CASE REPORT

Sinonasal malignant melanoma

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ABSTRACT

Sinonasal malignant melanoma is a rare, aggressive tumor, associated with a poor prognosis, accounting for 8-15% of all head and neck melanomas and 0.5-2% of all melanomas. The diagnosis is given by histopathological and immunological examination. Elective treatment consists of surgical excision with free resection borders, and adjuvant chemotherapy / radiotherapy / immunotherapy / checkpoint inhibitors can be used to control local recurrence and distant metastases. We chose to present the case of an unresectable ethmoidal malignant melanoma at the time of diagnosis, pembrolizumab treatment converting it to resectability, with improving patient's quality of life, even if the patient developed an adrenal metastasis.
KEYWORDS: melanoma, sinonasal, ethmoid, unresectable, pembrolizumab.

INTRODUCTION

First described by Lucke in 1869[1], sinonasal malignant melanoma is a rare, aggressive tumor, associated with a poor prognosis. It represents 8-15% of all melanomas of the head and neck and 0.5-2% of all melanomas in males and Caucasians over 60 years of age[2-5]. The sinonasal cavities allow, by their size, the growth of melanomas without a specific symptomatology, many of the patients being diagnosed late, reason for which the pathology has a low rate of long-term survival. The diagnosis is given by histopathological and immunological examination. Elective treatment consists of surgical excision, and adjuvant chemotherapy can be used to control local recurrence and distant metastases[6]. New systemic monoclonal antibody therapies have already been shown to be effective in cutaneous malignant melanomas, with promising prospects and positive effects in mucosal malignant melanoma. The most frequently used agents are nivolumab, ipilimumab and pembrolizumab[7]. The reported frequency of mutations in sinonasal localization varies between different studies (KIT 20-40%, NRAS 40-48% and BRAF 0-3%)[8].

We chose to present the case of an unresectable ethmoidal malignant melanoma at the time of diagnosis, pembrolizumab treatment converting it to resectability, with improving patient's quality of life, even if the patient developed an adrenal metastasis.

CASE REPORT

A 54-year-old female from an urban environment presented to the ENT outpatient clinic, with the diagnosis of sinonasal malignant melanoma with left ethmoidal starting point operated on, with local evolution, treated with pembrolizumab 5 cycles, one cycle at 6 weeks. The symptoms at the time of presentation consisted of recurrent left epistaxis, left fronto-parietal headache and intermittent left ear hearing loss.

The patient was diagnosed a year and a half before in another ENT Department, where she presented with left nasal obstruction with an insidious onset three years previously, with progressive evolution. Endoscopic examination at that time revealed the presence of unilateral ethmoidal polyps and deviation of the nasal septum. Native sinus CT scan was performed, the interpretation of which described hypertrophic nasal turbinates with a polypoid appearance, the case being interpreted as chronic rhinosinusitis with unilateral nasal polyps, which is why surgery was per-

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Received for publication: April 10, 2022 / **Accepted:** May 19, 2022

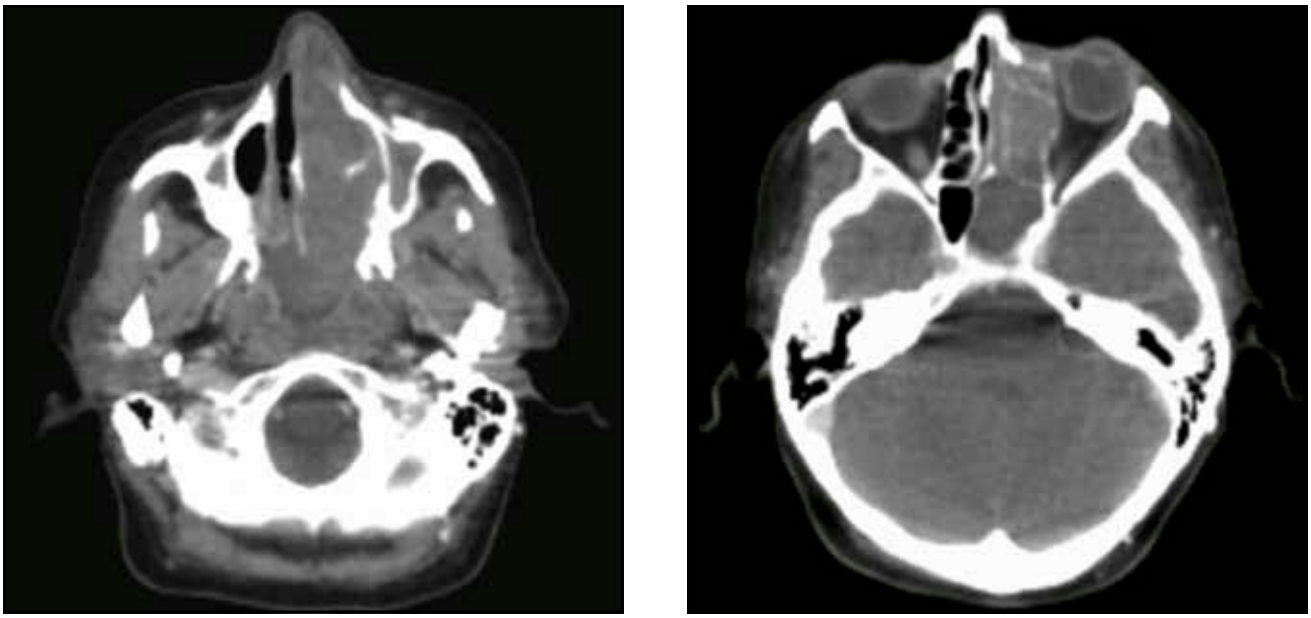

Figure 1. Cranial CT scan, contrast-enhanced (axial slices) – the tumor completely occupies the left ethmoidal sinus, extended to the nasal cavity and left orbit; hypodense content in the left sphenoid and maxillary sinuses (hypoplastic).

formed. The histopathological result was sinonasal malignant melanoma. At 2 months postoperatively, the patient was recommended to have a PET / CT scan to perform a lesion assessment, but the patient did not show up for personal reasons. She also did not receive any other treatment during this time. At 5 months postoperatively, a new imaging examination (contrast-enhanced cranial CT scan) showed a massive local evolution: tissue mass occupying the left ethmoid, extended to the nasal fossa (which completely obstructed it) and the left orbit; hypodense content in the left sphenoid sinus and left maxillary sinus (hypoplastic), most likely fluid retention by ostial block (Figure 1). The surgical consultation considered the tumor unresectable and recommended oncological therapy.

Prior to oncological treatment, typing was performed for BRAF V+60 gene mutations, highlighting the lack of

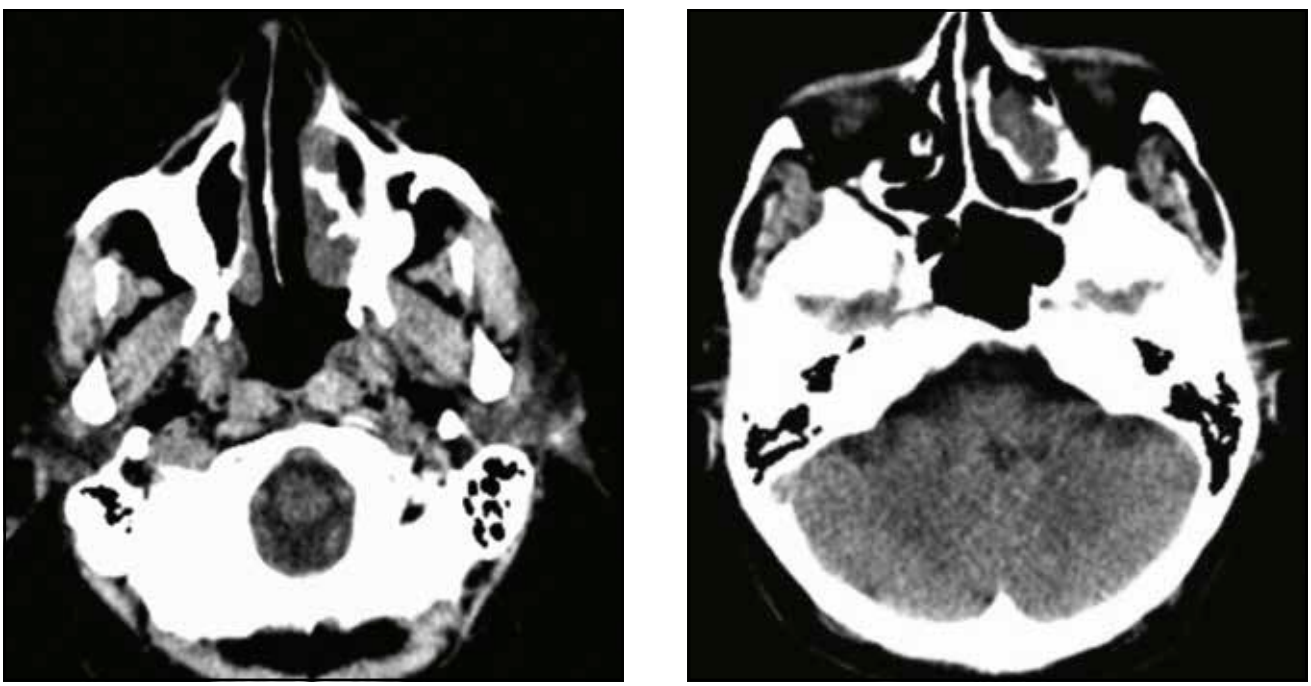

Figure 2. Cranial CT scan (axial slices) - tumor at the level of the left ethmoid, smaller than at the previous examination.

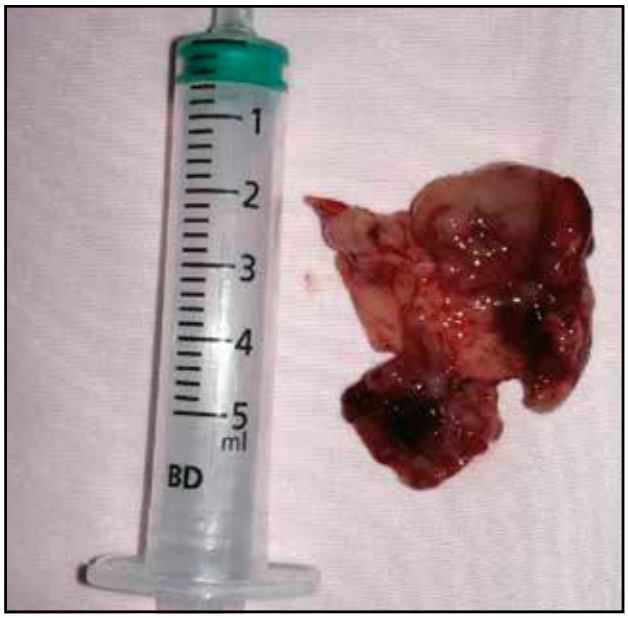

Figure 3. Surgical resection specimen.

driver mutations. Pembrolizumab line I (400 mg) was chosen for immunological treatment. After 5 cycles, the CT imaging evaluation revealed a good quality tumor response, and the patient was surgically re-evaluated in our service to assess the opportunity for radical surgery.

Nasal endoscopy at admission revealed the presence of a tumor formation in the left nostril, yellow-pink, gelatinous consistency, slightly bleeding on instrumental palpation, about 2/2 cm, plunging into the nasal cavity; the presence of a flange that blocked the middle meatus and the left middle nasal meatus. The contrast-enhanced CT examination of the skull, neck, thorax and abdomen performed preoperatively revealed a hypodense tissue mass occupying the left ethmoid and extending into the left nasal fossa, hypoplastic maxillary sinuses with hypodense (liquid) content on the left; at the neck, mediastinal and lumbo-aortic levels several images of lymph nodes with millimetre dimensions, interpreted as nonspecific, were detected (Figure 2).

Taking into consideration the tumor reduction after chemotherapy, radical surgery under general anaesthesia on the laryngeal mask was decided, the size and extent of the tumor allowing the endoscopic approach. Resection was performed en bloc (Figure 3) after hydro decollation of the ethmoidal mucosa with 1% adrenaline serum, including anterior ethmoidectomy, the posterior ethmoid being ossified, resection of the flange with release of the middle meatus and evacuation of fluid from the left maxillary sinus. Bone erosion of the papyraceous lamina has been reported. Biopsies were taken to establish tumor-free resection borders from the left periorbital, lower nasal turbinate, posterior 1/3 of the septal cartilage, pituitary mucosa at the posterior margin of the left maxillary antrum. Postoperatively, antibiotic monotherapy (Amoxicillin + clavulanic acid 1.2g 2x1 / day), antacids (Famotidine 40 mg, 1x1f / day), analgesic as needed were instituted.

The histopathological result reconfirmed the presence of a relic of malignant melanoma ypT3L1V0Pn0R0. The rest of the pieces sent, consisting of the edges of the resection, were free of malignant elements.

Two months postoperative imaging identified postoperative scarring as hypodense tissue in the left ethmoid. The local evolution was refuted by nasal endoscopy (after the release of the nasal cavity from crusts and adherent mucous secretions). Sections of the abdomen revealed a 32 mm straight adrenal hypodense node, with a secondary determination suspected (Figure 4).

The patient is still undergoing oncological follow-up, with the following recommendations for the next period: c-kit adrenal gland biopsy, SBRT on the adrenal gland in case of positive biopsy; PET / CT FDG for lesion balance, supplemented with cerebral and facial MRI with contrast agent and abdominal MRI with contrast agent; adjuvant radiotherapy 60 Gy / 30 fr on the tumor bed.

DISCUSSIONS

The management of patients diagnosed with sinonasal malignancies who have undergone tumor debulking in primary diagnostic centers can be difficult when presenting them in a tertiary center to institute multimodal, complex treatments. The main goal is to correctly diagnose the lesions and provide the patient with the best treatment methods[9]. Initial suboptimal surgical therapy requires a new resection with curative intent, if possible. Sinonasal malignant melanomas are a special category of malignancies, with a long evolution, delayed diagnosis by the possi-

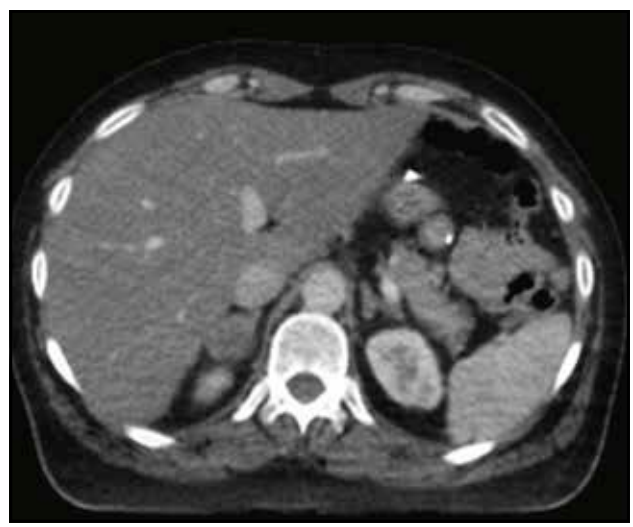

Figure 4. Abdomen CT scan (axial slice) - suspicion of right adrenal secondary determination of ethmoidal malignant melanoma.

bility of growing inside large cavities, with few symptoms at onset and nonspecific[10]. In addition, their macroscopic appearance can be easily confused with a nasal polyp accompanying a chronic rhinosinusitis, in many cases the anatomopathological result being a surprise[9].

The incidence of mucosal malignant melanoma is lower than that of skin malignant melanoma. The pathology mainly affects people over the age of 60, with a slightly higher incidence in the male population. The most common locations are in the nasal cavity, the nasal septum, lower and middle meatus, the lateral wall of the nasal cavity with extension in the paranasal sinuses, less often primitively affected (and more often the maxillary sinus)[10,11]. The etiopathogenesis is still unclear, with no specific risk factors involved. The long-term presence of melanosis is clearly demonstrated for melanoma of the oral mucosa. Occupational exposure to formaldehyde has been classified as a possible risk factor[12]. The present case concerns the occurrence of ethmoidal sinus melanoma in a female patient and young age, without identifying risk factors.

The differential diagnosis consists in the histopathological differentiation of a chronic inflammation or a sinonasal malignancy (intestinal or non-intestinal adenocarcinoma, squamous cell carcinoma with different degrees of keratinization, undifferentiated carcinoma, adenoid-cystic carcinoma). The primary tumor site / initial tumor origin is usually difficult to determine due to the extent of the lesion[13]. Our patient consulted an ENT doctor after several episodes of nasal bleeding, but the macroscopic appearance of the lesion led to a preoperative diagnosis of chronic rhinosinusitis with nasal polyposis, the histopathological examination showing malignant melanoma of the sinonasal mucosa.

Cervical lymph node metastases occur in 10-50% of patients. Distant metastases occur in 40-76% of patients in the lungs, liver, brain, skin and the orbit[10,13,14]. In our case in particular, no lymph node metastases were detected, both at diagnosis and in oncological follow-up, but the last imaging examination raised the suspicion of a distant, right adrenal metastasis, which is to be biopsied to establish certainty.

The treatment of choice is ablative surgery with free resection margins. However, the complex anatomy of the sinonasal cavities near some vital structures makes it impossible to obtain tumor-free resection margins, with important aesthetic and functional sequelae, unjustified by a distant metastasis rate of more than 40%[12-15]. The approach used may be endoscopic, external, or combined, depending on the extent of the lesion. Radical cervical dissection is indicated in the N + stage; prophylaxis in the case of N0 is not recommended, given the low risk of occult lymph node metastases[9]. Local recurrence occurs in 29-79% of cases, despite aggressive local surgery. Some authors recommend adjuvant radiotherapy for local disease control[10,14], while other authors have reported a lack of beneficial response to survival rate[9,11,13]. Irradiation dose information and technique are inconsistent in the current literature. In contrast, stereotactic radiotherapy (1,200 cGy in 2 fractions) is recommended for adrenal metastasis[15]. Systemic therapy does not bring the desired effects in survival[16]. Chemotherapeutic agents – actinomycin D and cisplatin – are used in advanced stages, usually for palliative purposes or when surgery is contraindicated. Immunotherapeutic agents are usually indicated in metastatic disease and to control local recurrence[16]. Interleukin 2 and interferon alpha-2 adjuvants for systemic chemotherapy have not been shown to be effective[15]. Checkpoint inhibitors (nivolumab, ipilimumab) in combination have been shown to be more effective than single administration[17]. In the case of our patient, the orbital invasion of the stationary disease decided the subsequent therapeutic conduct, preferring the administration of pembrolizumab for tumor reduction and conversion to resectability of the tumor. The patient is still undergoing oncology for confirmation of the suspicion of metastatic adrenal disease.

Unfortunately, the prognosis of sinonasal malignant melanoma is reserved, with more than 50% of patients dying within 3 years of diagnosis. Separate TNM staging at affected sites and metastatic disease are indicators of predicting the biological behaviour of these tumors[16].

CONCLUSIONS

Sinonasal malignant melanoma is an aggressive tumor with a high potential for locoregional recurrence and distant metastasis. Surgery has long been the primary method of treating pathology at the primary site, but new targeted immunotherapies have begun to change the approach to melanoma treatment, especially in patients with metastatic disease, in conjunction with radiotherapy or adjuvant chemotherapy.

Conflict of interest: The authors have no conflict of interest to disclose.

Contribution of authors: All the authors have equally contributed to this work.

REFERENCES

1. Pincet L, Lambercy K, Pasche P, Broome M, Latifyan S, Reinhard A. Mucosal melanoma of the head and neck: a retrospective review and current opinion. Front Surg. 2021;7:616174. DOI: 10.3389/fsurg.2020.616174.
2. Nardi C, Vignoli C, Vannucchi M, Pietragalla M. Magnetic resonance features of sinonasal melanotic mucosal melanoma. BMJ Case Rep. 2019;12(7):e229790. DOI: 10.1136/bcr-2019-229790.
3. Gasparyan A, Amiri F, Safdieh J, Reid V, Cirincione E, Shah D. Malignant mucosal melanoma of the paranazal sinuses: Two case reports. World J Clin Oncol. 2011;2(10):344-7. DOI: 10.5306/wjco.v2.i10.344.
4. Alves ISS, Berriel LGS, Alves RT, Pinto MB, Oliveira CFP, Cazzotto AC, et al. Sinonasal melanoma: a case report and literature review. Case Rep Oncol Med. 2017;2017:8201301. DOI: 10.1155/2017/8201301.

5. Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD. Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngol Head Neck Surg. 2008;138(3):347-52. DOI: 10.1016/j.otohns.2007.12.013.
6. Kepekci AH, Kig C, Gundogan GI. The evaluation of malignant mucosal melanoma of nasal cavity with a rare occasion. Int J Physiol Pathophysiol Pharmacol. 2018;10(4):139-43.
7. Karn A, Khaddar S, Agrawal A, Kapoor A. Exceptional response to oral metronomic chemotherapy in a rare case of sinonasal mucosal melanoma. Ecancermedicalscience. 2021;15:1287. DOI: 10.3332/ecancer.2021.1287.
8. Amit M, Na'ara S, Hanna EY. Contemporary treatment approaches to sinonasal mucosal melanoma. Curr Oncol Rep. 2018;20(2):10. DOI: 10.1007/s11912-018-0660-7.
9. Na'ara S, Mukherjee A, Billan S, Gil Z. Contemporary multidisciplinary management of sinonasal mucosal melanoma. Onco Targets Therapy. 2000;13:2289-98. DOI: 10.2147/OTT.S182580.
10. Koch SE, Lange JR. Amelanotic melanoma: the great masquerader. J Am Acad Dermatol. 2000;42(5 Pt 1):731-4. DOI: 10.1067/mjd.2000.103981.
11. Gilain L, Houette A, Montalban A, Mom T, Saroul N. Mucosal melanoma of the nasal cavity and paranasal sinuses. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131(6):365-9. DOI: 10.1016/j.anorl.2013.11.004.
12. Uysal IÖ, Misir M, Polat K, Altuntaş EE, Atalar MH, Tuncer E, et al. Primary malignant melanoma of the nasal cavity. J Craniofac Surg. 2012;23(1):e2-5. DOI: 10.1097/SCS.0b013e3182420575.
13. Çomunoğlu C, Kuzey GM, Inançli M, Baba F, Özkayalar H. Mucosal malignant melanoma of nasal cavity recurring a year after radiotherapy. Turk Patoloji Derg. 2017;33(1):66-9. DOI: 10.5146/tjpath.2013.01218.
14. Letievant JC, Poupart M, Ambrun A, Colin C, Pignat JC. Single-center retrospective series of fourteen patients with mucosal melanoma of the nasal cavity and paranasal sinuses. Eur Ann Otorhinolaryngol Head Neck Dis. 2016;133(6):387-91. DOI: 10.1016/j.anorl.2016.07.003.
15. Chao TN, Kuan EC, Tong CCL, Kohanski MA, Grady MS, Palmer JN, et al. Surgical treatment of sinonasal mucosal melanoma in patients treated with systemic immunotherapy. J Neurol Surg B Skull Base. 2020;82(Suppl 3):e148-54. DOI: 10.1055/s-0040-1701219.
16. Andrianakis A, Kiss P, Pomberger M, Wolf A, Thurnher D, Tomazic PV. Sinonasal mucosal melanoma: treatment strategies and survival rates for a rare disease entity: A single center experience and review of literature. Wien Klin Wochenschr. 2021;133(21-22):1137-47. DOI: 10.1007/s00508-021-01847-6.
17. D'Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol. 2017;35(2):226-35. DOI: 10.1200/JCO.2016.67.9258.