Original Article

Sinonasal Mucosal Melanoma: A 9-Year Experience from a Tertiary-Cancer Centre in South India

Abstract

Sinonasal tract malignancies are uncommon, representing not more than 5% of all head and neck neoplasm. Primary sinonasal mucosal melanomas (SNMM) are rare and constitute 1% of all melanomas and about 4% of all sinonasal tumors. Mucosal melanomas are biologically distinct from cutaneous melanomas. Etiology of mucosal melanomas is still under speculation. We retrieved nine cases of SNMM from our archives over a period of 9 years from 2010 to 2018. The aim was to identify the clinical characteristics, histopathological features, disease progression, and treatment of this disease. The most common symptom was epistaxis. The mean duration of symptoms was 3 months. Nasal cavity along with maxillary sinus was the most common site. The male to female ratio was 4:5 and the mean age was 63 years. The tumors showed varying histomorphology including epithelioid, spindle cell, and undifferentiated types. Immunohistochemical studies confirmed the diagnosis with positive reactions for S100 and melanocytic markers HMB45, Melan A. Surgery was the first line of management with postoperative radiotherapy (RT) for margin positive cases. Three inoperable cases were given palliative RT. Four cases developed recurrence. Recurrences were managed with RT in most cases. Three patients died due to disease. The 1 year recurrence-free survival (RFS) rate was 44% and 2 years' RFS rate was 22%. The 5-year overall survival rate was 28%. More studies are required to understand the utility of chemotherapy and immunotherapy in treatment of this rare entity. Multi-institutional studies are needed for better understanding this rare malignancy.

Keywords: *Melanoma, mucosal, sinonasal*

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Introduction

Sinonasal mucosal melanoma (SNMM) is a rare tumor and hence only minimal literature is available on this entity, most of which are case series from single institutions. The etiopathogenesis of SNMM is not yet well established unlike cutaneous melanomas which have strong association to sun exposure. However, the presence of melanocytes which are dendritic cells of neuroectodermal origin are well known in sinonasal mucosa. Greater melanocyte density in the sinonasal mucosa compared to other locations may explain the relative frequency of primary mucosal melanoma in the sinonasal cavities.[1]

Like other sinonasal tumors, SNMM presents with nonspecific symptoms related to mass in nasal cavity or sinuses such as nasal block, nasal mass, epistaxis, and pressure symptoms. Radiological features are also nonspecific and hence diagnosis is confirmed in biopsy specimens by histopathology along with immunohistochemistry using melanocytic markers. SNMM can be melanotic or amelanotic and when amelanotic a whole lot of differentials are to be excluded before reaching a histopathological diagnosis. Entities which are more common in the sinonasal region; small round cell tumors such as olfactory neuroblastoma, rhabdomyosarcoma, Ewing sarcoma/primitive neuroectodermal tumor; epithelial malignancies like sinonasal undifferentiated carcinoma, nuclear protein in testis (NUT) carcinoma, SMARCB1 deficient carcinoma, and hematopoietic malignancies like plasmacytoma and lymphomas come in the differential.

The prognosis of SNMM is dismal as many of the patients present at an advanced stage. Surgery is the prime modality of treatment along with postoperative radiotherapy (RT) for close or positive margins. The overall survival is <30% at 5 years.[2]

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Materials and Methods

For selection of cases SNMM was defined as malignant melanoma arising from the mucosa of the nasal cavity, nasopharynx, or sinuses according to the final histopathology report. Patients with cutaneous melanomas, including cutaneous melanomas encroaching on the sinonasal area and melanomas of other head and neck subsites were excluded from the study. Patients were selected from our database, using keywords "melanoma" and "sinus," or "sinonasal," or "nasal cavity." In this way, every patient with a diagnosis of SNMM (excluding skin) between 2010 and 2018 at our tertiary cancer care center could be retrieved and included in the study.

A total of nine cases designated as "SNMM," who had treatment at our tertiary cancer care center during 2010–2018 were retrieved from the pathology archives and consult files of our institute. The medical records of all these patients were reviewed. The clinical, radiological, and treatment details of these cases were retrieved. The clinical features such as age at presentation, sex, symptoms, duration of symptoms, site of involvement, and findings on nasal endoscopy were recorded. Radiological details from reports of computed tomography (CT) and magnetic resonance imaging (MRI) of head and neck regarding tumor origin, extent of disease, metastasis were noted.

The histopathology slides were reviewed and features such as cell morphology, presence of melanin pigment, ulceration, necrosis, mitotic activity, lymphovascular emboli, perineural invasion, and positivity for immunostains were noted. The follow-up clinical status was updated till December; 2019. Treatment details including details of primary surgery, postoperative RT were noted. Details of recurrences, mortality were recorded. This study had approval from our Institutional Review Board (IRB No. 12/2018/01).

Results

Of the nine patients the distribution of disease was almost equal for both sex (5:4), five females and four males. Age of our patients ranged from 50 years to 78 years with mean age 63 years. The most common symptom was epistaxis (7/9, 77%), followed by mass (2/9, 22%), and obstruction (1/9, 11%). The duration of onset of symptoms to presenting to a medical facility ranged from 3 weeks to 6 months with a mean duration of 3 months. Primary location of tumors were in the nasal cavity (100%), maxillary sinus (55%), ethmoid sinus and frontal sinus (2/9 each, 22%), and sphenoid sinus (1/9, 11%). There was one case with involvement of orbit and another with intracranial extension as per CT findings. Most of the patients had disease involving multiple sites. Only two patients had disease limited to only nasal cavity. Lymph node involvement was noted in only one patient who had involvement of level Ib node. Distant metastasis was also present for only one patient. The site of metastasis was to lung. Nasal endoscopy in all the patients showed mostly polypoidal growths in the nasal cavity some of which showed blackish coloration. Biopsy was taken.

The diagnosis was based on histopathological features along with immunohistochemical confirmation. Four of the cases showed intracytoplasmic melanin pigment making the diagnosis relatively easy. Five cases showed epithelioid cell morphology (55%), three cases showed spindle cell morphology (33%) and one case showed poorly differentiated appearance (11%) [Figure 1a-c]. Prominent nucleoli, a characteristic finding in melanomas was observed in three cases. Peritheliomatous pattern, i.e., neoplastic cells arranged loosely around a fibrovascular core giving pseudo papillary pattern mentioned in literature was prominent in one of our case [Figure 1d]. One case showed ulceration of overlying epithelium. S100 and melanocytic markers, HMB45, and Melan A were positive in all cases [Figure 2a and b]. Apart from the four cases with intracytoplasmic melanin pigment the rest five cases were poorly differentiated and amelanotic. The differential diagnosis considered in these cases included carcinoma, sarcoma, lymphoma, and melanoma. A larger panel of immunohistochemical markers including pan cytokeratin, desmin, leukocyte common antigen (LCA) in addition to S100 and other melanocytic markers were required for reaching a diagnosis.

CT scan and/or MRI were done to evaluate the extent of disease and to plan surgery [Figure 3]. Surgery was the initial line of management in all operable cases and based on extent of disease ranged from endoscopic resection of tumor to extended medial maxillectomy. Cases where R0, could not be attained intraoperatively, i.e., two cases with positive surgical margins in final histopathology were given postoperative RT. Three patients who at initial presentation were inoperable (one patient with lung metastasis and two

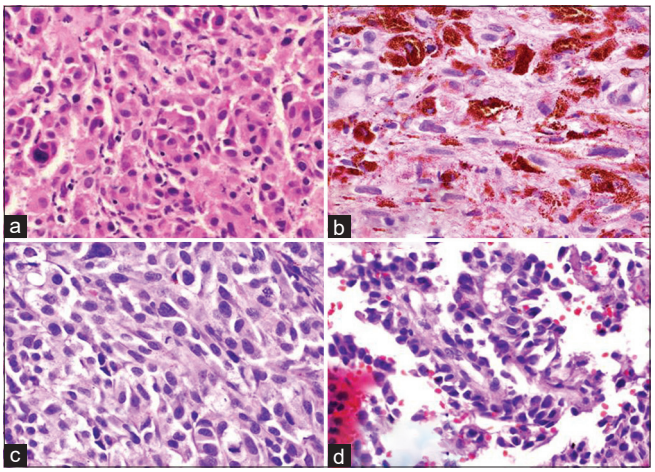

Figure 1: (a) Nests of cells with epithelioid morphology (H and E ×400) (b) Spindly cells with intracytoplasmic melanin pigment (H and E ×400) (c) Undifferentiated morphology (H and E ×400) (d) Peritheliomatous pattern showing cells loosely arranged around vascular cores (H and E ×400)

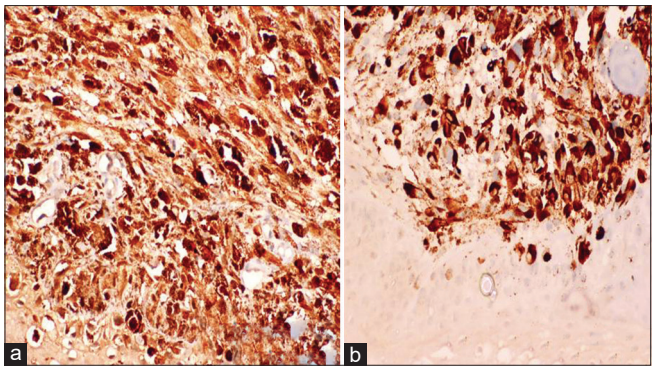

Figure 2: (a) Strong positivity for S100 (IHC × 200) (b) Strong positivity for HMB45 (IHC × 200)

with extensive local disease) were treated primarily with palliative RT. Four patients developed recurrence during follow-up; three were managed with RT while one patient underwent revision surgery. None of our patients received targeted therapy.

The follow-up of all patients was updated till December 2019. While on follow-up, four patients developed recurrence. Recurrence was noted as early as within 1 year of initial diagnosis and as late as after 4 years of initial diagnosis. Recurrence-free survival (RFS) ranged from 1 year to 6 years with median RFS of 2 years (24 months). The 1 year RFS rate was 44% and 2 years' RFS rate was 22%. The 5 years' overall survival rate was 28% in our study. Out of the nine cases diagnosed during this period, three patients succumbed to the illness. Two of these patients died following recurrent disease after 2 years of initial diagnosis. One patient died within 1 year of initial diagnosis. The remaining six patients are alive as on December 2019 at 84 months, 72 months, 48 months, 36 months, 12 months (2 patients) from the time of initial diagnosis.

The clinicopathologic features are summarized in Table 1.

Discussion

SNMMs are primary mucosal malignant melanoma of the nasal cavity, paranasal sinuses, and nasopharynx. SNMMs are rare and constitute1% of all melanomas and about 4% of all sinonasal tumors.[3] Although mucosal melanomas are rare it is interesting to note that head and neck is the commonest site for mucosal malignant melanoma. Melanocytes, derived from neural crest tissue, are distributed throughout the upper respiratory tract and oral cavity where they are found in the mucosa and stroma of adults of nearly all races, although to a greater degree in blacks.[4] Whether arising from the surface epithelium or from melanocytic cells in the stroma, primary SNMM seems to arise *de novo* rather than from a preexisting nevus or as a metastasis from a cutaneous primary.[5]

SNMM typically involves nasal cavity or paranasal sinuses but can encroach to multiple subsites and in advanced

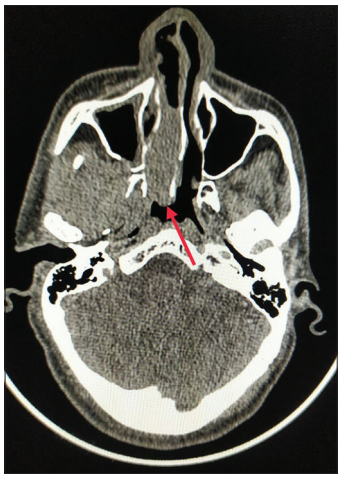

Figure 3: Computed tomography scan from one of the cases showing mass lesion in right nasal cavity

stages can involve orbit or can show intra cranial extension. In our series of cases, nasal cavity and maxillary sinus were the most common sites of involvement and the most common presenting symptom was epistaxis. This is similar to other studies in the literature. Narasimhan *et al*. in their study of 18 cases observed maxillary sinus and nasal cavity as the most common sites.[6] Dréno *et al*. also observed in their study that nasal cavity along with paranasal sinuses together constituted the most common site of SNMM as compared to nasal septum, turbinate and nasopharynx.[7]

SNMM are distinct from cutaneous melanoma which is evident from the fact that at genetic level cutaneous melanoma shows BRAF mutation where as the most common mutation in SNMM is KIT mutation. Unlike cutaneous malignant melanoma wherein male predominance is noted no sex predilection was noted for SNMM in our study. This observation is in concordance with other studies in the literature.[5] The male predominance observed in cutaneous malignant melanoma can be attributed to the finding that the most common etiological factor of cutaneous melanoma is sun exposure which is more in males due to occupational exposure. However, the exact etiological factors for SNMM as not yet been elucidated with speculation still remaining over factors like melanocytosis.[8] Age of our patients ranged from 50 years to 78 years with mean age 63 years. This is comparable to other studies in the literature wherein the mean age was in 60s.[5,6] Thus, the age for SNMM is later in life than cutaneous malignant melanoma. The duration of onset of symptoms to presenting to a medical facility ranged from 3 weeks to 6 months with an average duration of 3 months in our series. There are studies where the average duration of symptoms was much longer like 8.2 months and others where it was shorter, 1 month.[5-7] Patients with symptoms like epistaxis may seek medical help earlier while patients with nasal block and other not so alarming symptoms may take more time to seek medical help.

Table 1: Clinicopathological features

Sinonasal mucosal melanoma	
Mean age	63 years (50-78)
Male:female	4:5
SITES OF INVOLVEMENT	NUMBER OF CASES
Nasal cavity	9
Ethmoid	2
Maxillary	5
Frontal	2
Sphenoid	1
SYMPTOM	
Epistaxis	7
Nasal mass	2
Nasal obstruction	1
HISTOPATHOLOGY	
Epithelioid morphology	5
Spindle cell morphology	3
Undifferentiated	1
Melanotic	4
Amelanotic	5

The histopathological diagnosis of primary SNMM can be challenging especially when the tumor is amelanotic. Malignant melanomas are great mimickers and can masquerade as various malignancies ranging from poorly differentiated carcinomas to sarcomas to malignant round cell tumors based on individual cell morphology. A wide range of differentials from malignant round cell tumors to sarcomas may have to be ruled out using appropriate immunohistochemical antibody panels. Variable cellular morphology is present from case to case and within individual cases, ranging from epithelioid/undifferentiated cells to spindled, plasmacytoid, and rhabdoid cells, with or without prominent nucleoli. Malignant round cell tumors are common in sinonasal region and hence lymphoma, rhabdomyosarcoma, olfactory neuroblastoma, Ewing Sarcoma/peripheral neuroectodermal tumor comes in the differential.

Plasmacytoma, poorly differentiated carcinoma come in differential when neoplastic cells are plasmacytoid or epithelioid. When cells are spindly, sarcomas come in differential. We had three cases with spindle cell morphology. However, all these cases showed intracytoplasmic brownish-black melanin pigment. When melanin pigment is present diagnosis is easier. However, many a times, the pigment can be minimal and hence careful observation is needed to notice this finding. In our series of cases four cases showed intracytoplasmic melanin pigment, three with spindle cell morphology and one with epithelioid morphology. Thompson *et al*. showed that elevated melanin pigment levels were a highly predictive factor, with achromic melanoma having poorer prognosis.[5] Peritheliomatous pattern, i.e., neoplastic cells arranged loosely around a fibrovascular core giving pseudopapillary pattern mentioned in literature was prominent in one of our case.

The immunohistochemical panel that we used in our cases was a combination of S100 along with melanocytic markers HMB45, Melan A. In cases where the histomorphology was that of a poorly differentiated malignant neoplasm a larger panel of antibodies was used, CK, desmin, LCA, S100, HMB45, and Melan A. All cases showed positive staining with S100, HMB45, and Melan A. In diagnosis of melanoma, especially amelanotic ones it is always advisable to put a panel of markers rather than a single one. S100 is the sensitive marker while HMB45 is more specific.Spindle cell melanomas are known to be frequently negative for HMB 45 and positive for S100, hence the need for a panel rather than single melanocytic markers.[9]

The primary management of SNMM is surgery. Various studies in the literature on this area totally agree that surgery with an adequate clearance or negative margin is the cornerstone of management.[10] However, due to the anatomical constraints and difficult accessibility of this region margin clearance is not always achieved and hence based on the final histopathology report if margins are positive or close postoperative RT is given. Of the nine patients in our study, six were managed with primary surgery. Extended medial maxillectomy was the most common procedure. In two cases because of inadequate margin adjuvant RT had to be given. Three inoperable cases were managed upfront with palliative RT. Disease recurrences were also managed with RT except in one case where revision surgery was possible. There are studies in the literature which substantiates the role of adjuvant RT in SNMM wherein they noted an increase in DFS and OS. Kingdom and Kaplan noted that postoperative RT lengthened disease-free intervals and OS.[11] Gilligan and Slevin's study concluded that definitive RT could be employed for melanoma of the nasal cavity.[12] Although melanomas are generally thought to be radio resistant there are studies which suggest that with increased doses they may be radiosensitive.[12] None of our patients received chemotherapy or immunotherapy, however, there are few studies in the literature that are of the opinion that these therapies may be beneficial.[13] However, more investigations are required for the confirmation of this observation. Because of the rarity of this entity there are hardly any prospective studies on treatment. Mucosal melanomas unlike cutaneous melanomas are known to have higher rates of KIT mutation and not BRAF mutation. Previous studies show that though KIT-mutant tumors have shown response to KIT inhibitor therapy, the response was not durable.[14]

The 5-year overall survival rate was 28% in our study. This is comparable to other studies on SNMM. Lund *et al*. reported a 28% 5-year OS rate.[15] Brandwein *et al*. reported a 36% 5-year survival in their retrospective review of 25 patients.[16] The 1 year RFS rate was 44% and 2-year RFS rate was 22% in our study.

Conclusion

SNMM though rare, are distinct mucosal neoplasm that generally affects elderly people of both sex. In our study the mean age was 63 years with no gender predilection. Histopathology was the cornerstone for diagnosis as clinical and radiological features were nonspecific. Nonpigmented lesions were diagnostically challenging with a whole lot of differentials and required appropriate immunohistochemistry panel. Primary management was surgery with adequate margins. Postoperative RT was given for incomplete surgeries. The scope of chemotherapy and immunotherapy in the treatment of SNMM requires further studies. Because of the rarity of this entity multi-institutional studies will be of use in better understanding this entity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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