignant nasal cavity neoplasm.[9] They arise from olfactory portion of mucous membrane lining nasal fossa of the upper nasal cavity, seen in pediatric age.[10] Differential diagnosis for this entity includes SNUC, malignant lymphoma and small-cell neuroendocrine tumor, and small-round-cell tumor

Table 1: Spectrum of small-round-blue-cell tumors with immunohistochemical profile (*n*=20)

Type of malignancies	Number of cases, *n* (%)	Mean age (years)	IHC	
			Positive	Negative
Epithelial malignancies				
SNUC	4 (20)	60.8	CK7, CK19	CK5/6, synaptophysin
NUT carcinoma	1 (5)	42	NUT1, P63, PanCK	CK7, CD99, synaptophysin
Mesenchymal malignancies				
Atypical EWS	1 (5)	60	CD99, NSE, PanCK, CK5/6, synaptophysin	LCA, CK7, CD34, S100
EWS	1 (5)	20	CD99, NSE, PanCK, CK5/6, synaptophysin	LCA, CK7, CD34, S100
RMS (embryonal)	2 (10)	21.5	Desmin, MyoD1	NSE, PanCK, CK7
Malignant melanoma	2 (10)	70	HMB45, S100	LCA, synaptophysin
ONB	2 (10)	16.5	NSE, S100, chromogranin	LCA, CK5/6
Neuroendocrine carcinoma	1 (5)	65	NSE, PanCK, P63, synapto, chromogranin	LCA, S100
Lymphoid malignancies				
DLBCL (ABC type)	2 (10)	65.2	LCA, CD20, MUM - 1, BCL2-50%, Ki67-65%	CD3, CD10, CD30, BCL6
ENKTCL (EBV positive)	1 (5)	59	LCA, CD5, CD56, EBV (LMP1)	PanCK, CD20, CD3, NSE, ALK-1, EMA, CD10, BCL6
ENKTCL (EBV negative)	1 (5)	64	CD2, CD30, CD56	EBV (LMP1), CD4, CD3
Extramedullary plasmacytoma	2 (10)	60	CD138, kappa chain	LCA, lambda chain
Total number of cases			20	

SNUC: Sinonasal undifferentiated carcinoma, IHC: Immunohistochemistry, ONB: Olfactory neuroblastoma, RMS: Rhabdomyosarcoma, EWS: Ewing's sarcoma, DLBCL: Diffuse large B-cell lymphoma, ENKTCL: Extranodal NK/T-cell lymphoma, EBV: Epstein-Barr virus, ABC: Activated B-cell

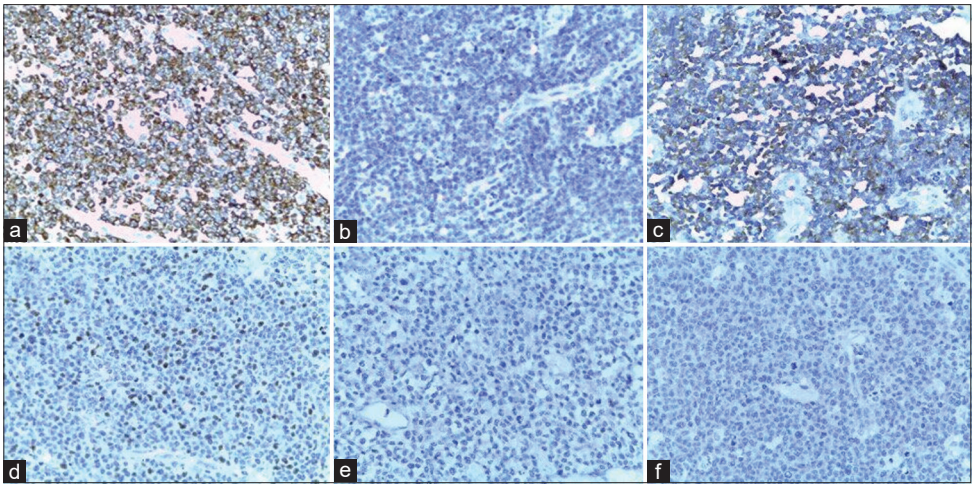

Figure 5: (a) Immunohistochemistry of the aforesaid tumor for CD 2 is positive (immunohistochemistry, ×200); (b) Tumor cells are negative for CD3 immunohistochemically (immunohistochemistry, ×200), (c) Immunohistochemistry CD56 is positive is the tumor cells (immunohistochemistry, ×200); (d) Ki67 labeling index is 60% (immunohistochemistry, ×200); (e) The tumor cells are negative for CD20 (immunohistochemistry, ×200); (f) EBER negativity in the tumor cells (immunohistochemistry, ×200)

of the bone and soft tissue, especially when it shows extensive crushing artifact.[9,10] The diagnostic feature such as Homer Wright rosettes, fibrillary cell processes, high degree of cell heterogeneity and positivity for synaptophysin, NSE, and S100 for sustentacular cells are helpful in diagnosis.[10,11] Our study showed ONB in a 18-year-old male who presented as a nasal mass showing NSE, synaptophysin positivity, and S100 highlighting the sustentacular cells.

Mucosal malignant melanoma

It occurs in nasal cavity mucosa as polypoid lesion presenting with epistaxis and occurs in higher age.[9] These are distinguished from other malignancies such as melanotic ONB by HMB45, vimentin positivity.[1,12] One of our cases presented with nasal mass clinically diagnosed with inverted papilloma. Mucosal MM if amelanotic easily confuses with ONB and SNUC. The prognosis of mucosal type MM is worse than its cutaneous counterpart.

Extraosseous Ewing's sarcoma

It usually affects the younger age group causing great diagnostic difficulty with SNUC, ONB, and SRBCT of bone and soft tissue.[13] It is distinguished by CD99 positivity and EWSR-FLI fusion. Although common incidence is found in childhood, the bimodal presentation can be seen as that of our case which occurred at higher age, having anaplastic morphology (atypical EWS).[4]

Rhabdomyosarcoma

Both embryonal and alveolar RMS frequently occur in the nasal cavity and sinuses in children and young adults.[1,14]The alveolar RMS usually occurs in older age and has a typical alveolar pattern of neoplastic cells.[14] It may be misleading as SNUC, ONB, and EWS/primitive neuroectodermal tumor (PNET) as there is focal CD56, CK, and CD99 positivity.[15] However, Desmin, MyoD1, and molecular translocation of PAX3-FOXO1 and PAX7-FOXO1 fusion help in definite diagnosis.[16]

Extramedullary plasmacytoma

It chiefly affects those above 65 years and involves sinonasal/nasopharyngeal area.[17] Immature plasma cells may show EMA and CK positivity misleading as carcinoma.[3] Confirmation is done by CD38, CD138, and kappa or lambda light chain restriction. EBV positivity can be a feature as found in our study. The bone involvement and abnormality in peripheral blood have to be excluded to rule out the possibility of plasma cell myeloma.

Extranodal natural killer/T-cell lymphoma

It is the second most common tumor following squamous cell carcinoma in the sinonasal tract. Malignant lymphoma, in general, constitutes 3.5% of sinonasal tract malignancy.[18] They present as polypoidal mass exclusively in the nasal cavity. The most common type of non-Hodgkin lymphoma is angiocentric T-cell lymphoma, followed by DLBCL in Japan but DLBCL in other studies in Western countries.[19] ENKTCL frequently affects Asians and Latin Americans.[5] We had an equal incidence of DLBCL and NK/T-cell lymphoma (2 cases each). Necrosis, angioinvasion along with propensity for the destruction of bone, and showing positive CD56 and negative CD3 are the characteristic immunohistology.[20] Demonstration of EBV positivity in IHC as well as fluorescent *in situ* hybridization is seen. These are aggressive malignancy showing infiltration to skull base which is worse in the case of EBV-negative tumors where death is imminent in few months. Our patient died postoperatively before the tissue diagnosis was obtained; meanwhile, the rest cases received chemotherapy and are doing well.

Conclusion

Malignancies arising sinonasal tract are heterogeneous. Accurate diagnosis of SRBCT is challenging due to the overlapping of clinical, radiological, and histological features. It is further complicated due to small biopsy yield, as the tumors are usually surgically unresectable. Advancements in IHC and molecular study play a great role in establishing the precise diagnosis which greatly helps in instituting correct treatment protocol reducing significant morbidity and mortality encountered in these tumors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that their name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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