# CASE REPORT

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# Malignant melanoma of the left nasal fossa – case report

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## Abstract

Mucosal malignant melanoma is an extremely rare tumor of the nose, with an aggressive character, low prognosis and frequent recurrences. The authors present a case of a 60-year-old male patient, diagnosed five years ago with adenoid cystic carcinoma, for which he had surgery and radiotherapy, who was admitted in our Clinic with unilateral epistaxis and obstruction of the nasal cavity. Clinical exam revealed an obstructive polypoidal bleeding mass of the left nasal cavity. Biopsy was performed and the histopathological exam showed malignant mucosal melanoma. Wide local endoscopic surgery was practiced for two times in the last two years, and for now, there is no recurrence. Malignant melanomas are tumors with high mortality rate, which necessitate an early diagnosis and immediate treatment.

*Keywords*: nasal tumor, malignant melanoma, endoscopic sinus surgery.

## Introduction

Head and neck cancers are one of the most frequent malignant tumors worldwidely, with a high morbidity and mortality [1–3]. According to some recent data, head and neck cancers affect more than 4.6 million people all over the world [4, 5]. These epidemiological data show that head and neck malignant tumors represent the seventh most frequent localization of cancer [6].

Most head and neck tumors (over 90%) are represented by squamous cell carcinomas, localized in the oral cavity, pharynx, nasal cavities or paranasal sinuses [1, 7]. A small number of malignant tumors (about 10%) are represented by adenoid cystic carcinomas of salivary glands, lymphomas, sarcomas and melanomas [8, 9].

Malignant melanomas represent approximately 4% of the (total) malignant tumors localized in the nasal cavities. The most frequent localization of sinonasal melanomas is represented by the lateral nasal wall (the inferior and the middle turbinate), followed by the nasal septum, the maxillary sinus and the ethmoid sinus [10]. This disease is not a sex-related one, affecting both genders equally. The incidence of the malignant melanoma varies widely amongst its different possible sites throughout the human body. Therefore, whilst the melanoma of the skin is described more frequently in recent years, the incidence of the sinonasal melanoma has remained constant [11].

Sinonasal malignant melanomas are characterized by a reserved prognosis at the five-year mark post-surgery, with a survival rate of 8–48%, the median being lower than 25% [10]. Due to the rarity of the sinonasal localization, there have only been conducted studies on small groups of patients [12]. In addition, while the malignant melanoma of the skin is caused mainly by repetitive sun exposure, the nasal melanoma has a single known risk factor – the professional exposure to formaldehyde [13]. Diagnosing this disease as soon as possible and the extensive surgical treatment represent the optimal therapeutic approach.

The aim of this paper is to point out some particularities of a case report with its pathological and clinical features.

## Case presentation

In the following section, we present the case of a 60-year-old man (SSV) who was admitted into our Clinic – "Prof. Dr. Dorin Hociotă" Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania, patient chart No. 3133, in May 2015, for recurrent epistaxis and unilateral nasal obstruction on the left side.

The patient was known with cystic adenoidal carcinoma of the left nasal cavity for which he underwent surgery and radiotherapy in 2010, with no recurrences detected at follow-ups in the next five years. The patient was hypertensive, suffered of insulin-dependent type II diabetes mellitus. The anamnesis revealed a hereditary background of breast cancer and colon cancer (mother) and bladder neoplasm (father). Despite this, the patient's history presented no other risk factors as he worked as a pilot, did not smoke and consumed alcohol occasionally.

Endoscopic examination of the left nasal cavity revealed a bleeding, friable, gelatinous mass that was occupying the entire cavity (Figure 1).

No other pathological structures were identified by

other means of clinical examination. Therefore, we decided to ask for a complete ophthalmologic examination, which turned out normal. The computed tomography (CT)-scan revealed a vegetative, multilobulated mass, 30/40 mm in diameter, situated in the left nasal cavity, in contact with the left inferior turbinate. In addition, a circumferential, nodular thickening of the left maxillary sinus mucosa was visible. The tumor from the left nasal cavity determined bone erosions of the inferior turbinate as well as the maxillary sinus medial wall (Figure 2). Biological parameters of the patient have proper values.

Under general anesthesia, the patient underwent endoscopic surgery in order to perform a "piece-meal" resection of the tumor, whose fragments were sent for a histopathological examination. In order to ensure oncological safety margins, we also performed middle maxillectomy and left anterior ethmoidectomy. Microscopy revealed a stratified, squamous mucosa without areas of keratinization, but with a massive malignant proliferation, described as both junctional and subepithelial. Tumor cells, identified as epithelioid and fusiform, were grouped in nests and isles, with an important lack of intercellular cohesion. Moreover, one could note important nuclear atypias, frequent atypical mitoses and significant accumulation of melanocytic pigment in the tumor cells. In addition, there were identified areas of tumor necrosis, vascular invasion, ulcerations and tumor proliferation in all the tissue margins, without any signs of regression (Figure 3, a and b).
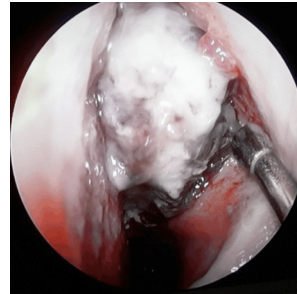


**Figure 1 – *Endoscopic aspect of malignant melanoma: black tumoral mass covered with purulent discharge.***



**Figure 2 – *CT scan: vegetative, multilobulated mass, situated in the left nasal cavity, in contact with the left inferior turbinate.***
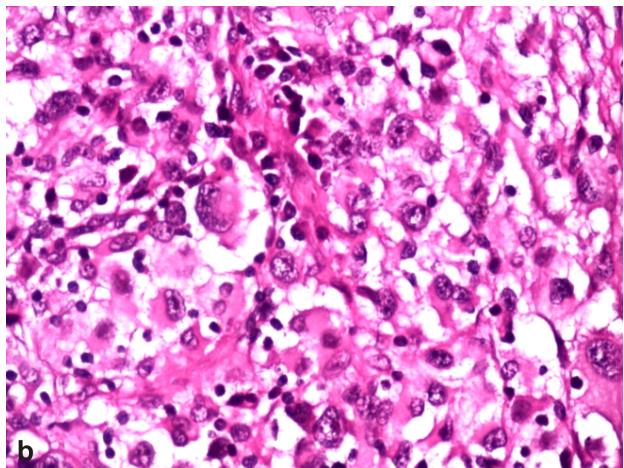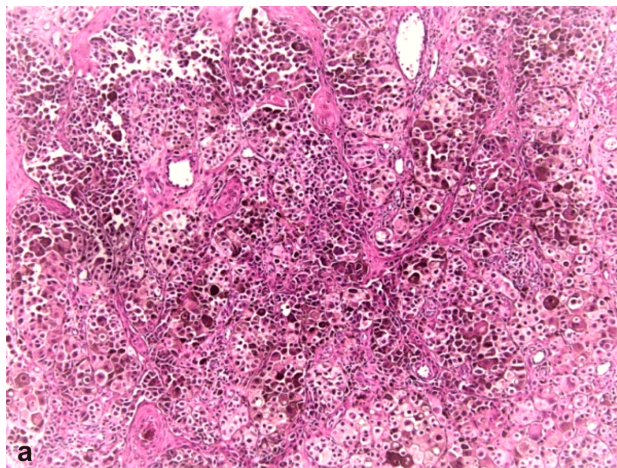


**Figure 3 – *(a) Nest of epithelioid large cells, some of them heavily pigmented, other with clear cytoplasm; significant atypia are seen; (b) Detail of an unpigmented area; morphology of tumor cells is readily visible: they are large, epithelioid, polymorphous cells, without any melanin pigment. HE staining: (a) ×100; (b) ×400.***

Immunohistochemical (IHC) examination reveals positive proliferation for melan-A and human melanoma black (HMB)-45 and negative for cytokeratin AE1/AE3 (positive in the squamous epithelium), with a Ki67 index of 30%. The final diagnosis was of nodular, ulcerated, malignant melanoma of the nasal cavity. The patient underwent six rounds of treatment with 1700 mg of Imidazole Carboxamide every three weeks. We followed-up the patient by repeating endoscopic examinations every three months, none of which revealing signs of local recurrence. The six-month post-operative CT was clear of tumor.

On September 2016 (one year after finishing chemotherapy), positron-emission tomography (PET)-CT reveals a left ethmoidal tumor, this being the reason why we decided to operate on the patient one more time, removing the tumor in an endoscopic approach (Figure 4). The result of the surgery was the complete removal of the tumor with oncological safety margins from the lateral nasal wall (Figure 5).
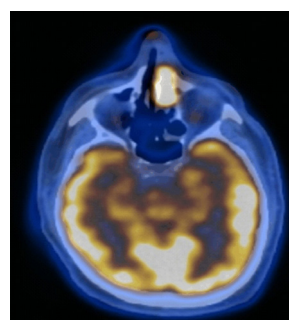


**Figure 4 – *PET-CT scan: tumoral mass metabolically active, infiltrative in the left ethmoidal cells, occupying 2/3 of the superior part of the left nasal fossa.***
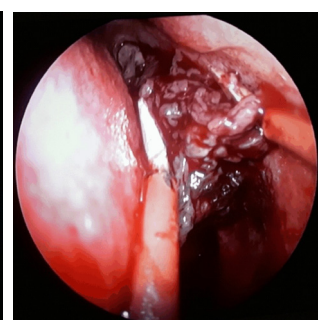


**Figure 5 – *Hemostasis with bipolar electrocautery of the tumor mass.***

The histopathological examination of the endoscopic resection pieces was performed on samples fixed in 10% formalin, included in paraffin and stained with

Hematoxylin–Eosin (HE) and the green light trichrome, Goldner–Szekely (GS). The microscopic examination of histological samples highlighted the presence of melanic cells of various sizes and shapes, with a variable content of melanomas, isolated or grouped in cell islands, diffusely disseminated or arranged nodularly in the lamina propria (Figure 6, a and b). On some exeresis pieces, there were observed some extended necrosis areas of the covering epithelium (Figure 7).

For the differential diagnosis of the tumor, there were performed various IHC examinations. Of the biological material included in paraffin, there were performed sections with a 4 μm thickness in the Microm HM350 rotary microtome, equipped with a section transfer system on a water bath (STS, microM), which were collected on the poly-L-lysine covered slides. Then, the sections followed the classical protocol: deparaffinization, hydration, demasking of specific antigens, blocking of endogenous peroxidase, followed by the blocking of non-specific sites. The sections were then incubated with primary antibodies, for 18 hours (overnight), in a fridge, at $4^0$C. The next day, there was applied the secondary biotinylated antibody for 30 minutes, at room temperature, after which there was applied the green Streptavidin–Horseradish peroxidase (HRP) (for differentiating the

reaction of the specific antigen from the melanic pigment present in the tumor cells). IHC reaction was stopped by washing in 1% phosphate-buffered saline (PBS). There followed the contrasting with Mayer's Hematoxylin, dehydration in alcohol, clarification in xylene and fixing of slides using a DPX environment (Fluka).

The antigen–antibody reaction was highlighted by a green light. For the IHC study, we used the following antibodies: anti-melan-A (clone A103, Dako, 1/50 dilution), anti-HMB-45 (clone HMB-45, Dako, 1/100 dilution), anti-Ki67 (clone MIB-1, Dako, 1/50 dilution), anti-p53 (clone DO-7, Dako, 1/100 dilution), anti-S100 (clone DO-7, Dako, 1/1000 dilution).

The IHC examination highlighted an intensely positive reaction for the immunomarkers melan-A (Figure 8) and HMB-45 (Figure 9). There was observed that some tumor cells containing melanic pigment in high quantity presented a negative reaction to the two non-specific antibodies. The reaction to the Ki67 tumor proliferation antigen was, also, intensely positive, more than 30% of the tumor cells being positive for this antigen (Figure 10). Still, the reaction for p53 was more moderate, about 10–15% of the tumor cells being positive (Figure 11). Also, a moderate reaction of the tumor cells was also observed in the anti-S100 antibody (Figure 12).
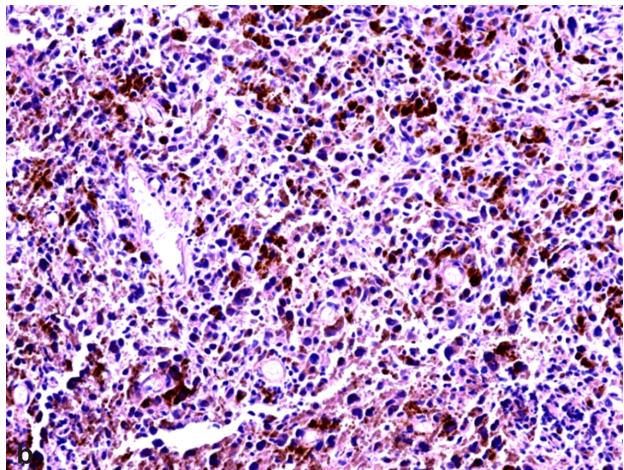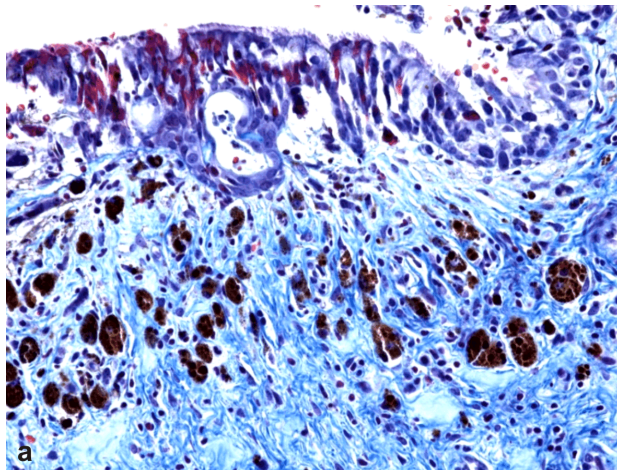


Figure 6 – (a) Respiratory mucosa with a pseudostratified ciliated, complete surface epithelium and with numerous melanocytes, isolated or grouped, present in the subjacent chorion (GS trichrome staining, ×200); (b) Extended area of melanic cells, grouped nodularly, disseminated in the chorion of the rhinosinusal mucosa (HE staining, ×100).
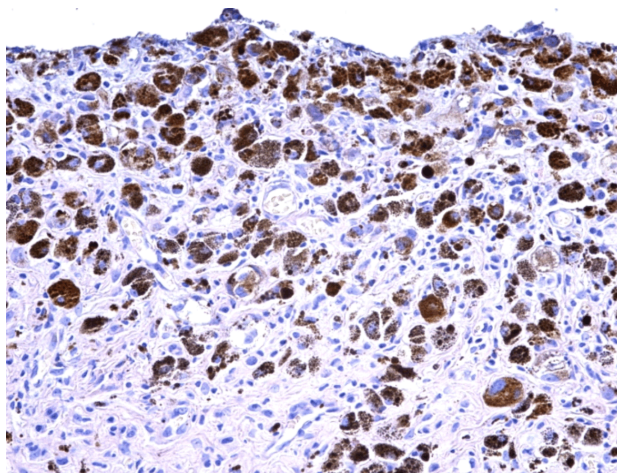

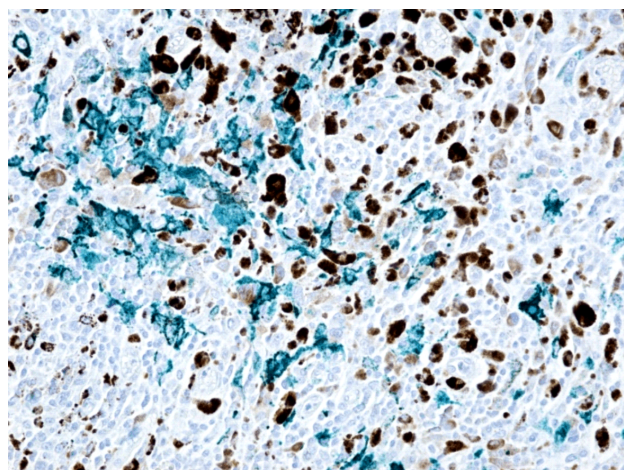
Figure 7 – Microscopic image of a tumor area, where there can be observed the necrosis of the surface epithelium (HE staining, ×200).
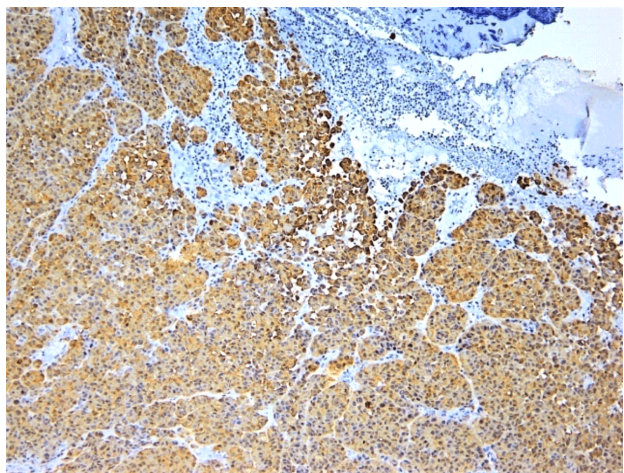
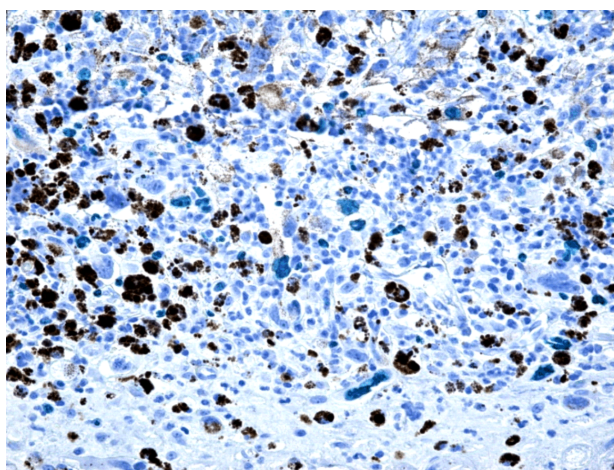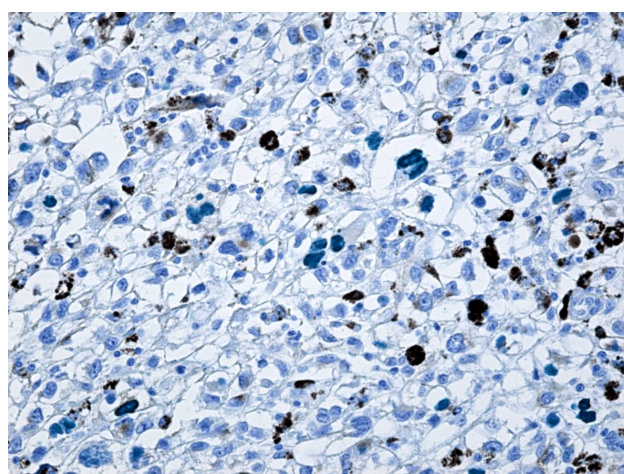Figure 8 – Tumor cells are diffusely positive for melan-A (Anti-melan-A antibody immunostaining, ×40).

**Figure 9 – *Tumor cells with an intense reaction to the anti-HMB-45 antibody (green) (Anti-HMB-45 antibody immunostaining, ×200).***



**Figure 10 – *Intense reaction of tumor cells to the anti-Ki67 antibody (green) (Anti-Ki67 antibody immuno-staining, ×200).***



**Figure 11 – *Moderate IHC reaction to the anti-p53 antibody (green) (Anti-p53 antibody immunostaining, ×200).***
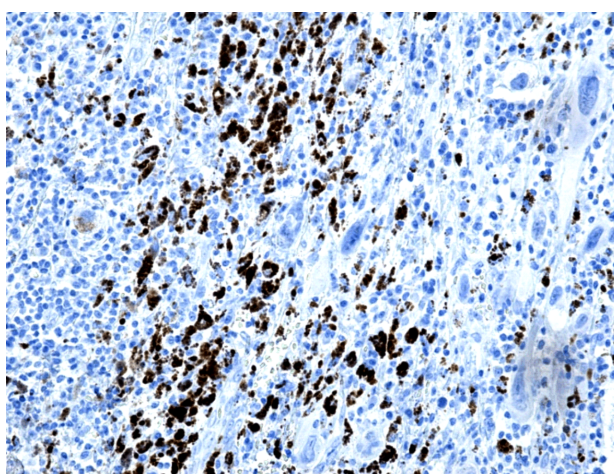


**Figure 12 – *Moderate reaction of tumor cells to the anti-S100 antibody (green) (Anti-S100 antibody immuno-staining, ×100).***

The patient's post-operatory evolution was favorable, both within the first three months post-surgery, as well as at the follow-up after another three months (the first year post-intervention), when we examined the patient through endoscopy, imaging techniques and biologically.

## ⊟ Discussion

The primary melanoma located in the nasal sinus mucosa is a rare disease, usually a terminal one, with a high rate of relapse and distance metastases [14, 15]. As far as the localization is concerned, the sinonasal malignant melanoma represents less than 1% of all the sites where it may develop. Moreover, it has an incidence of 1/1 000 000 to 1/500 000. The typical age at which it is diagnosed varies between 60–80 years, with a median of 65 years [16, 17].

Malignant melanomas originate from melanocytes, which, in turn, are derived from the neural crests. Therefore, one can deduct that the most affected areas (nasal cavity, maxillary sinus, hard palate, upper gums) are also characterized by a high density of melanocytes. Normally, melanocytes can be detected in approximately 21% of the population. Apart from the exposure to formaldehyde, other identified risk factors included

genetic mutations affecting the tyrosine kinase receptor [18].

Initial symptoms are non-specific, thus delaying the diagnosis. The most important signs are unilateral epistaxis and nasal obstruction, which is also one-sided, progressive and permanent. Other symptoms may include rhinorrhea (which may become purulent in case of an infection), headaches, epiphora (when the lachrymal apparatus is affected). Moreover, in more severe cases, facial defor-mities and sight changes may be described. Therefore, one must also take into consideration a possible ocular pathology and, eventually, a facial sensitivity defect because of cranial nerves damage. Clinical examination reveals a sessile, friable and bleeding mass, which is brown or black in color. In addition, the tumor is described as gelatinous, covered by puss and with signs of necrosis. The endoscopic surgical approach consists in a "piece-meal" tumor removal, with a thorough intra-operatory hemostasis. Moreover, when the malignant melanoma comes in contact with adjacent bone structures and nasal mucosa, the resection must be extended to nearby structures.

The majority of the tumors affect the lateral wall of the nasal cavity, followed by the nasal septum. Inter-

disciplinary examinations must be requested from the dermatology and ophthalmology departments, in order to look for a possible primary site of the tumor.

As far as imaging techniques are concerned, malignant melanomas present no particular characteristics. A CT-scan with 1 and 3 mm wide slices is required in order to identify the affected bone structures. Magnetic resonance imaging (MRI) may reveal high signal intensity in T1 sections, if there is hemorrhage present and low signal intensity in T2 sections, due to the properties of melanin. Based on the quantity of melanocytic pigment, the signal's intensity may vary. Moreover, some authors consider that the formation of free radicals are responsible for the T1 high signal intensity, while others associate this with the iron ions found in the structure of melanin [19]. The differential diagnosis includes other tumors, such as angiosarcoma, cylindroma, esthesioneuroblastoma. A PET-CT scan is recommended in order to check for distant metastasis that may be present at the time of diagnosis, as well as to monitor the evolution during the treatment.

The Ballantyne classification is the oldest one and it does not include the tumor size, extension and histology (stage I – localized lesions; stage II – single node metastasis; stage III – distant metastasis). The *American Joint Committee on Cancer* (AJCC) omits stages I and II and starts directly from stages III and IV, due to the aggressive nature of the melanoma. Prasad *et al.* suggests a classification based on the depth of the invaded mucosa (level 1 – *in situ*; level 2 – lamina propria; level 3 – in-depth) [10]. The evolution of malignant melanomas is characterized by local recurrences or by distant metastasis in lymph nodes and in other organs, thus representing one of the most dangerous forms of sinonasal cancer.

Like in other cancers, the histopathological and IHC diagnosis are essential [20, 21]. Most frequently, the usual HE and GS trichrome stainings manage to highlight the melanic cells. Other times, there is used the Fronterra–Masson staining, due to the high affinity of tumor cells for these stains.

A couple of histological parameters must be assessed in order to obtain a correct and complete diagnosis: melanocytic pigment, tumor necrosis, vascular invasion, tumor ulceration, atypical mitoses, all of these indicating an unfavorable prognosis. However, due to the resemblance to the undifferentiated sinonasal carcinoma, one might find it difficult to distinguish it from the malignant melanoma. IHC examination is required in order to confirm the diagnosis by highlighting the S100 protein, vimentin (VIM), HMB-45, melan-A, CD45, melanoma-associated antigen recognized by T-cells (Mart)-1, tyrosinase and microphthalmia transcription factor (MITF), Ki67 [22–24].

The majority of the nasal malignant melanomas mainly require surgery. Based on the tumor size, the ENT specialist decides on the best surgical approach, either external or endoscopic. However, endoscopy might prove to be too challenging for those who do not have enough experience. It is of utmost importance that the tumor resection is performed with oncological safety margins. Therefore, a negative safety margin may be defined as being larger than 5 mm on the histopathological examination. Since there are several controversies regarding metastatic lymphadenopathies, at the moment there is no protocol certifying the necessity of a radical cervical dissection.

The indications of post-operatory radiotherapy vary significantly as the tumor is characterized by a reduced radiosensitivity, but there are studies that confirm the fact that a certain dose of radiations (>50 Gray) could have optimal results. There are several techniques of radiotherapy, such as neutron beams, gamma-knife, that proved to be especially useful in the treatment of small tumor recurrences [10]. Chemotherapy is only recommended in case of surgical failure and to patients with multiple metastases. A couple of multimodal treatment courses have been tested, which involved the association of chemotherapy with immunotherapy [interleukin-2 (IL-2) or interferon), but they are still under review [18]. There have also been reported cases of adjuvant treatment with bacillus Calmette–Guérin (BCG) [19].

Future strategies involve defining a staging algorithm, as well as using molecular markers such as S100 and tyrosine kinase for identifying patients with an increased risk of melanoma. In addition, the recent discovery of a mutation developed by the BRAF oncogene (v-Raf murine sarcoma viral oncogene homolog B) from melanocytes could mark a future primary target for therapies.

The most important prognostic factor is the presence of metastases at the moment of diagnosis. Due to its rarity and, thus, the lack of extensive studies, the sinonasal malignant melanoma presents an unfavorable prognosis, even worse than when localized strictly on the skin. The five-year mark statistics depend heavily on the site and, therefore, the nasal localization is characterized by a 30% survival rate, while the sinus localization determines a less than 1% survival rate. Some authors affirm that mucosal melanomas tend to be more aggressive and with a worse prognosis than the cutaneous malignant melanomas: only 10–15% survival rate at five years [25]. The Ki67 antigen represents a marker of proliferation and, when its values are below 35%, the patients' prognostic becomes more favorable [17].

In our case, the patient was admitted in the hospital with epistaxis and chronic nasal obstruction. Macroscopically, the tumor was brown, covered in purulent secretions and bleeding. The PET-CT revealed a metabolically active mass occupying the left ethmoidal cells, extending in the nasal cavity. Complementary examinations for melanomas of the skin turned out negative, thus confirming the fact that it was a primary tumor. The patient was classified as stage II Ballantyne, or as T3N1M0 according to AJCC.

Microscopically, the patient presented all the negative prognostic factors: vascular invasion, tumor proliferation in the safety margins, accumulation of melanocytic pigment, ulcerations. IHC examination revealed positive tumor proliferation for melan-A, HMB-45, S100 protein, Mart 1 and turned out negative for CD45, with a Ki67 index of 30%.

Considering all things, based on microscopy, IHC, local recurrences, we can sum up that the patient had an unfavorable prognostic despite the endoscopic surgery that completely removed the tumor with oncological safety margins and also associating middle maxillectomy and left anterior ethmoidectomy.

## ⊟ Conclusions

Early diagnosis of the malignant melanoma represents the most important factor that influences the prognostic.

Therefore, any patient more then 50 years of age that presents with chronic unilateral nasal obstruction and epistaxis, should be thoroughly investigated for a melanoma of the nasal cavity. The gold standard for diagnosis is strictly histopathological and IHC. Treatment must be chosen carefully depending on the tumor's localization, extension and its IHC parameters. Last but not least, the patient's quality of life must always be taken into consideration when deciding a course of treatment. The future holds the further development of biological and immunomodulatory treatments.

### Informed consent

Written informed consent was obtained from patient who participated in this study.

### Conflict of interests

No conflict of interests was declared by the authors.

### Financial disclosure

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