 DOI: 10.1515/rjr-2017-0026

CASE REPORT

Primary sinonasal mucosal melanoma – Case report and literature review

Anca Evsei[1,2], Adelina Birceanu-Corobea[2], Violeta Melinte[1,3], Codrut Sarafoleanu[1,3]

[1]CESITO Center, "Sfanta Maria" Clinical Hospital, Bucharest, Romania

[2]Department of Pathology, "Sfanta Maria" Clinical Hospital, Bucharest, Romania

[3]ENT&HNS Department,"Sfanta Maria" Clinical Hospital, Bucharest, Romania

ABSTRACT

BACKGROUND. Primary sinonasal mucosal melanoma is a rare tumor with a poor survival rate. There is an inherent difficulty in diagnosing these lesions, especially because their complex anatomic locations and symptoms can be frequently confused with other benign or malignant processes. The purpose of our study was to report a difficult case and review the literature and recent research on therapeutic modalities.

MATERIAL AND METHODS. We herein report a 61-year-old female patient, with a history of right eye enucleation and prosthesis, who presented with obstruction of the left nostril, anterior and posterior mucopurulent rhinorrhea, anosmia, left facial numbness, left exophthalmia accompanied by ipsilateral epiphora and decreased visual acuity.

RESULTS. Clinical and imagistic testing revealed a large, grayish, fleshy tumor localized in the left maxillary sinus, with extension to the left orbit (producing osteolysis of the inferior and medial orbital walls), nasopharynx, ethmoidal cells and left frontal sinus. Pathological and immunohistochemical examination confirmed the diagnosis of mucosal melanoma. Other primary sites were excluded. The patient succumbed shortly after, following only palliative treatment.

CONCLUSION. Early diagnosis of primary sinonasal mucosal melanoma is essential but very difficult to detect. Any symptoms such as unilateral epistaxis or nasal obstruction in a patient over the age of 60 should be rendered suspicious. Pathological and immunohistochemical examination for diagnosis and prognostic factors are important. Although surgery is the first option for treatment, one must consider, according to tumor staging, radiotherapy and chemotherapy with immunotherapy as a viable course of treatment for advanced cases.

KEYWORDS: mucosal melanoma, nasal cavity, paranasal sinuses, differential diagnosis.

INTRODUCTION

Primary sinonasal mucosal melanomas are rare, accounting for less than 1% of all melanomas[1]. However, head and neck is one of the most common regions for mucosal melanomas, constituting almost 50% of all mucosal melanomas[2]. The sinonasal tract is the most frequent site for this type of malignancy.

Etiopathogenesis is relatively poorly understood, but it is a known fact that their origin lies in the melanocytes present in the mucosa of the nasal cavity and paranasal sinuses[3].The nasal cavity is the most frequent location (80%), especially the lateral wall of the nasal cavity, according to recent literature, with only 20% involvement of the paranasal sinuses[4]. The most frequent clinical symptoms reported are epistaxis and nasal obstruction, but these are hardly specific features.

Pathological diagnosis is often difficult, mostly because this tumor does not present with intracellular melanin pigment. Adding differential diagnosis to the challenging clinical presentation and pathological examination makes for a difficult overall diagnosis. Immunohistochemical tests are crucial in this situation

Corresponding author: Anca Evsei, Department of Pathology, CESITO Center, "Sfanta Maria" Clinical Hospital, 37-38 Ion Mihalache Blvd., District 1, Bucharest, Romania
e-mail: ancaevsei@yahoo.com
Received for publication: September 19, 2017 / **Accepted:** October 3, 2017

and various melanocytic markers are available for confirmation: S100, HMB45 (Human Black Melanoma 45), Melan A, Sox 10, etc.[5].

Surgery represents the first option for treatment, but it has its limitations regarding the complete tumor excision or the accessibility to the tumor site. Postoperative radiotherapy is a frequent recommendation for these patients[6]. In order to improve survival in advanced mucosal melanoma, the course of action includes adjuvant chemotherapy and palliation[6]. New immunologic and targeted therapies are always developing, but in the case of mucosal melanoma, especially the head and neck region, BRAF mutation, which is common in cutaneous melanoma, is very rare for this site[7]. Recent studies have found NRAS and c-Kit mutations in mucosal melanoma and new therapeutic agents targeted for these mutations have been researched in various clinical trials. One study has shown that association of targeted therapies and immunotherapy with checkpoint inhibitors appears to show the highest response rates and longest progression-free survival in advanced cases[8].

Despite a better knowledge of this tumor, the 5-year overall survival remains poor, does not exceed 40% in any of the published studies and usually it is diagnosed in an advanced stage of disseminated disease[9].

CASE REPORT

We report a case of a 61-year-old female patient, with a history of right eye enucleation and prosthesis, who presented with obstruction of the left nostril, anterior and posterior mucopurulent rhinorrhea, anosmia, left facial numbness, left exophthalmia accompanied by ipsilateral epiphora and decreased visual acuity (Figure 1A). Clinical symptoms appeared 6 months before presentation, having a progressive evolution.

The clinical ENT examination revealed a fungating, purple-grey mass completely occupied the left nostril (Figure 1B) and extended to the nasopharynx. In addition, the patient also presented with left exophthalmia, prominence and congestion of the caruncula lacrimalis and left inferior palpebral ecchymosis. On palpation, there was no bone in the projection area of the left ethmoidal sinus. Standard ophthalmic examination showed asymmetrical grade III left exophthalmia. The ocular globe showed inferior-medial deviation and movement abolition, a very slow photomotor reflex, optic atrophy secondary to the external compression and no papilledema.

Contrast-enhanced cranio-facial CT and brain MRI examinations described the presence of a tumor with malignant features (dimensions 6.1/4.8/3.7 cm) located in the left maxillary sinus with extension to the left orbit (producing osteolysis of the inferior and medial orbital walls), nasopharynx, ethmoidal cells and left frontal sinus (Figure 2). No brain metastases were identified on cranio-facial CT scan.

A chest and abdomen contrast-enhanced CT scan was performed revealing multiple lungs, liver, chest and abdominal soft tissue lesions (distant metastases).

Having a complete clinical and imagistic examination, the medical decision made in our clinic was to take a biopsy from the intranasal mass for frozen section. Using the external approach type Moore, the tumor comprising the left nasal fossa, the left lateral nasal wall, the left maxillary sinus, infiltrating the anterior, posterior and superior walls of the maxillary sinus, left Tenon capsule, frontal and ethmoidal si-

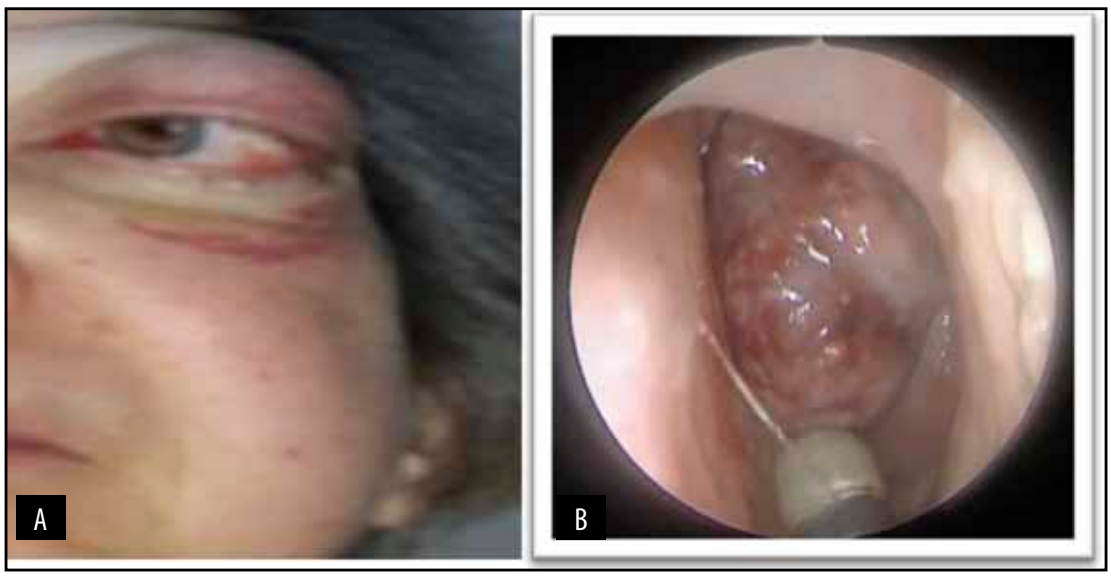

Figure 1 Preoperative clinical examination. **A.** Left exophthalmia, prominence and congestion of the caruncula lacrimalis and left inferior palpebral ecchymosis. **B.** Endoscopic nasal examination – purple-grey mass completely occupying the left nasal fossa.

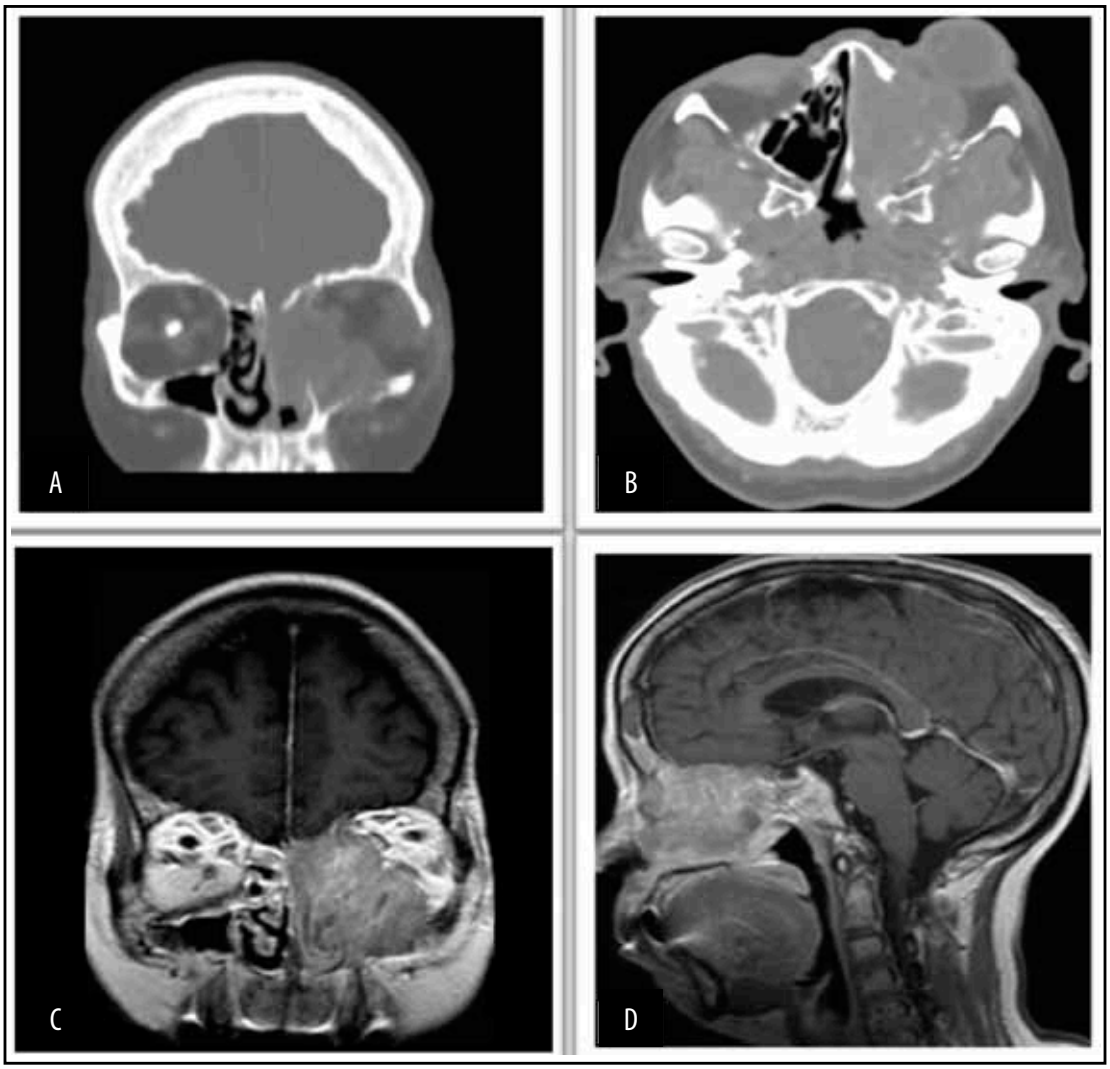

Figure 2 Cranio-facial CT scan (coronal **(A)** and axial **(B)** sections) and brain MRI (coronal **(C)** and sagittal **(D)** slices) – tumor mass located in the left maxillary sinus with extension to the left orbit (producing osteolysis of the inferior and medial orbital walls), nasopharynx, ethmoidal cells and left frontal sinus.

nuses and the roof of the left nostril was removed in a piece-meal manner. After surgery, there was a significant improvement of the ocular protrusion.

Frozen section was performed. Gross examination showed multiple tissue fragments with dimensions between 0.5/0.5/0.5 and 1.5/0.6/0.5 cm, brown-yellowish in colour and elastic in consistency. Microscopic examination of the frozen section revealed a tumor proliferation with a nested architectural pattern. The malignant cells were round, epithelioid-like and focally, spindle; the cytoplasm was prominent, eosinophilic; the nuclei were large, pleomorphic, hyperchromatic with irregular nuclear membranes. Large areas of tumor necrosis were identified. In consequence, the frozen section exam raised the suspicion of an undifferentiated epithelioid malignant tumor. Extensive grossing was done. Specimen samples were fixed with 10% buffered formalin. Then, they were processed by conventional histopathological methods using paraffin embedding, sectioning and Hematoxylin–Eosin (HE) staining. Microscopic examination showed a tumor proliferation with a nested and insular growth pattern (Figure 3A) composed of large malignant cells with marked cytological and nuclear pleomorphism with frequent giant, monstrous cells.

The cytoplasm was abundant, eosinophilic and focally with intracytoplasmic deposition of brown, melanin pigments (Figure 3B). The nuclei were pleomorphic, hyperchromatic with high mitotic activity. Extensive vascular, lymphatic (Figure 3C) and neural invasions were observed. Tumor necrosis was identified in a large percentage. Adjacent respiratory mucosa revealed extensive infiltration of surface epithelium and of underlining cartilage and bone tissue.

Immunohistochemical tests were also performed. The paraffin blocks were sliced at a microtome resulting in sections of 3-µm thickness that were mounted on slides covered with poly-Lysine. The sections were

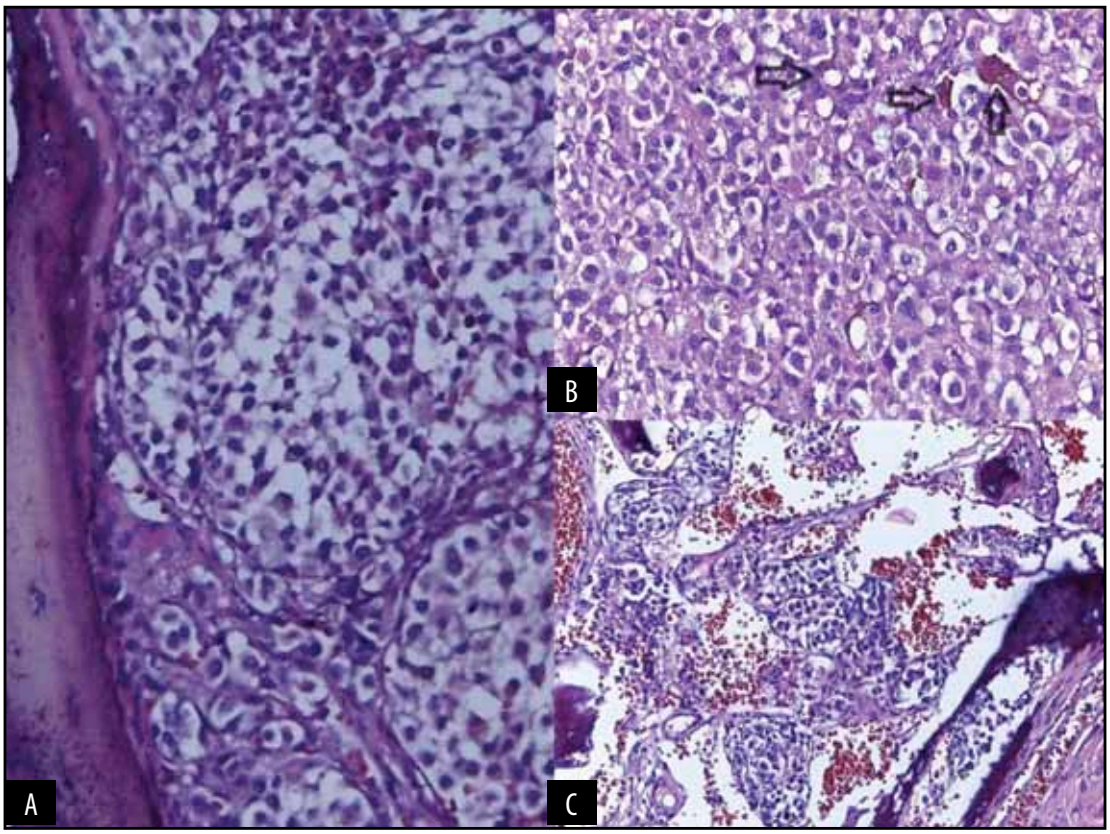

Figure 3 Primary sinonsal mucosal melanoma. **A**: HE 200x: Tumor proliferation with a nested and insular growth pattern which infiltrates the adjacent bone tissue. **B**: HE 400x: Large malignant cells with marked cytological and nuclear pleomorphism with frequent giant, monstrous cells. The cytoplasm is abundant, eosinophilic and focally with intracytoplasmatic deposition of brown, melanin pigment (arrows). **C**: HE: 200x: Extensive angiolymphatic invasion.

deparaffinized in toluene and alcohol successive baths for one hour (15 minutes by bath), rehydrated (three successive alcohol baths with decreased concentration: 96%, 80% and 70% (10 minutes in each bath) and followed by a distilled water bath, in which the sections were held for 10 minutes).Washing in PBS (phosphate-buffered saline), incubation with normal serum for 20 minutes, incubation with primary antibody over-night, Dako LSAB (Labeled StreptAvidin Biotin) kit, washing in carbonate buffer and development in 3,3'-diaminobenzidine hydrochloride/ hydrogen peroxide and nuclear counterstain with Mayer's Hematoxylin were performed.

We performed the following immunohistochemical markers: S100 (Figure 4A), HMB45 (Figure 3B) and Melan A (Figure 3C) which were intensely positive in cytoplasm; SOX10 (Figure 3D) was intensely positive in nuclei; Ki67 was positive in 80% of the tumor nuclei; AE1/AE3 was negative (Figure 3E). In addition, as a prognostic factor useful for possible treatment options, we performed the C-kit (CD117) marker, which was negative.

The case particularity consists in the fact that the nasal cavity and the paranasal sinuses are an uncommon location for primary mucosal melanoma, assuming that metastases from other primary sites have been excluded clinically. Furthermore, considering the fact that this tumor usually presents in advanced stages, the need for an experienced surgeon is necessary for correct clinical diagnosis and treatment. After surgery, the patient was referred to the oncology service in order to start palliative treatment. Unfortunately, she died two months later.

DISCUSSIONS

Head and neck mucosal melanomas are very rare and aggressive neoplasms. Primary sinonasal mucosal melanoma accounts for 0.5-2% of all malignant melanomas and 4% of all head and neck melanomas[10]. The first case of mucosal melanoma in English literature was published by Lincoln et al. in 1885[11]. The mean age at diagnosis is between 65 and 70 years[12]. Our case, on the other hand, is younger. Both sexes are affected equally, without favouring a race in particular, although some studies have shown a higher percentage in the Japanese population[1].

Because of its hidden location and rich blood supply, this type of melanoma usually presents at a more

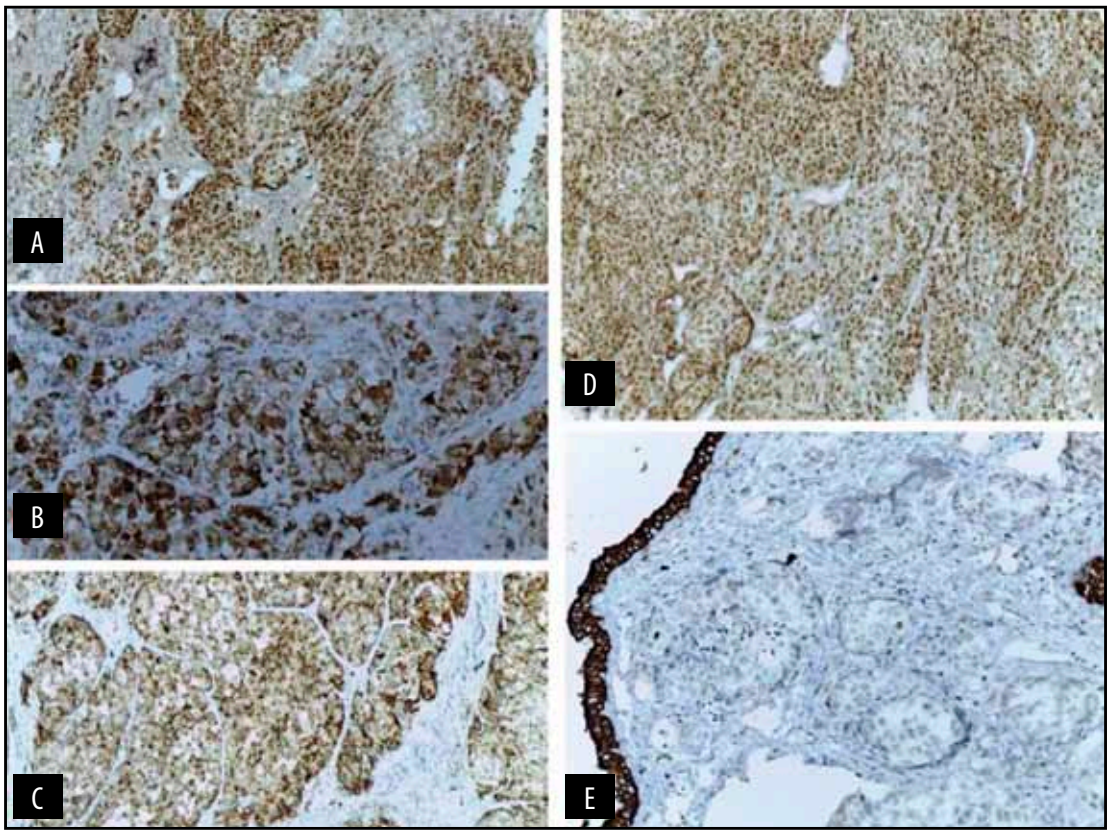

Figure 4 **A:** 100x: S100 marker positive in tumor cells nuclei and focally, in cytoplasm. **B:** 200x: HMB45 marker positive in tumor cells cytoplasm. **C:** 200x: Melan A marker positive in tumor cells cytoplasm. **D:** 100x: SOX10 marker positive in tumor cells nuclei. **E:** 200x: AE1-AE3 marker negative in tumor cells, positive in the adjacent respiratory epithelium.

advanced stage and, therefore, it is associated with a higher mortality rate than its cutaneous forms[13]. Established risk factors for cutaneous melanoma such as sun damage, atypical nevi or family history, do not apply for this particular site. Although the air-irritant compounds, such as tobacco smoke or formaldehyde, have been implicated in the development of head and neck mucosal melanoma, their etiopathogenic role is not yet demonstrated. However, one study revealed that the hyperproduction of melanocytes in oral mucosa was connected to smoking and resulted in a greater prevalence of oral lesions[14]. Our patient was a non-smoker and did not report any kind of exposure to a toxic environment.

Mucosal melanoma originates from benign intramucosal melanocytes that can be located in the mucosa of the upper digestive tract (paranasal sinuses, oral cavity, pharynx and larynx). The nasal cavity is the predominant location, approximately 80% of the melanomas arising from the sinonasal tract and 20% developing in the paranasal sinuses[4]. The most frequent sites of origin are represented by the nasal septum and the lateral wall of the nasal cavity, while the maxillary and the ethmoid sinuses are the most common in what the paranasal sinuses are concerned[15]. The exact origin of sinonasal lesions is often difficult to pinpoint mainly because this tumor can spread into multiple subsites and it is frequently locally advanced at presentation[4].

The most common presenting complaints are nasal obstruction and epistaxis. Other symptoms are represented by diplopia and proptosis[4]. Nasal obstruction is usually unilateral, permanent and progressive, frequently associated with other symptoms, while epistaxis can be abundant or minimal[12]. In most cases, patients do not have early symptoms. There are different studies that have noted a lag time from the symptoms appearance to evaluation by a health care professional from several weeks to 2 years[4]. Our case fits the description, as this tumor was already very advanced when the patient presented with left exophthalmia, left nasal obstruction, epiphora and left facial paraesthesia that have been progressing for 2 months. Clinical examination by fiberscopic or endoscopic investigation is useful, but they cannot appreciate the extent of the disease or guide towards a diagnosis. In some cases, multiple lesions (for instance, satellite lesions) can be frequently observed, even centimetres away from the main tumor, with spreading occurring along the mucosal/submucosal planes[16]. Macroscopically, the tumor was reddish-crimson, covered by greyish exudates and very friable, which consists in the fact that one third of mucosal melanomas are achromic[17].

Imagistic tests for sinonasal melanoma are of the utmost importance as they represent a key feature in tumor staging. The CT appearance of this type of tumor is nonspecific and consists of a mass lesion with contrast enhancement and tumor infiltration of the adjacent bone[18]. The MRI examination depends on several histological features of the tumor (melanotic versus amelanotic) and presence of haemorrhage within the lesion[19]. Mucosal melanomas with a heavy quantity of intracytoplasmic pigment typically exhibit T1 hyperintensity and an intermediate-hypointense pattern on T2-weighted MRI, while amelanotic mucosal melanomas are hypointense on T1- and hyperintense on T2-weighted sequences. On gadolinium-enhanced MRI, these lesions appear as mild to moderate enhancement[19]. The differential diagnosis of T1 hyperintense lesions includes haemorrhage in primary nasal lesions such as haemangioma and juvenile angiofibroma, proteinaceous secretions in mucoceles, fat-containing lesions and haemorrhagic metastases. In addition, MRI is very helpful in determining the anatomical relationship between the tumor and the orbit and skull base in revealing any brain metastasis. Chest, abdominal and pelvis CT are very valuable in determining distant metastasis. Our case followed the radiological protocol. CT and MRI examination raised the suspicion that the lesion was malignant. Furthermore, chest and abdominal CT scans showed multiple metastasis in lungs, liver and soft tissue.

The diagnosis is based on histological examination, which usually shows a malignant proliferation with a nesting growth pattern and marked cytological pleomorphism[17]. The presence of intracytoplasmic melanin pigment can be detected by the affinity for Fontana stain, but, if it is present, it is usually visible on hematoxylin-eosin. Several parameters are evaluated on histological examination: morphology and cellular architecture, pigmentation, presence of ulceration, percentage of necrosis, number of mitoses, inflammation, perineural, lymphatic and vascular invasion. Confirmation of the diagnosis is based on immunohistochemistry using a panel of markers[12].

S100 is an acidic protein, 100% soluble in ammonium sulphate at neutral pH, a common marker used in pathology. Its purpose is mainly represented by cytoplasmic and nuclear positivity in melanoma and neural tissue, but it has a wide area of tumors where it can be used. In consequence, although S100 protein may be a sensitive marker, it is a nonspecific one[20]. Regarding primary mucosal melanomas, one study showed 88% positivity for this marker, placing S100 in an immunohistochemical panel of high positivity rate[21].

The Melan-A gene, also known as MART-1 (Melanoma Antigen Recognised by T-cells), was cloned from a melanoma cell line. This marker is thought to be associated with melanosomes and endoplasmic reticulum, but this fact has not yet been established. Malignant melanoma of various locations and melanocytes present in the skin and ocular globe generally express this marker[22]. Some studies have shown 85% positivity for this marker in sinonasal mucosal melanomas and 100% positivity in oral mucosal melanomas[23]. In addition, it was shown to be very specific in distinguishing metastatic melanoma from other lesions such as sarcomas of varying histogenesis, poorly differentiated carcinomas, high-grade lymphomas, Leydig tumors or myelomas[20].

HMB45 (Human Black Melanoma 45) is a monoclonal antibody originally identified from melanoma extract. It has the property of recognizing melanosomal glycoprotein gp100 (Pmel17). This antigen reacts with melanoma and junctional nevus cells. Staining appears to be more appropriate to lesions with pigment content compared to those with less pigmentation[24]. The sensitivity of HMB45 was shown to be 66-97%, the percept decreasing in metastatic lesions as compared to primary lesions[25]. Prasad et al. has shown 91% positivity for this marker in sinonasal melanomas and 71% positivity in oral mucosal melanomas[23].

Recent studies have shown that Sox10 is a sensitive melanocytic marker for cutaneous melanoma[26]. During the embryonic development, Sox10, as a transcription factor of the Sox group E, directs melanocytes derived from neural crest in their migration to skin and mucosal epithelia[27]. Expression of Sox10 is continuous throughout the differentiation pathway toward mature melanocytes[28]. This marker is essential for the specification and differentiation of melanocytic lineage, characteristic which makes it a useful melanocytic marker. Although Sox10 can be highlighted in epidermal melanocytes and cutaneous melanomas and it is used frequently, there is little research on Sox10 expression in sinonasal melanomas. One study reported a Sox10 expression in all 28 cases of sinonasal melanomas with diffuse and strong nuclear staining[29]. Several authors reported that Sox10 had a higher sensitivity and specificity for cutaneous malignant melanoma as well as for metastatic melanoma in sentinel lymph nodes than other immunohistochemical markers such as S100 protein, HMB-45 or Melan-A[30].

C-kit protein is a transmembranous receptor tyrosine kinase. Therapy based on KIT gene targeting, specifically treatment with inhibitors such as imatinib, is based on the expression of c-kit protein. In most subtypes of melanoma, c-kit expression can be detected in immunohistochemistry, including superficial spreading cutaneous melanomas (53.7%), primary anorectal melanomas (75%), more than 80% metastatic melanomas and acral lentiginous/mucosal melanomas (84%)[31]. Hong et al. found in their study a 85.7% positivity for c-kit in 28 cases of sinonasal melanomas[29]. Other studies showed 91% positivity in primary mu-

cosal melanomas, similar to other locations, such as anal/rectal or oral cavity. In contrast, other research showed only 4% positivity for c-kit in sinonasal melanomas by gene detection, suggesting that c-kit expression is highly variable between different sites for mucosal melanomas[32]. In our case, c-kit was negative, meaning that our patient would not have been eligible for treatment with c-kit inhibitors.

In addition to c-kit, BRAF and NRAS mutations stand out in melanoma pathogenesis and represent targets for emerging molecules in new therapies. Both mutations take part in the mitogen-activated proteinkinase (MAPK) pathway, which is involved in melanoma development[33]. Although both mutations occur in a high percentage in cutaneous melanoma, mucosal melanomas have very low frequencies in BRAF mutation (4%) and higher in NRAS mutation (11%)[15]. Other studies confirmed the same finding which suggested that targeted treatments with selective BRAF inhibitors (vemurafenib and dabrafenib that were shown to improve overall and progression-free survival in cutaneous melanomas) are not of use in mucosal melanomas, especially in the head and neck site[34-36].

The new staging system according to the 8th Edition of the American Joint Committee on Cancer (AJCC)[37] established a novel approach on T, N and M categories. Thus, only the T3, T4a and T4b categories are maintained, similar to the 7th edition of AJCC, omitting T1 and T2 categories because of the very poor prognosis for small, superficial lesions (Table 1). Regarding the N category, the cervical lymph nodes are the primary lymphatic drainage, but due to the rarity of this disease, nodal metastasis are currently classified in present (N1) or absent (N0). The role of extranodal extension (ENE) is not yet established[37]. Distant metastases (M1) are usually common at clinical presentation and are usually located in lung and liver (Table 2).

Definitive diagnosis is based on immunohistochemistry. Great care should be taken with diagnosis if immunohistochemistry is not performed[38]. In the present case, the challenge was represented by the frozen section because the cells did not show intracytoplasmic pigment. On hematoxylin-eosin, after extensive grossing, we could identify intracytoplasmatic melanin accumulation. We performed the immunohistochemical marker AE1/AE3 to exclude a poorly differentiated carcinoma. Due to the difficulty in diagnosing a malignant sinonasal melanoma, differential diagnosis must be made with sinonasal undifferentiated carcinoma, lymphoma, rhabdomyosarcoma, angiosarcoma, neuroendocrine carcinoma, neuroblastoma, and plasmacytoma[39]. Unfortunately, metastasis from a primary tumor located elsewhere (skin, ocular globe, other mucosal locations) cannot be distinguished from a primary sinonasal mucosal melanoma using immunohistochemistry. In this case, the patient should be thoroughly investigated and the primary lesions should be excluded. In our patient situation, the dermatologist excluded a skin primary, so our final diagnosis was primary sinonasal mucosal melanoma.

There are no randomized trials studying mucosal melanoma treatment modalities such as surgery, radio-

Table 1
Definition of primary tumor (T) according to American Joint Committee on Cancer (AJCC), 8th Edition, 2017

T category	T Criteria
T3	Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or non-pigmented lesions of the oral cavity, pharynx and larynx.
T4	Moderately advanced or very advanced.
T4a	Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone or overlying skin.
T4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves [IX, X, XI, XII], masticator space, carotid artery, prevertebral space or mediastinal structures.

Table 2
Definition of regional lymph node (N) and distant metastasis (M) according to American Joint Committee on Cancer (AJCC), 8th Edition, 2017

N category	N Criteria	M category	M Criteria
Nx	Regional lymph nodes cannot be assessed.	M0	No distant metastasis.
N0	No regional lymph nodes metastases.	M1	Distant metastasis present.
N1	Regional lymph node metastases.		

therapy, or chemo- and immunotherapy[2]. Surgery associated with or without radiation therapy is the primary treatment for stage III mucosal melanoma, while surgery followed by radiation therapy or systemic therapy is the primary treatment for stage IV mucosal melanoma[40]. Surgical treatment is usually the first option but, unfortunately, complete excision is rarely possible with free margins as the sinonasal tract is in close proximity of critical anatomical structures[31]. The indication for surgery must also take into account a high local recurrence rate.

Radiation therapy is often recommended in the postoperative management of mucosal melanomas. Primary size or thickness is not used as a risk factor when considering the primary site of the lesion. All invasive primaries are considered at high risk for local recurrence. For sinonasal primary sites, target volumes may include the primary site without elective treatment of the neck. Because oral cavity primary sites are believed to be at a higher risk for neck metastatic lymph nodes, elective management with neck dissection and radiotherapy may be taken into consideration as treatment modality.

Intensity modulated RT may be very helpful not only for the dose distribution at the primary site, but also for sparing critical organs, especially in paranasal sinus sites[41]. Good outcomes have been reported with the use of hypofractionation in cutaneous melanomas. Thus, there is no clear advantage in cancer control. If used, hypofractionation must be carefully planned and delivered due to the proximity of neural structures and risk of late effects[40].

Chemotherapy and immunotherapy are usually used with an adjuvant or palliative intention. The most frequently used chemotherapy agents are dacarbazine, the platinum analogues, the nitrosoureas and the microtubulartoxins. Immunotherapy has proved its efficacy in a small percentage of patients with malignant melanoma. An increased response rate has been observed when associating interleukin 2 and interferon-alpha with cisplatin.

Survival rates for mucosal melanoma of head and neck according to the national cancer database have been registered as 54% in 2 years and 32% in 5 years[42]. Recent series suggest that, specifically for mucosal melanoma of nasal cavity and paranasal sinuses, the mean survival does not exceed 40% in 28 months[12]. Depending on location, disease-specific survival at 5 years was 36.66% for those patients with nasal cavity disease, 23.80% for patients with maxillary sinus disease and 18.20% for patients with ethmoid sinus disease[43]. One large meta-analysis of patients with primary sinonasal melanoma has shown that there is no survival advantage for combined radiotherapy and surgery or chemoradiotherapy plus surgery versus surgery alone[44]. The average overall survival in this study was 27.41 months for all therapies, confirming the dismal prognosis of this rare malignancy.

Local recurrences appear in almost 50% of cases. This fact is explained mostly by the multifocal nature of these lesions and lymphatic and vascular invasion. The most common metastatic sites are lungs, liver, bone and rarely brain and adrenal glands[12]. Metastases are found in about 50% of cases, sometimes during the course of the disease, while lymph nodes are found in 20-40% of cases[45]. Our present case unfortunately already presented with advanced disease and metastases in lung, liver and soft tissue. Although the initial medical decision was chemotherapy, the patient received only palliation. Overall survival from diagnosis to exitus was 4 months, with no oncological treatment.

CONCLUSIONS

Primary mucosal melanoma of the sinonasal region is a rare occurrence with different clinical and histopathological presentations, invasive tumor behaviour, frequent local recurrence, poor prognosis and various treatment modalities. Pathological and immunohistochemical analysis contributes to an accurate and precise diagnosis and if this lesion is detected early in its stages, it can provide a proper panel of prognostic and prediction factors, useful for a targeted treatment. Frequent controversies focus on the surgical management that is difficult to instate in order to obtain free resection margins or total excision of the tumor. Radiotherapy and chemotherapy focus on cases with advanced diseases, but considering the rapidly evolving therapies which target specific molecules, this kind of treatment may represent a viable solution for a disease with a dismal prognosis.

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

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

REFERENCES

1. Barnes L, Eveson JW. (eds.) WHO Classification of Tumors. Pathology and Genetics of Head and Neck Tumors. IARCPress: Lyon; 2017.
2. Aleksić A, Gajanin R, Djurdjević D, Novaković Z, Vranjes D, Spremo S, Travar D, Guzina-Golac N, Tomić-Spirić V. Melanoma of the sinonasal mucosa: A report on the two cases and a review of the literature. Vojnosanit Pregl. 2015;72(10):937-41.
3. Wagner M, Morris CG, Werning JW, Mendenhall WM. Mucosal melanoma of the head and neck. Am J Clin Oncol. 2008;31(1):43–8. DOI: 10.1097/COC.0b013e318134ee88.
4. Seetharamu N, Ott PA, Pavlick AC. Mucosal melanomas: A case-based review of the literature. Oncologist. 2010;15(7):772–81. DOI: 10.1634/theoncologist.2010-0067. Epub 2010 Jun 22.

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. Temam S, Mamelle G, Marandas P, Wibault P, Avril M, Janot F, et al. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. Cancer. 2005;103(2):313–9.
7. Carvajal RD, Spencer SA, Lydiatt W. Mucosal melanoma: a clinically and biologically unique disease entity. J Natl Compr Canc Netw. 2012;10(3):345-56.
8. Schaefer T, Satzger I, Gutzmer R. Clinics, prognosis and new therapeutic options in patients with mucosal melanoma: A retrospective analysis of 75 patients. Medicine (Baltimore). 2017;96(1):e5753. DOI: 10.1097/MD.0000000000005753.
9. Moreno MA, Roberts DB, Kupferman ME, DeMonte F, El-Naggar AK, Williams M, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M.D. Anderson Cancer Center. Cancer. 2010;116(9):2215-23. DOI: 10.1002/cncr.24976.
10. Alves IS, Berriel LG, Alves RT, Pinto MB, Oliveira CF, Cazzotto AC, et al. Sinonasal Melanoma: A Case Report and Literature Review. Case Rep Oncol Med. 2017;2017:8201301. DOI: 10.1155/2017/8201301. Epub 2017 Jan 31.
11. Lincoln RP. A case of melano-sarcoma of the nose cured by galvanocauterization. N Y Med J. 1885;42:406–7.
12. Gilain L, Houette A, Montalban A, Mom T, Saroul N. Mucosal melanoma of the nasal cavity and paranasal sinuses. European Annals of Otorhinolaryngology, Head and Neck Diseases. 2014;131(6):365-9.
13. Wong JH, Cagle LA, Storm FK, Morton DL. Natural history of surgically treated mucosal melanoma. Am J Surg. 1987;154(1):54-7.
14. Axéll T, Hedin CA. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. Scand J Dent Res. 1982;90(6):434–42.
15. Göde S, Turhal G, Tarhan C, Yaman B, Kandiloğlu G, Öztürk K, et al. Primary Sinonasal Malignant Melanoma: Effect of Clinical and Histopathologic Prognostic Factors on Survival. Balkan Med J. 2017;34(3):255-62. DOI: 10.4274/balkanmedj.2016.0503. Epub 2017 Apr 6.
16. Ascierto PA, Accorona R, Botti G, Farina D, Fossati P, Gatta G, et al. Mucosal melanoma of the head and neck. Critical Reviews in Oncology / Hematology. 2017;112:136-52. DOI: 10.1016/j.critrevonc.2017.01.019.
17. Saint-Blancard P, Kossowski M. Mélanomes des muqueuses nasosinusiennes. Presse Med. 2006;35(11 Part 1):1664–7.
18. Keraliya AR, Krajewski KM, Braschi-Amirfarzan M, et al. Extracutaneous melanomas: a primer for the radiologist. Insights Imaging. 2015;6(6):707-17. DOI: 10.1007/s13244-015-0427-8.
19. Yoshioka H, Kamada T, Kandatsu S, Koga M, Yoshikawa K, Matsuoka Y,et al. MRI of mucosal malignant melanoma of the head and neck. J Comput Assist Tomogr. 1998;22(3):492–7.
20. Snyder ML, Paulino AF. Melan-A as a useful diagnostic immunohistochemical stain for the diagnosis of primary sinonasal melanomas. Head Neck. 2002;24(1):52-5.
21. Yu CH, Chen HH, Liu CM, Jeng YM, Wang JT, Wang YP, et al. HMB-45 may be a more sensitive maker than S-100 or Melan-A for immunohistochemical diagnosis of primary oral and nasal mucosal melanomas. J Oral Pathol Med. 2005;34(9):540–5.
22. Bishop PW. An immunohistochemical vademecum. Available at http://e-immunohistochemistry.info/web/histopathology_help.htm. Version date October 2012.
23. Prasad ML, Jungbluth AA, Iversen K, Huvos AG, Busam KJ. Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. Am J Surg Pathol. 2001;25(6):782-7.
24. Weinstein D, Leininger J, Hamby C, Safai B. Diagnostic and prognostic biomarkers in melanoma. J Clin Aesthet Dermatol. 2014;7(6):13-24.
25. Modabbernia S, Bashardoust N, Bagheri SS. Malignant Mucosal Melanoma of the Maxillary Sinus. Journal of Dentomaxillofacial Radiology, Pathology and Surgery. 2017;5(4):32-6.
26. Nonaka D, Chiriboga L, Rubin BP. SOX10: a pan-schwannian and melanocytic marker. Am J Surg Pathol. 2008;32(9):1291–8. DOI: 10.1097/PAS.0b013e3181658c14.
27. Gershon TR, Oppenheimer O, Chin SS, Gerald WL. Temporally regulated neural crest transcription factors distinguish neuroectodermal tumors of varying malignancy and differentiation. Neoplasia. 2005;7(6):575–84.
28. Kelsch RN. Sorting out SOX10 functions in neural crest development. Bioessays. 2006;28(8):788-98.
29. Liu HG, Kong MX, Yao Q, Wang SY, Shibata R, Yee H, et al. Expression of Sox10 and c-kit in sinonasal mucosal melanomas arising in the Chinese population. Head Neck Pathol. 2012;6(4):401–8. DOI: 10.1007/s12105-012-0375-2. Epub 2012 Jun 27.
30. Jennings C, Kim J. Identification of nodal metastases in melanoma using sox-10. Am J Dermatopathol. 2011;33(5):474–82. DOI: 10.1097/DAD.0b013e3182042893.
31. Medina JE, Ferlito A, Pellitteri PK, Shaha AR, Khafif A, Devaney KO, et al. Current management of mucosal melanoma of the head and neck. J Surg Oncol. 2003;83(2):116–22.
32. Zebary A, Jangard M, Omholt K. KIT, NRAS and BRAF mutations in sinonasal mucosal melanoma: a study of 56 cases. Br J Cancer. 2013;109(3):559-64. DOI: 10.1038/bjc.2013.373. Epub 2013 Jul 16.
33. Sullivan RJ, Flaherty K. MAP kinase signaling and inhibition in melanoma. Oncogene. 2013;32(19):2373–9. DOI: 10.1038/onc.2012.345. Epub 2012 Sep 3.
34. Turri–Zanoni M, Medicina D, Lombardi D, Ungari M, Balzarini P, Rossini C, et al. Sinonasal mucosal melanoma: Molecular profile and therapeutic implications from a series of 32 cases. Head Neck. 2013;35(8):1066-77. DOI: 10.1002/hed.23079. Epub 2012 Jul 12.
35. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16. DOI: 10.1056/NEJMoa1103782.
36. Hauschild A, Grob JJ, Demidov LV, Jouray T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358–65. DOI: 10.1016/S0140-6736(12)60868-X. Epub 2012 Jun 25.
37. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. (Eds.). AJCC Cancer Staging Manual. Eighth Edition. Springer International Publishing; 2017.
38. Enee V, Houliat T, Truilhe Y, Darrouzet V, Stoll D. Malignant melanoma of the nasosinal mucosa. Retrospective study apropos of 20 cases. Rev Laryngol Otol Rhinol (Board). 2000;121(4):243–50.
39. Clifton N, Harrison L, Bradley PJ, Jones NS. Malignant melanoma of nasal cavity and paranasal sinuses: report of 24 patients and literature review. J Laryngol Otol. 2011;125(5):479–85. DOI: 10.1017/S0022215110002720. Epub 2011 Jan 21.
40. Pfister DG, Ang KK, Brizel DM, Burtness B, Cmelak AJ, Colevas AD, et al. Mucosal Melanoma of the Head and Neck: Clinical Practice Guidelines in Oncology. JNCCN. 2012;10(3):320-38.
41. Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2010;78(4):998–1004. DOI: 10.1016/j.ijrobp.2009.09.067. Epub 2010 Mar 24.
42. Chang AE, Karnell LH, 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;83:1664-78.
43. Khan MN, Kanumuri VV, Raikundalia MD, et al. Sinonasal melanoma: survival and prognostic implications based on site of involvement. Int Forum Allergy Rhinol. 2014;4(2):151-5. DOI: 10.1002/alr.21243. Epub 2013 Nov 4.
44. Gore MR, Zanation AM. Survival in Sinonasal Melanoma: A Meta-analysis. J Neurol Surg B Skull Base. 2012;73(3):157-62. DOI: 10.1055/s-0032-1301400.
45. Bachar G., Loh KS, O'Sullivan B, et al. Mucosal melanomas of head and neck: experience of the Princess Margaret Hospital. Head Neck. 2008;30(10):1325-31. DOI: 10.1002/hed.20878.