

Primary sinonasal mucosal melanoma – A diagnostic and histological conundrum.

Ikmal Hisyam BAKRIN¹, Kong Yew LIEW², Hasni MAHAYIDIN¹, Hasyma ABU HASSAN³, Mohamad DOI⁴

¹Department of Pathology, ²Department of Surgery and ³Department of Imaging, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia 43400 UPM Serdang, Selangor.

⁴Department of Otorinolaringology, Hospital Serdang, Jalan Puchong, 43000 Kajang, Selangor.

ABSTRACT

Primary sinonasal mucosal melanomas (PSMM), a rare subtype of melanomas offers significant diagnostic challenge clinically and histologically especially when amelanotic, as they can show many histologic mimics that require immunohistochemical and molecular studies to confirm the diagnosis. We report the case of a 50-year-old male presented with persistent left nasal blockage and epistaxis secondary to a fleshy and friable lobulated mass occupying the left nasal cavity and nasopharynx. The tumour was excised endoscopically and histology confirmed a malignant tumour consisting of small round blue cells with hyperchromatic nuclei, in solid sheets with areas of angiocentric pattern (H&E staining). The cells were positive for S100 protein and focally positive for HMB-45 and Melan A and a diagnosis of PSMM was made. However, he defaulted the subsequent radiotherapy and presented back a few months later with tumour recurrence locally and nodes metastasis. Despite undergoing radiotherapy, he died after two cycles due to an episode of acute coronary syndrome.

Keywords: HMB-45 protein, Melanoma, Amelanotic, Nasal Cancers, S100 protein, Radiotherapy

INTRODUCTION

Primary sinonasal mucosal melanomas is a rare subtype of melanomas which arise from melanocytic cells found in the mucous membranes, accounting for less than 1% of all melanomas and <5% of all sinonasal tract neoplasm.^{1, 2}

It offers significant diagnostic challenge for the clinician due to its non-specific clinical features such as epistaxis, nasal polyp, pain and nasal discharge which can be the usual complaints of sinonasal pathology. Similarly, it presents a diagnostic dilemma for clinicians especially when amelanotic, as they can show many histologic mimics that require immunohistochemical and molecular studies to confirm the diagnosis. We present a case of an aggressive primary sinonasal mucosal amelanocytic melanomas in a 50 year old Malay gentleman which was resected but recurred within a few months and discussed the

Correspondence author: Ikmal Hisyam Bakrin MD, MPath
Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.
Tel: +60389472671, Fax: +60389412787
Email: ikmalhisyam@upm.edu.my

diagnostic and management options of such malignancy.

CASE REPORT

A 50-year-old Malay businessman, with no known underlying medical illness presented to the Department of Otorhinolaryngology (ORL) outpatient clinic complaining of persistent left nasal blockage and epistaxis for four months. He was a chronic smoker for the past 30 years. He denied any alcohol consumption.

Naso-endoscopic examination revealed a fleshy and friable lobulated mass which was covered by slough occupying the left nasal cavity. A contrast enhanced Computed Tomography (CT) of paranasal sinuses was performed, which showed a heterogeneously enhancing lobulated mass occupying the left nasal cavity with expansion of the nasal cavity (Figure 1). There was associated deviation of the nasal septum to the right and scalloping of the medial wall of the left maxillary sinus with obliteration of the left ostiomeatal complex. Posteriorly, the mass was obliterating the left posterior nasal choana and left postnasal space. The mass was also seen crossing the midline to the right causing partial obliteration of the right posterior nasal choana. Superiorly, the mass extended into the ethmoid and sphenoid sinuses. There was no evidence of distant metastasis.

Microscopic examination of the tumour biopsy using H&E staining showed a cellular tumour mass covered by partially ulcerated nasal mucosa composed of small round blue cells arranged in solid sheets with hypercellular and hypocellular areas. Within the hypercellular areas, the tumour cells showed angiocentric pattern, whereas at the hypocellular areas the tumour cells were surrounded by myxoid stroma (Figure 2). The tumour cells displayed round hyperchromatic nuclei, some with prominent nucleoli and clear to eosinophilic cytoplasm. Tumour cells with

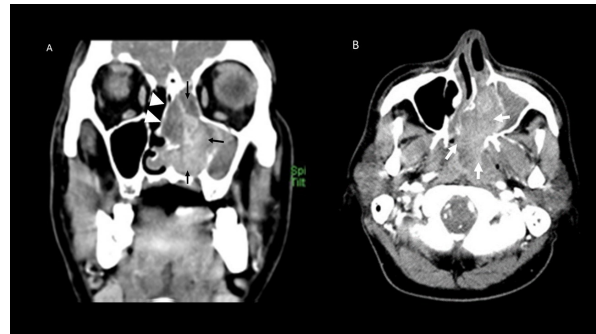


Figure 1: CT paranasal sinus in (A) coronal plane showing a heterogeneously enhancing lobulated mass occupying the left nasal cavity (black arrow) causing expansion of the cavity and right sided deviation of the nasal septum (arrow head); (B) Axial image of the nasal cavity showing the mass (white arrow) extending into the nasopharynx, obscuring the left posterior nasal choana and nasopharynx. (Click to enlarge)

intranuclear inclusion were also occasionally seen in areas. Mitotic figures were frequently seen including abnormal forms. There was no melanin pigment seen. The tumour cells were immunoreactive for S-100 protein and focally positive for HMB-45 and Melan-A (Figure 3). Other markers to rule out differential diagnoses of small round blue cell tumours of the sinonasal tract were negative (CK AE1&AE3, desmin, myogenin, FLI-1, CD99, chromogranin A, synaptophysin, LCA and Tdt). Histopathological diagnosis of primary sinonasal mucosal melanoma was confirmed with the absence of previous or concurrent melanocytic lesions elsewhere, particularly in the cutaneous and ocular sites.

The patient underwent endoscopic ex-

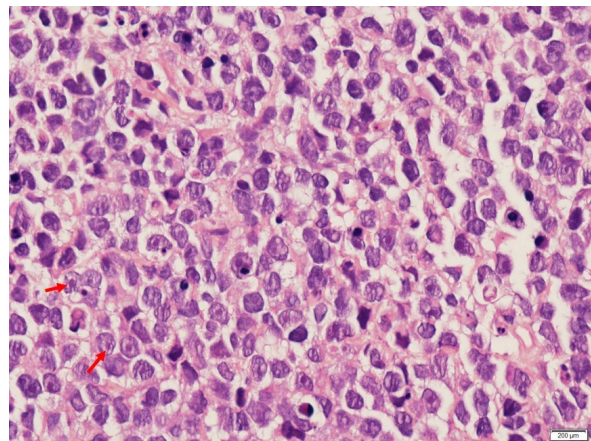


Figure 2: Malignant small round blue cell tumour with occasional malignant cells displaying prominent red-cherry nucleoli (arrow) (Hematoxylin and eosin stain, original magnification x 600). (Click to enlarge)

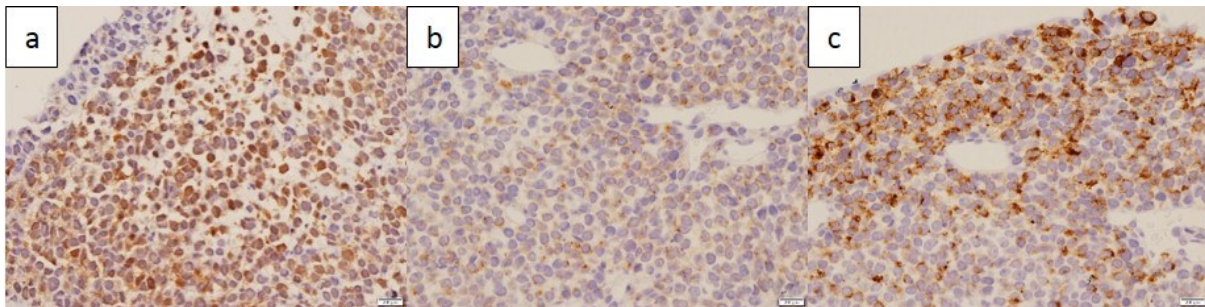


Figure 3: The malignant cells show strong diffuse cytoplasmic staining to (a) S-100, (b) focally for Melan-A and (c) HMB-45 (Immunohistochemical stain, original magnification x400).

cision of the tumour under general anaesthesia. Intra operatively, there was left nasal mass (Figure 4) superficially attached to the superior part of the left soft palate. It extended laterally to the left maxillary sinus and medial pterygoid plate; and superiorly to the anterior and posterior ethmoid sinuses. There was no direct tumour extension into the left orbit.

Unfortunately prior to commencement of radiotherapy, he presented to the Emergency Department with sudden onset chest pain and ST elevation on the electrocardiogram with a diagnosis of acute ST elevation myocardial infarction (STEMI). He underwent coronary angiogram and primary percutaneous coronary intervention on the same day and was discharged well with dual antiplatelet therapy. He defaulted subsequent ORL follow up for a few months and presented back with

new complaints of progressive bilateral nasal obstruction associated with epistaxis. A new left level II cervical lymph node measuring 2 by 2 cm was found. Naso-endoscopy revealed recurrence of the tumour within the entire left nasal cavity and nasopharynx. The patient was discussed at a multidisciplinary tumour board and it was noted that the tumour had now involved the left orbit superiorly and the pterygoid plates posteriorly during the radiotherapy CT simulation. As the patient has had a recent STEMI, he was deemed unfit for surgery and proceed with radiotherapy without tumour debulking. He managed to complete two cycles of radiotherapy before succumbing to another episode of an acute coronary syndrome.

DISCUSSION

PSMM is extremely rare with a reported inci-

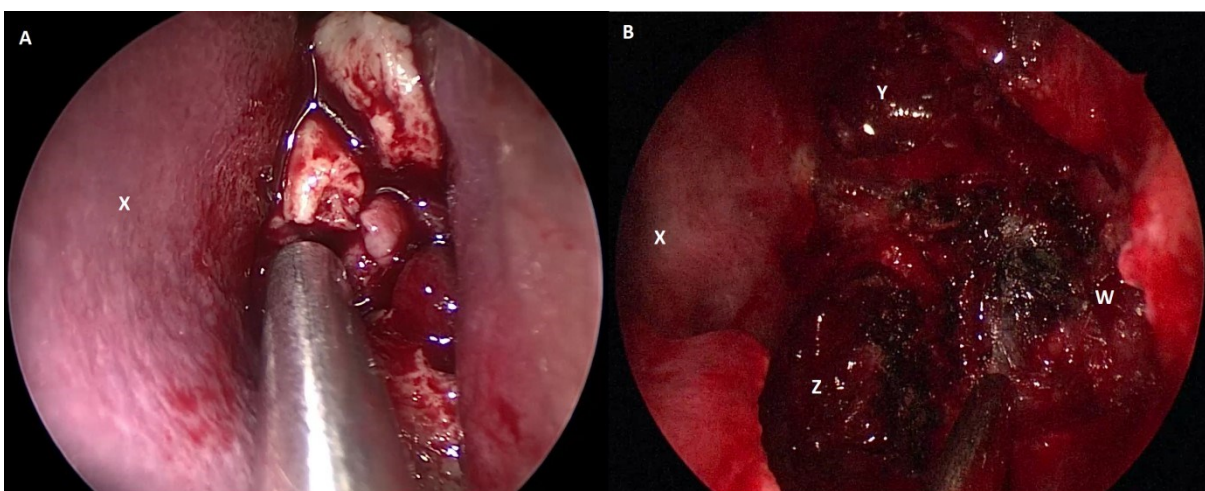


Figure 4: (A) Intraoperative endoscopic view of the tumour prior to excision and (B) after completion of excision. (W: maxillary sinus with removed lateral nasal wall; X: nasal septum; Y: opened sphenoid sinus; Z: nasopharynx.)

dence of 0.5 per million per year and carries a poor prognosis.³ Due to non-tumour specific signs and symptoms, the patients then to present at an advanced stage of the tumour with poor overall survival. Regional or distant metastases are seen in 80% of patients at the time of diagnosis with five-year survival of less than 10%.⁴ As compared to cutaneous (80.8%) and ocular melanomas (74.6%), PSMM have the lowest percentage of five-year survivals (25%).²

Risk factors for developing PSMM have not been fully identified. Ultraviolet radiation, a well-known risk factor for cutaneous (sun-exposed skin) melanoma is unlikely to play a significant role in PSMM since the mucosa are not exposed to constant sunlight. Viral infections such as human papilloma viruses, human herpes viruses and polyomavirus have been implicated with pathogenesis of mucosal melanomas but the evidence have not been consistent.^{5, 6} Exposure to formaldehyde was suggested as a possible risk factor for sinonasal mucosal melanoma, since there were cases reported among workers exposed to this substance.⁷

The most frequent sites of PSMM are in the maxillary sinus, nasal cavity, and nasal septum.⁸ Majority of patients have symptoms of nasal obstruction or epistaxis or both. On endoscopic examination nasal melanomas show variable findings from small to bulky friable masses which can easily bleed on contact. Clinical appearance of the tumours can also mimic benign nasal polyps.⁹

Histologically, PSMM can show a wide range of histological features which includes small round blue cell tumour. Diagnosis of small round blue cell tumours of the sinonasal tract are often difficult and challenging. The differential diagnoses include olfactory neuroblastoma, sinonasal undifferentiated carcinoma, undifferentiated (lymphoepithelioma-like) carcinoma, lymphoma, Ewing's sarcoma/

peripheral neuroectodermaltumour (PNET) and rhabdomyosarcoma.¹⁰ Amelanotic appearance which can also be seen in PSMM cases makes diagnosis even more difficult and challenging.

A panel of antibodies for relevant immunohistochemical stains to exclude the differential diagnoses are essential for definitive diagnosis. In our case, LCA and cytokeratin were performed to rule out lymphoma and carcinoma respectively. Desmin, myogenin, FLI-1, CD99, chromogranin A and synaptophysin were performed to exclude rhabdomyosarcoma, Ewing's sarcoma/PNET and olfactory neuroblastoma. In this case, the diagnosis of MM was concluded from the immunohistochemistry studies which showed positivity for S-100 protein, HMB-45 and Melan-A.

Among immunohistochemistry panel for melanomas, HMB-45 showed almost 100% specificity, as compared to Melan-A which is less specific. A study by Morris *et al.* concluded that PNL-2 is a highly sensitive marker for mucosal melanoma.¹¹ This marker showed similar specificity with Melan-A and superior than S-100 protein. Therefore, the authors suggested the inclusion of PNL-2 as one of the important immunohistochemical panel in the evaluation of primary MM.

Genetic differences have been shown between cutaneous melanomas and MM. *BRAF* mutations, in particular the *BRAF V600E* mutation were frequently detected in cutaneous melanomas. On the other hand, high frequency of mutations of the *KIT* gene were seen in cases of MM.¹² These findings support the role of targeted therapy with tyrosine kinase inhibitors such as c-KIT blockers in patients with MM.

Exclusion of metastatic lesion from primary cutaneous or ocular melanoma is essential when diagnosing primary MM. This becomes even more challenging with the pos-

sibility of regressed primary cutaneous melanomas that have metastasized to mucosal sites. Therefore, in cases without previous history of melanoma, a thorough examination of the whole-body skin and eye are necessary to exclude the presence of cutaneous or ocular primary melanoma.

CONCLUSION

In conclusion, primary MM of the sinonasal is an uncommon yet aggressive malignant tumour of the respiratory tract. Clinically, the presentation is rather non-specific and histologically, it can show a wide range of histological features from pleomorphic, spindle to undifferentiated small blue cell tumour. This case reminds us that melanoma truly is the great mimicker, both clinically and histologically.

ACKNOWLEDGEMENT

The authors would like to thank the Director of Health Malaysia for permission to publish this paper. The authors declare that there is no conflict of interest to disclose.

Poster abstract has been presented at the 3rd annual scientific meeting of International Academy of Pathology, Malaysian Division.

REFERENCES

- 1: Ballantyne AJ. Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. *Am J Surg.* 1970;120(4):425-31.
 - 2: Chang AE, Karnell LH, and Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1998;83(8):1664-78.
 - 3: Mikkelsen LH, Larsen AC, von Buchwald C, Drzewiecki KT, Prause JU, Heegaard S. Mucosal malignant melanoma - a clinical, oncological, pathological and genetic survey. *APMIS.* 2016;124(6):475-86.
 - 4: Terada T, Saeki N, Toh K, *et al.* Primary malignant melanoma of the larynx: a case report and literature review. *Auris Nasus Larynx.* 2007;34(1):105-10.
 - 5: Dahlgren L, Schedvins K, Kanter-Lewensohn L, *et al.* Human papilloma virus (HPV) is rarely detected in malignant melanomas of sun sheltered mucosal membranes. *Acta Oncol.* 2005;44(7):694-9.
 - 6: Lundberg R, Brytting M, Dahlgren L, *et al.* Human herpes virus DNA is rarely detected in non-UV light-associated primary malignant melanomas of mucous membranes. *Anticancer Res.* 2006;26(5B):3627-31.
 - 7: Holmstrom M and Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. *Br J Ind Med.* 1991;48(1):9-11.
 - 8: Narasimhan K, Kucuk O, Lin HS, *et al.* Sinonasal mucosal melanoma: a 13-year experience at a single institution. *Skull Base.* 2009;19(4): 255-62.
 - 9: Mochel MC, Duncan LM, Piris A, *et al.* Primary mucosal melanoma of the sinonasal tract: a clinicopathologic and immunohistochemical study of thirty-two cases. *Head Neck Pathol.* 2015;9(2):236-43.
 - 10: Iezzoni JC and Mills SE. "Undifferentiated" small round cell tumors of the sinonasal tract: differential diagnosis update. *Am J Clin Pathol.* 2005;124 Suppl:S110-21.
 - 11: Morris LG, Wen YH, Nonaka D, *et al.* PNL2 melanocytic marker in immunohistochemical evaluation of primary mucosal melanoma of the head and neck. *Head Neck.* 2008;30(6):771-5.
 - 12: Curtin JA, Fridlyand J, Kageshita T, *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005;353(20):2135-47.
-