Original Research Article

Small round cell tumours of the sinonasal tract: Five years experience at a tertiary cancer institute in India

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ABSTRACT

Purpose/Background: Sinonasal malignancies (SNM) constitute nearly 3% of Head & Neck cancers. Though rare, they still are one of the most challenging conditions to manage. Immunohistochemical (IHC) evaluation using relevant antibodies has become an indispensable ancillary technique for differentiating these tumours. An early and definitive diagnosis is important for optimally managing these aggressive tumours.

Materials and Methods: This study was done in the department of Head & Neck Surgery in association with department of Oncopathology of a tertiary Cancer Hospital in Northeast-India. Hospital records of all patients who received treatment for a sinonasal malignancy between the years 2013 to 2017 were retrospectively reviewed. Patients reported having a ‘Small round cell tumour’ in their initial histopathological examination (HPE) of biopsied tissue were included in the study.

Results: The study included 31 patients of Sinonasal SRCT, nearly 38% of the total 81 patients diagnosed with a sinonasal malignancy during the study period of 5 years. The median age of these patients was 43 +/- 8 years (range 8-82 years). With a gender ratio of 1.6: 1 (M: F), SRCTs was found slightly commoner in males. Epistaxis and nose block (unilateral or bilateral) were the commonest symptoms. Mean symptom duration was approximately 3 months.

Conclusion: Establishing a precise diagnosis of Sinonasal SRCT is important not only in determining how aggressive the tumor might be, but is especially critical in deciding treatment modalities and their sequences. Immunohistochemistry plays an important role in proper histopathological diagnosis and further treatment planning.

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1. Introduction

Sinonasal malignancies (SNM) constitute nearly 3% of Head & Neck cancers. Though rare, they still are one of the most challenging conditions to manage. Sinonasal ‘Small round cell tumors’ (SRCT) comprises a small-heterogeneous group of malignancies originating from varied cell lines eg. epithelial, hematolymphoid, neuroectodermal or mesenchymal, in the nose and the paranasal sinuses. They are grouped together as they share similar histopathological features often overlapping and in distinctive, characterized by a monotonous population of undifferentiated tumor cells with high nuclear to cytoplasmic ratio and high mitotic activity in conventional H&E light microscopy.1

Immunohistochemical (IHC) evaluation using relevant antibodies has become an indispensable ancillary technique
for differentiating these tumours. With the arrival of ultrastructural, cytogenetic and molecular techniques the accuracy in classifying these tumours has improved in recent times. Differentiating and deriving an accurate histotype of these tumours, is imperative because they exhibit unique tumour-behavior, respond differently to treatment modalities and have different prognoses. An early and definitive diagnosis is important for optimally managing these aggressive tumours.

Here, we share our experience of sinonasal ‘Small round cell tumours’ with emphasis on their clinical presentation and diagnostic approach.

2. Materials and Methods

This study was done in the department of Head & Neck Surgery of a tertiary Cancer Hospital in Northeast-India. Hospital records of all patients who received treatment for a sinonasal malignancy between the years 2013 to 2017 were retrospectively reviewed. Patients reported having a ‘Small round cell tumour’ in their initial histopathological examination (HPE) of biopsied tissue were included in the study. Details of their clinical presentation, haematological tests, CT scan &/ or MRI scans of the nose & paranasal sinuses (PNS) were noted. Immunohistochemical (IHC) evaluation reports of all these patients were analyzed. The immunophenotypic panel of markers which were used in the study to differentiate and categorize the small round blue cell tumors were CD45/LCA (the lymphocyte common antigen), CD20, CD3, CK, CD99, desmin, EMA (epithelial membrane antigen), synaptophysin, chromogranin.

Patients diagnosed with a nasopharyngeal cancer or having a 2nd primary outside nose & PNS were excluded from our study. Of total 81 patients diagnosed having a sinonasal malignancy, 31 had a SRCT and were included in the study.

3. Results

This study includes 31 patients of Sinonasal SRCT, nearly 38% of the total 81 patients diagnosed with a sinonasal malignancy during the study period of 5 years. The median age of these patients was 43 +/- 8 years (range 8-82 years). With a gender ratio of 1.6:1 (M: F), SRCTs was found slightly commoner in males. Patient symptomatology at presentation is shown in Table 1. Epistaxis and nose block (unilateral or bilateral) were the commonest symptoms. ‘Mean symptom duration’ which denotes the time period from symptom onset to hospital presentation, was approximately 3 months. The final histotypes of SRCTs, their histo-pathological features in light microscopy and the immunohistologic antibody panel used to differentiate them is shown in Table 2.

4. Discussion

Sinonasal SRCTs are very rare and precludes any randomized trails. Existing literature are from case series and institutional experiences. In this study we had 31 patients reported as SRCT in initial HPE. SRCTs comprised 38% of the total 81 patients diagnosed with a sinonasal malignancy during the study period of 5 years. Compared to a median age of 51 +/- 12 years for 81 patients with sinonasal malignancy, patients diagnosed with SRCTs were younger (median age= 43 +/- 8 years), age ranging from
8 to 82 years. Generalizing a median age for SRCTs will be inappropriate as distribution was not uniform. Ewing’s sarcoma (mean age = 22 years) and olfactory neuroblastoma (15 years) had a propensity to affect younger individuals, where else SNUC and Non-keratinizing SCC involved patients in their 5th and 6th decades. A sex ratio of 1.6: 1 (M:F) for patients with SRCTs reflects similar distribution as in sinonasal malignancy in general. Symptoms at presentation for SCRT, except for a shorter ‘mean symptom duration’, were also similar as in sinonasal malignancies in general. Epistaxis and nose block were the commonest symptoms. A shorter ‘mean symptom duration’ for SRCTs (3 versus 5 months) may be because of their aggressive nature; but it may also reflect the difference in mean age at presentation. Patients above 50 years of age were found to neglect their early symptoms more than their younger counterparts.

In absence of data on relative frequencies of different histotypes of undifferentiated SRCTs, it is believed to follow a similar distribution as the general population, where epithelial tumors are by far more frequent than non-epithelial tumors. This was reflected in the study with epithelial tumors comprising about 2/3rd of all SRCTs. Though grouped together because of common overlapping and indistinctive histopathological features, Sinonasal SRCT is a heterogeneous group of malignancies, which have contrasting tumour behaviors, different prognoses and varied response to treatment modalities. For example, sinonasal Neuroendocincal carcinomas (NEC), melanoma, lymphoma, and Sinonasal Undifferentiated Carcinoma (SNUC) can develop in the same anatomical region as Olfactory Neuroblastoma (ONB) and all can present with similar clinical, histological, and radiological features. In 2012 17 centres presented a collaborative study and reported the role of craniofacial resection in Esthenioneuroblastoma they found Five-year overall survival was 78% and 5-year recurrence-free survival was 64%. SNUC and NEC are aggressive tumors with a high risk of locoregional and distant recurrence. Despite a radical treatment approach, prognosis for these tumors still remains very poor with a reported median survival of 10-18 months. Surgery resection along with chemoradiation in adjuvant or neoadjuvant set-up is considered an optimum treatment for ONB and SNUC. In contrast, NETs are sensitive to chemotherapy and radiation to an extent where surgery is considered inappropriate for their management. Surgery as a modality has no role in the management of sinonasal lymphoma once its diagnosis is confirmed. Therefore, differentiating and deriving an accurate histotype for sinonasal SRCTs using immunohistochemical evaluation, cytogenetic and molecular study is imperative for their optimum management.

4.1. Epithelial SRCTs of the sinonasal area

4.1.1. Sinonasal Undifferentiated Carcinoma (SNUC)

SNUC is a rare, very aggressive carcinoma, most frequently arise in nasal cavity and ethmoid sinus. Spread to orbital apex, skull base and brain is seen in about 60% of cases. Usually originating in the ethmoid sinuses and nasal cavity, SNUC has a tendency of growing along the mucosal surface and early lymphovascular spread. Of the 6 patients (mean age 52 years) in our study, 3 had orbital involvement, with anterior skull base erosion and disease abutting the dura in one of them. Histologically, SNUC was found characterized by small to medium size cells arranged in lobules, nest, sheets or ribbons without evidence of squamous or glandular differentiation. SNUC has variable immunoreactivity for neuron specific enolase, EMA and p53. A study in 2011 has shown strong diffuse positivity for p16 in absence of HPV DNA expression. This was further supported by studies reporting its variable reactivity for neuron specific enolase (NSE), chromogranin, and synaptophysin. Recent report of a higher frequency of p16 positivity in SNUC (78.6%) is interesting, as p16 positive tumors had shown significantly better prognosis. SNUCs in our study showed positive immune-reactivity for pan-cytokeratins, simple keratins eg CK 7 & CK 8 and
| Diagnosis | Cases (n) | Age: range (mean) | Histopathological Features | Cytomorphology | Mitosis/Atypia | Immunohistochemistry |
|-----------|-----------|-------------------|---------------------------|---------------|---------------|---------------------|
| 1) Malignant Epithelial Small Round Cell Tumour | | | | | | |
| A) SNUC | 6 | 23- 82 (52) yrs | Lobules, nest, ribbons or sheets of tumour cells. No evidence of Squamous or glandular differentiation. | Small to medium size cells with scant cytoplasm and prominent nucleoli. | Common | Pankeratin, CK 7, CK 8, EMA NSE & Chrm (variable) |
| B) Non-keratinizing SCC | 4 | 48-72 (58) yrs | Strands, nest and ribbons. +/- Cords of neoplastic cells connecting with overlying epithelium. Poorly differentiated small cells with scant cytoplasm and prominent nucleus. | Small size cells with scanty cytoplasm, vesicular nuclei with prominent nucleoli. | Variable-common | Pankeratin, EMA, CK 8, CK 13, CK 14, CK 19. |
| C) Neuroendocrine Carcinoma | 4 | 15 – 65 (45) yrs | Sheets & ribbons of closely packed cells + frequent nuclear molding | | | |
| 2) Neuroectodermal small round cell tumours | | | | | | |
| A) Ewing’s sarcoma/PNET | 4 | 8-32 (22) yrs | Lobules & sheets of uniform round tumour cells. Homer Wright rosettes | Round to oval intermediate sized cells with scant/vacuolated cytoplasm. | Infrequent | CD99, Vimentin, FLI1, NSE & Syn (variable) |
| B) Malignant melanoma | 3 | 35 –68 (54) yrs | Infiltrative and pseudopapillary architecture | Epithelioid, pleomorphic spindle cells with nuclear molding, +/- Melanophages. | Common | HMB 45, S-100, Vimentin |
| C) Olfactory neuroblastoma | 1 | 38 yrs | Nodular/ lobular pattern with a fibrillary background. +/- rosettes | Small cells having scant cytoplasm, round nuclei with granular chromatin. | Infrequent | CD 56, CD99, Syn, Keratin (rarely), S 100 (sustentacular cells). Chrm - negative |
| 3) Hematolymphoid small round cell tumours | | | | | | |
| A) Extramodal NK/T cell & NHL | 5 | 12-67 (53) yrs | Diffuse angiocentric neoplastic pleomorphic lymphoid proliferation + inflammatory cells. | Small, medium to large or anaplastic cells with oval/irregular nuclei, and cytoplasmic granules. | Common | CD2, CD3e, CD 56, CD 45, CD 20, Cyclin D1 |
| B) Extra medullary plasmacytoma | 1 | 65 yrs | Diffuse pleomorphic neoplastic plasma cell infiltrate. +/- Amyloid deposits. | Poorly differentiated cells with intra-cytoplasmic crystals & coarse nuclear chromatin. | Infrequent | CD 38, CD 138, CD 45, kappa & lambda light chains. |
| 4) Mesenchymal small round cell tumours | | | | | | |
| A) Synovial sarcoma (poorly differentiated) | 2 | (16-60)/38 yrs | Solidly packed small cells with prominent vascular channels. | Small cells with high Nuclear to Cytoplasmic ratio. +/- high grade spindle cells. | Variable | Cytokeratins, EMA, BCL2, Vimentin, S100 (occasionally) |
| B) Rhabdomyosarcoma | 1 | 15 yrs | Nest of tumour cells in loose myxoidstroma with few fibrous septa. | Small round cells with scanty cytoplasm, scattered rhabdomyoblasts. | Frequent | Desmin, myogenin (nuclear), actin, Vimentin, CD 56, Myosin |

*EMA = epithelial membrane antigen, NSE = Neuron specific enolase, Syn = synaptophysin, Chrm = Chromogranin.*
epithelial membrane antigen (EMA). They showed variable reactivity for neuron specific enolase (NSE), chromogranin, and synaptophysin. SNUC’s usual non-reactivity with p63 and p40 was useful in differentiating it from poorly differentiated SCC and lymphoepithelioma.

4.1.2. Poorly Differentiated, Non-keratinizing Squamous Cell Carcinoma (PDNK SCC)

Well-differentiated keratinizing Squamous Cell Carcinoma is the commonest sinonasal malignancies and is easily recognizable under conventional microscopy. Where else, the poorly differentiated, non-keratinizing variant may show overlapping/ indistinguishable histological features as other Sinonasal SRCTs. Our study includes 4 cases of PDNK SCC, all males with a mean age of 58 years, presenting at an advance stage (AJCC stage IV). Epistaxis and unilateral nose block were the commonest symptoms. Under light microscope occasional cords of neoplastic cells connecting with overlying epithelium were unique for these tumors. PDNK SCCs were distinguished from olfactory neuroblastoma (ONB) because of their immunoreactivity with cytokeratin. Absence of immunoreactivity for synaptophysin, chromogranin and CD56 was used to differentiate it from small cell carcinoma neuroendocrine type (SCC- NET).

4.1.3. Small Cell Carcinoma: Neuroendocrine type (SCC-NET)

Neuroendocrine carcinomas (NEC) have been traditionally divided into a) Carcinoid, b) Atypical carcinoid and c) Small cell carcinoma. Sinonasal neuroendocrine carcinomas are usually small cell undifferentiated carcinoma, an aggressive tumor commonly associated with regional lymphatic spread and distant metastasis. Believed to originate from the glandular epithelium of the exocrine glands of the olfactory mucosa, it usually occurs in the superior part of nasal cavity rapidly extending into the ethmoid and maxillary sinuses. This study includes 4 cases of SCC-NET (3 males & 1 female) with a mean age of 45 years, a younger age group considering NECs are usually reported affecting individuals in their 60s and 70s.

Histologically, they exhibited sheets and ribbons of closely packed small size neoplastic cells with scanty cytoplasm and vesicular nucleus. Conformity of adjacent cell nuclei to one another (nuclear molding) was noticed along with extensive apoptosis and confluent necrosis. Documenting mitotic activity is important, because in presence of similar immunoreactivity, SCC-NET is distinguished from moderately differentiated neuroendocrine tumor (atypical carcinoids) based on mitotic count. In the study, SCC-NETs were found immune-reactive with pan-cytokeratins and neuroendocrine markers usually CD56. Variable immunoreactivity was seen with synaptophysin and chromogranin (Figure 1). Immunoreactivity for cytokeratins helped in separating it from other undifferentiated tumors showing neuroendocrine differentiation e.g. olfactory neuroblastoma and melanoma.

Recently described Sinonasal ‘HPV-related carcinoma with adenoid cystic-like features and ‘Basaloid squamous cell carcinoma’ were not found among our cases, and in absence of molecular studies, cases of NUT midline carcinoma and SMARCB1 (INI-1)- deficient sinonasal carcinoma couldn’t be ascertained.

4.2. Neuroectodermal small round cell tumours

4.2.1. Ewing’s sarcoma (ES / Primitive Neuro-Ectodermal Tumour (PNET))

Sino nasal Ewing’s sarcoma / PNET usually affects younger population. Compared to other sinonasal malignancies, the 4 patients of ES/ PNET included in our study had the least mean-age at presentation of 22 years (range 8-32 years).

Histologically ES/ PNET shows a uniform population of intermediate sized round cells, with scant clear cytoplasm, occasionally showing Homer Wright rosettes formation. Bishop et al reported ES/ PNET showing prominent focal squamous epithelial differentiation designated “adamantinoma-like” Ewing Family Tumor. Another study hinting towards similar feature reported ES/ PNET showing immune-positivity for cytokeratins in up to 30% of cases. They are also reported occasionally exhibiting neuroendocrine differentiation. These morphologic and immunophenotypic diversity of ES / PNET is responsible for diagnostic dilemmas while distinguishing it from sinonasal epithelial and myoepithelial neoplasms.

In this study, CD99 and FLI1 immunoreactivity of ES/ PNET was useful in distinguishing it from most other sinonasal SRCTs (Figure 2). From recent updates, the detection of EWSR1 and FLI1 rearrangements are considered desirable to confirm its diagnosis.

4.2.2. Mucosal malignant melanoma

Sino nasal melanoma, which accounts about 7 % of all sinonasal malignancies, most commonly affects patients in their 6th and 7th decade of life. The 3 patients (M: F = 1:2) in this study had their age ranging from 35 to 68 years (mean 54 years). Originating mostly in the nasal cavity rather than the sinuses, melanomas were found grossly polyloid with a brown or black-pigmented surface. However, the amelanotic variant with small cell morphology are prone to misdiagnosis resulting in inappropriate management of these high-grade tumors. Thompson et al reported identifying melanin pigments inside the neoplastic cells or surrounding melanophages by light microscopy in 2/3rd of their cases assisting in its identification. S100 positivity may not always be present, so immunoreactivity for HMB-45, MART-1/melan-A, tyrosinase, Microphthalmia-associated transcription factor, Cytokeratin and Vimentin
are useful for definitive diagnosis as mentioned in literature.\textsuperscript{15,16}

In this study, diffuse staining for S-100 and vimentin; and immunoreactivity for melanocytic marker, HMB-45, helped in deriving a definitive diagnosis for the patients.

4.2.3. Olfactory neuroblastoma (ONB)

Olfactory Neuroblastoma is a tumour of neural crest origin arising from the olfactory neuroepithelium. It represents approximately 5-10\% of all sinonasal malignancies and has a bimodal age distribution peaking at 15 years and 50 years of age. This study reports a 38 years old male patient of ONB presenting with complaints of nasal obstruction, anosmia, facial pain and diplopia for the last 3 months. Nasoendoscopy revealed a polypoid growth filling up the superior portion of nasal cavity. CT scan showed an eroded lamina with MRI confirming intraorbital extension of the tumour.

Histologically, ONB showed a uniform population of round cells set in a fibrillar background with occasional Homer Wright or Flexner-Wintersteiner type rosettes. Recognizing a strong correlation between the grade of histopathological differentiation and tumor behavior, Hyam et al proposed a histological grading system for ONB.\textsuperscript{17} Tumor grade has been found to be an independent prognostic indicator, with higher grade being associated to worse survival. Also, the role of surgery in low grade tumors and adjuvant radiotherapy after resection in high grade ones have been found to be significant predictors of disease-free survival in ONB, thereby highlighting the superiority of multimodality therapy in its management.\textsuperscript{18}

Immunohistochemically, ONB in this study was found diffusely positive for synaptophysin, chromogranin, neurofilaments and CD56; but non-reactive with cytokeratin. ONB was distinguished from melanoma based on latter’s diffuse positivity for S100 protein and HMB45. Non-reactivity for CD99 separated it from Ewing’s sarcoma/PNET. And positivity for Desmin and Myogenin in Rhabdomyosarcoma formed a distinguishing basis.

As reported in literature, straining with CK may be focally positive in ONB due to entrapped normal residual epithelium causing diagnostic confusion.\textsuperscript{1}

4.3. Hematolymphoid small round cell tumours

A wide range of hematolymphoid malignancies, mainly lymphomas of B and T cell lineage, may involve the sinonasal tract. About 3\% of extranodal lymphomas involve the sinuses. This study consisted 3 cases of ‘Diffuse B cell’ and 2 NK/ T cell lymphomas. Facial pain/ swelling, nasal obstruction and epistaxis were the commonest presenting symptoms. The authors also report a rare case of Extra medullary plasmacytoma in a 65 years old male patient. Diffuse B cell lymphomas showed a uniform population of large plomorphic cells infiltrating the mucosa and were found immunoreactive to CD45, CD20 and cyclin D1. NK/ T cell lymphoma histologically comprises of angiocentric and angio-destructive pleomorphic neoplastic cells with significant inflammatory infiltrates. Tumor infiltrates was composed of small, medium-sized, large or anaplastic cells with irregular nuclei and cytoplasmic granules. Immunopositivity for CD2, CD3e, CD 56 and CD 45 was seen. Presence of EBV markers in NK/ T lymphoma, though not recorded in this report, is considered unique. Measurement of EBV DNA load by PCR may be used as a surrogate marker of tumour load and it directly relates to its prognosis.\textsuperscript{1,19}

A case of Extra medullary plasmacytoma (EMP) in a 65 years old male was also included in the study. Immunohistochemically, EMP was found positive for CD 38, CD138, CD 45, kappa & lambda light chains. Occasional EMA or cytokeratin positivity in cases of EMP may cause misdiagnosing it as a carcinoma.\textsuperscript{1} In our index case no immunoreactivity for EMP or cytokeratin was noted.

4.4. Mesenchymal small round cell tumours

This study consisted 2 cases of poorly differentiated synovial sarcoma (SS) and a case of Rhabdomyosarcoma (RMS). Synovial sarcoma very rarely arises from the sinonasal tract and only few cases has been describe involving the paranasal sinuses. There has been only 3 reported cases of Synovial sarcoma of ethmoid sinus,\textsuperscript{20–22} and few in maxillary sinus.\textsuperscript{23}

Synovial sarcoma when poorly differentiated presents with Ewing’s like morphology and is a diagnostic challenge. Molecular demonstration of the SS18 gene rearrangement is desirable to confirm the diagnosis.\textsuperscript{1,19} Immunoreactivity with Cytokeratins, EMA, BCL2, Vimentin and S100 assisted in deriving the diagnosis of this entity in present study.

Our study also consisted 1 case of Rhabdomyosarcoma in a 15 years old male child who presented with nose block and diplopia. Histologically RMS exhibited a population of primitive cells with variable degrees of skeletal muscle differentiation, and scattered rhabdomyoblasts. Immunostaining for desmin, myoD1, and myogenin supported its diagnosis in the study. As mentioned in literature, occasional positivity for cytokeratins and neuroendocrine markers may misdiagnose it as SNUC, SCCNET or ONB.\textsuperscript{10}

5. Conclusion

Malignancies arising in the nasal cavity and paranasal sinuses are heterogeneous. Accurate classification of sinonasal ‘Small Round Cell Tumors’ may be
6. Conflict of Interest

The authors declare that there is no conflict of interest.

7. Source of Funding

None.

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