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Mucosal melanoma of nasal cavity in 89–year-old woman – case report and review of the literature

Czerniak błony śluzowej jamy nosowej u 89-letniej kobiety – opis przypadku i przegląd literatury

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Manuscript Preparation
E – Literature Search
F – Funds Collection

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ABSTRACT: Mucosal melanoma constitutes 1,3–1,4% of all melanomas. 25–50% of these cases occurs in head and neck region. Primary melanoma of the head and neck mucous membranes is most often diagnosed in the nasal cavity (50%), maxillofacial region (20%), oral cavity (17%), and then nasopharynx, casuistic in the larynx. Recurrent nasal bleeding and persistent nasal obstruction are the most frequently presented symptoms. In comparison to skin melanoma, mucosal melanoma is diagnosed 1 decade later and has different etiology. It is usually diagnosed at an advanced stage when metastases are already present. Approximately 20% of patients have metastases to the lymph nodes at diagnosis and 10% distant metastases. Histopathological diagnosis is based on the detection of malanocyte markers: S-100, Melan-A, HMB-4, MITF-1 and vimentin. Mucosal melanoma can be misdiagnosed as olfactory neuroblastoma. In ⅓ of the cases, melanoma of mucous membranes occurs in the amelanotic form. Treatment of choice is radical resection and adjuvant radiotherapy. In the head and neck region radical disscection may be a challenge for operating surgeon because of closeness of anatomical structures and preservation of function. In advanced stadium immunomodulatory treatment can be applied. Overall 5-year survival is estimated for 12–44%. Based on presented case authors note the necessity of inclusion additional factors in geriatric oncology and generally discuss the diagnosis and treatment of mucosal melanoma.

KEYWORDS: mucosal melanoma, nasal obstruction, recurrent bleeding

STRESZCZENIE: Czerniak błony śluzowej stanowi 1,3–1,4% wszystkich czerniaków. 25–50% z nich występuje w regionie głowy i szyi. Pierwotny czerniak błony śluzowej głowy i szyi najczęściej rozpoznawany jest w: jamie nosowej (50%), masywie szczękowo-twarzowym (20%), jamie ustnej (17%), następnie w nosogardle oraz kazuistycznie w krtani. Zazwyczaj prezentuje się następujące jego objawy: nawracające krwawienie z nosa i utrzymujące się upośledzenie drożności. W porównaniu do czerniaka skóry, czerniak błony śluzowej występuje o dekadę później; ma też inną etiologię. Zwykle rozpoznaje się go w zaawansowanym stadium, gdy obecne są przerzuty. U około 20% pacjentów w momencie rozpoznania stwierdza się przerzuty do węzłów chłonnych, a u 10% – odległe przerzuty. Rozpoznanie histopatologiczne opiera się na wykryciu markerów malanocytów: S-100, Melan- A, HMB-45, MITF-1 i wimentyny. W ⅓ przypadków czerniak błony śluzowej występuje w formie amelanotycznej. Może być on mylony z nerwiakiem węchowym zarodkowym. Leczeniem z wyboru jest radykalna resekcja z następową radioterapią. Z uwagi na bliskość anatomiczną ważnych struktur, usunięcie guza zlokalizowanego w obrębie głowy i szyi w całości z zachowaniem funkcji czynnościowej stanowi wyzwanie dla operatora. W zaawansowanym stadium stosuje się leki immunomodulujące. Ogólne 5-letnie przeżycie kształtuje się na poziomie 12–44%. Na podstawie studium przypadku, autorki zwracają uwagę na konieczność uwzględnienia dodatkowych czynników w onkologii geriatrycznej oraz ogólnie omawiają diagnostykę i leczenie czerniaka błony śluzowej.

SŁOWA KLUCZOWE: czerniak błony śluzowej, nawracające krwawienia, niedrożność nosa

ABBREVIATIONS

AJCC – American Joint Committee on Cancer
CT – computed tomography
IHC – immunohistochemistry
IMRT – Intensity Modulated Radiation Therapy
IO – Institute of Oncology
MM – mucosal melanoma
MR – magnetic resonance imaging
NCCN – National Comprehensive Cancer Network
ONB – olfactory neuroblastoma
PET-CT – positron emission tomography combined with computed tomography
SLNB – sentinel node biopsy
UICC – Union for International Cancer Control
VMAT – volumetric modulated arc therapy

INTRODUCTION

Malignant melanoma is a cancer that begins in the melanocytes, which in embryonic development differentiates from the neuroectoderm and neural crest, and then migrates to the basal layer of the epidermis and mucous membranes [1, 2]. Mucosal melanoma, or MM accounts for 1.3–1.4% of all melanomas; 25–50% of these cases occur in the head and neck region [3]. The most common sites of primary mucosal melanoma of the head and neck are the nasal cavity (50%), maxillofacial region (20%), oral cavity (17%), followed by the nasopharynx, casuistically in the larynx. The density of melanocyte distribution affects predominance. Prevalence in the nasal cavity and oral cavity is associated with better prognosis (5-year survival of 31% and 12.3%, respectively), melanoma within the paranasal sinuses is associated with a worse prognosis (5-year survival – 0%) [3]. The main symptoms include recurrence of bleeding and impaired nasal patency. Macroscopically, MM appears as a polypoid tumor with a color ranging from white to gray, brown to black. Histopathological diagnosis is based on the detection of melanocyte markers: S-100, Melan-A, HMB-45, MITF-1 and vimentin [1, 4]. In ⅓ of cases, mucosal melanoma occurs in amelanotic form [3]. Etiological factors have not been precisely defined. The prevalence of mucosal melanoma is not associated with solar radiation, papilloma virus or herpes simplex virus. Smoking may predispose to oral melanoma [5], and exposure to formaldehyde may predispose to melanoma of the paranasal sinuses [6]. The patient age at diagnosis is between 60 and 80 years old, with the highest frequency between 65 and 70 years old [7]. Overall survival at 5 years is around 12–44%. The problem is the late diagnosis and aggressive nature of the cancer [8]. About 20% of patients are diagnosed with lymph node metastases at the time of diagnosis, and 10% of patients have distant metastases (to the lungs, liver, bone, brain, less often to the adrenal glands) [7, 3].

Esthesioneuroblastoma, olfactory neuroblastoma, or ONB is a rare malignant tumor that arises from an embryonic ectoderm from which the sense of smell organ develops. It accounts for 2–3% of nasal and sinus tumors. ONB can occur at any age, but the peak of diagnosis falls on the 2nd and 6th decades of life and affects both sexes equally [17]. The incidence in the population is 0.4 cases per million people [7]. Differential diagnosis of ONB includes: melanoma, sinonasal undifferentiated carcinoma, sinonasal neuroendocrine carcinoma, small-cell carcinoma, pituitary adenoma, rhabdomyosarcoma and lymphoma [10]. Immunohistochemical examination shows positive results for CK/AE3, NSE, S-100 and sometimes for GFAP [24].

Tab. I. T – primary tumor. TNM classification (according to AJCC 2017).

T3	Disease is limited to the mucosa.
T4a	Moderately advanced disease – cancer invades deep tissue, cartilage, bone, or skin.
T4b	Very advanced disease – the cancer infiltrates any of the following structures: brain, dura mater, skull base, cranial nerves (IX, X, XI, XII), area of the rumen, carotid artery, prevertebral space or mediastinal structures.

Tab. II. N – regional lymph nodes. TNM classification (according to AJCC 2017).

NX	Regional lymph nodes cannot be assessed.
N0	No metastasis in regional lymph nodes.
N1	Metastasis in regional lymph nodes.

Tab. III. M – distant metastases. TNM classification (according to AJCC 2017).

M0	Distant metastasis absent.
cM1	Distant metastasis present.
pM1	Distant metastasis present, confirmed by microscopy.

CASE STUDY

A patient of 89 years old was admitted to the ENT Department of the Provincial Specialist Hospital No. 4 in Bytom due to a periodically bleeding tumor completely filling the right nasal passage. Recurrent nosebleeds have persisted for 3 months since the patient was recommended anticoagulant prophylaxis after a second myocardial infarction. Previously, the patient did not report any impaired nasal patency or bleeding.

She had a history of myocardial infarction (2016 and 2018), chronic myocardial insufficiency NYHA II, hypertension, type 2 diabetes, chronic obstructive pulmonary disease, status post pulmonary tuberculosis, left breast cancer T2N0Mx after radiation therapy. The patient has been treated with hormone therapy since January of 2017. During a visit to the Department of Cardiology in 2016, in addition to lesions after a history of tuberculosis, a chest X-ray revealed a blotch fibrous lesion in the middle field of the left lung. Over the years 2016–2019, subsequent chest x-ray and CT scans revealed no progression of the lesion and therefore did not raise suspicion of metastasis.

A spherical, easily bleeding tumor emerging from the anterior part of nasal septum was excised under local anesthesia. Heavy bleeding was managed with bipolar coagulation. Histopathological examination of a macroscopically gray-brown tumor revealed a malignant tumor tissue, about 70% of the tumor pattern with necrotic lesions. Diagnostics was extended to include immunohistochemistry: S-100 (+), Vim (+), CK 5/6 (-), CK AE 1/AE3 (-). In correlation with clinical data, melanoma malignum showing focal surface ulceration, pT4, mitotic activity 1/mm^2 was diagnosed.

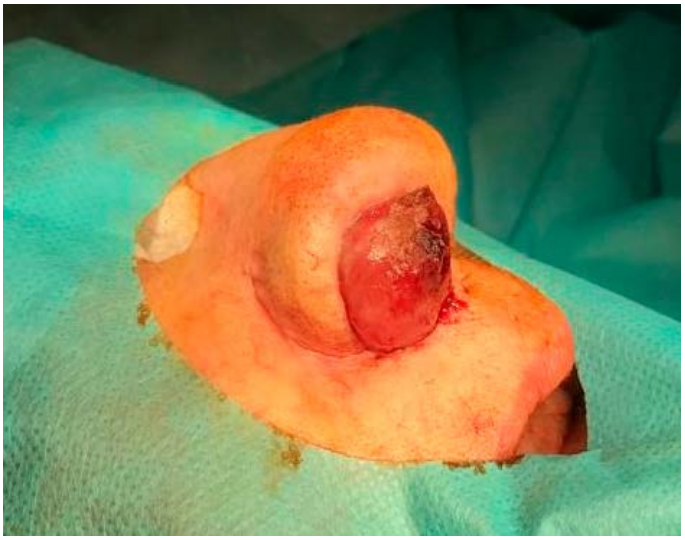

Fig. 1. An intraoperative photography of the tumor protruding from the right nostril.

Diagnostics were broadened to CT of the head and neck with contrast. The presence of residual tumor mass, suspicious lymph nodes, pathological contrast enhancement and bone destruction were excluded.

The patient was referred for further treatment at the Institute of Oncology (IO), she waited for PET-CT without any ailments. On February 7, 2019 she had a planned implantation of an artificial lens in the right eye due to cataract. On February 11, 2019, she suffered a petrochanteric fracture of the left femur. The patient was treated surgically and took increased doses of anticoagulants.

From February 2019, impaired nasal patency gradually increased, until the right nasal passage was completely obstructed with the protrusion of a bluish tumor from the right nostril (Fig. 1.). The tumor bled periodically after irritation. May 7, 2019 PET-CT revealed foci of increased uptake of fluorodeoxyglucose (FDG) SUVmax 3.97 in the parenchymal density filling the right nasal passage, the most intense in the lower part of the nasal passage, the mass protruded into the ethmoidal sinus on the right side.

Craniofacial CT revealed: in the right nasal passage a tumor of 45 mm × 20 mm × 27 mm (AP × CC × SD) (Fig. 2.), filling the end section of the lower nasal passage, not separable from the lower nasal turbinate and the inner contours of the passage wall. No signs of bone destruction were found at tumor level. The nasal septum slightly shifted to the left. In addition, no signs of pathological enhancement visible in the mouth, pharynx and larynx. No enlarged, radiologically suspicious lymph nodes were found.

The patient in the T4aN0M0 stage was qualified for surgery. May 24, 2019, a bluish, fragile, bleeding tumor together with the cartilaginous and bony part of the nasal septum and with a fragment of the right lower nasal turbinate was excised with perioperative antibiotic prophylaxis from lateral rhinotomy approach (Fig. 3.). During the procedure, a second tumor with a polyp-like appearance, occupying the upper nasal passage and ethmoid bone on the right side was visualized – the tumor was excised completely. The surgery course was uneventful. The bleeding was managed

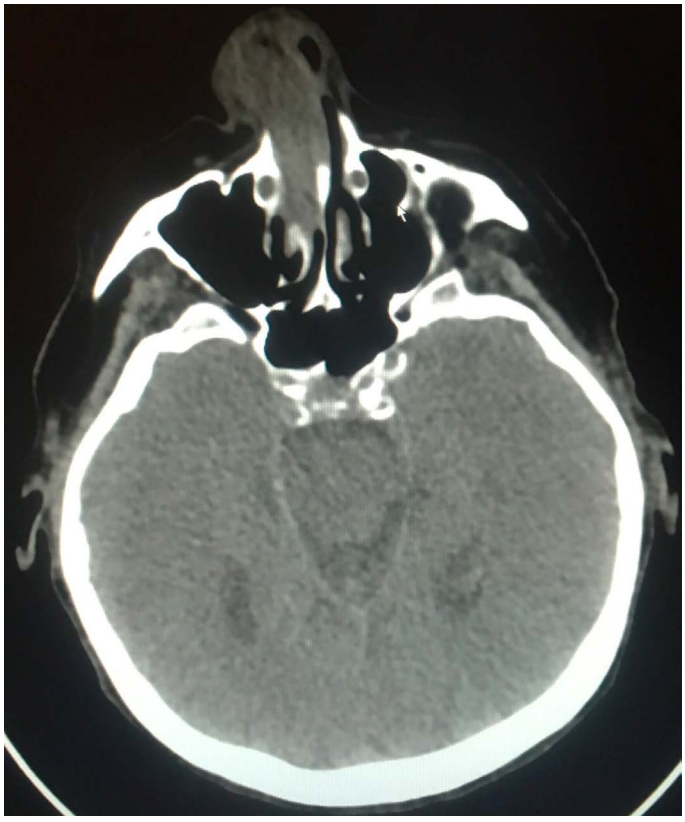

Fig. 2. Tumor of the right nasal cavity in CT.

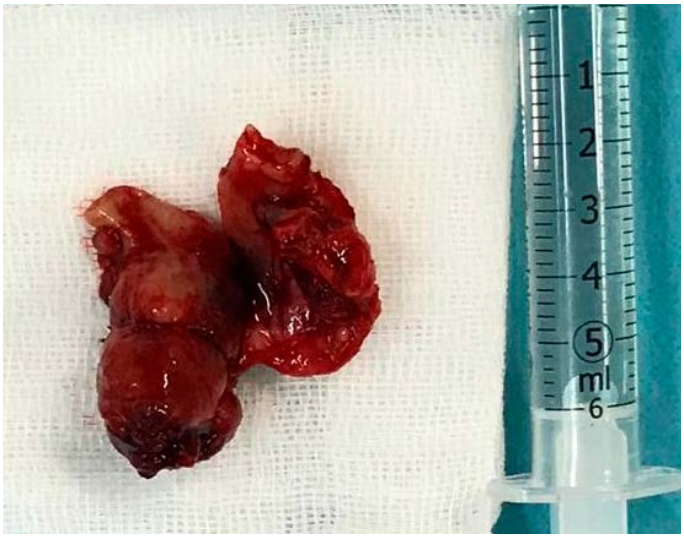

Fig. 3. Macroscopic appearance of the excised tumor.

with coagulation and nasal tamponade. After the procedure, the skin wound healed per primam, the nasal cavity required regular cleansing of crusted discharge. The patient was given 0.9% NaCl intranasally, Alantan ointment and Chlorocyclinum 3%. The external nose did not collapse (Fig. 4.).

Description of histopathological examination: in correlation with clinical data, the picture may correspond to a recurrence of melanoma, however, the phenotype is more characteristic of olfactory neuroblastoma. A polypoid tumor was not found in the tumor pattern. After pathomorphological consultation in tertiary referral

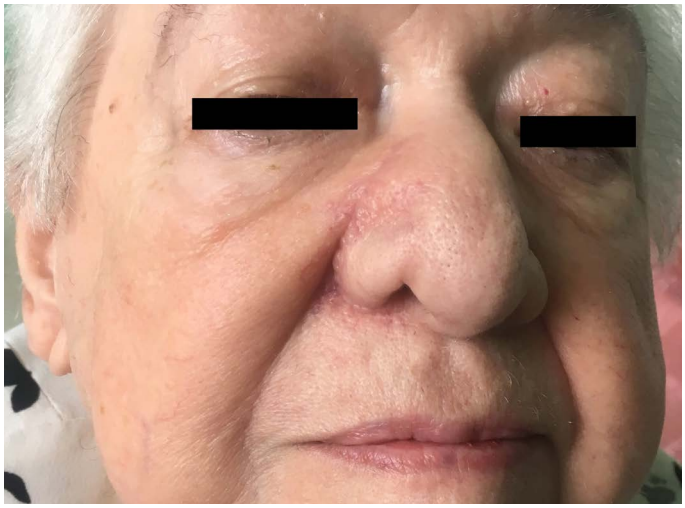

Fig. 4. A properly healed skin wound.

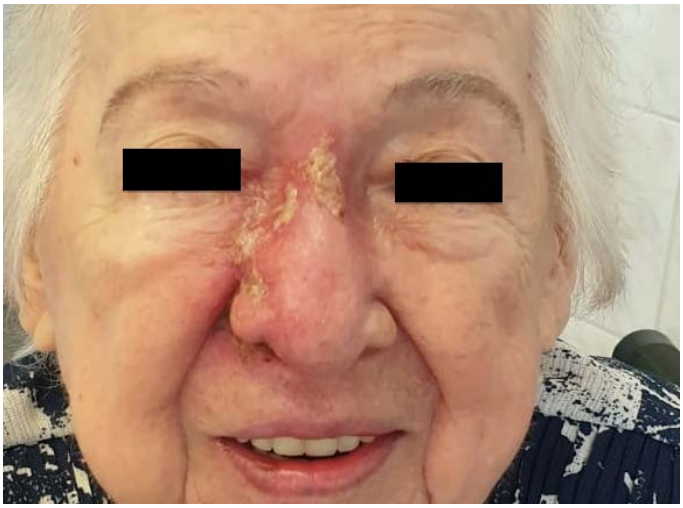

Fig. 5. Radiation-induced reaction of skin of the nose.

hospital based on the histological picture and results of the IHC preparations [CHR (-), HMB-45 (+) focally, Ki-67 (+) 60%, Melan A (+), S-100 Protein (+), Synaptophysin (-)] recurrence of melanoma was confirmed.

The patient underwent outpatient treatment with FFP 6MV photons in the right nasal passage with a df 2.0 margin, total dose 56.0 Gy of the planned 60.0 Gy. Due to the increased radiation-induced cutaneous skin reaction, the total dose was not given. Beside this, the treatment was tolerated well (Fig. 5.). Two months after the end of irradiation during an inspection in the ENT clinic, complete healing of the nasal skin and normal nasal patency were found. The nasal cavity was covered with a smooth mucosa without signs of recurrence.

DISCUSSION

Recurrent nosebleeds and persistent impaired patency should prompt to referring the patient to a specialist. Anticoagulation therapy in burdened patients of advanced age increases the risk of bleeding, but the coexistence of these factors does not exempt from the differential diagnosis of recurrent bleeding.

Geriatric oncology focuses on patients over 65; it is based on the principle of maintaining patient autonomy, obtaining clear clinical benefit of the patient during treatment, harmlessness and justice in decision making, which ensures an individual approach taking into account physical age measured by means of the Comprehensive Geriatric Assessment [11]. In the presented case, the patient's age exceeded the average age of diagnosis of melanoma and olfactory neuroblastoma. Cases of misdiagnosis of ONB have already been reported in the literature, Cohen cites twelve cases referred to a 3rd degree reference unit, where neuroma was confirmed in only two patients, which significantly changed the treatment plan [10]. Complete excision of the lesion during the first operation and the starting point on the nasal septum most likely had a positive effect on inhibiting the disease process, although recurrence occurred after 7 months from the first operation. Due to additional burdens, the patient returned for re-examination only when the symptoms of tumor regrowth had intensified, despite this, a standardized treatment regimen was used.

Diagnosis of maxillofacial tumors includes endoscopic examination, CT and MR of the head, a search for possible metastatic foci confirmed by fine needle aspiration biopsy. The NCCN (National Comprehensive Cancer Network) currently does not recommend elective surgery to remove cervical lymph nodes in melanoma of the nasal cavity and paranasal sinuses [12]. Sentinel node biopsy in melanomas of the head and neck region is a method is increasingly used, but it is not a diagnostic standard [13]. Prinzen et al. after a retrospective study of 50 patients with MM point to SLNB as an accurate predictive tool since patients with a negative SLNB score remained free from distant and regional disease [14].

Macroscopically, the tumor usually has a white to gray, brown to black polypoid appearance. Histopathological diagnosis is based on the detection of melanocyte markers: S-100, Melan-A, HMB-45 i MITF-1 and vimentin [1, 4]. In ⅓ of cases, mucosal melanoma occurs in amelanotic form [3]. Classification of mucosal melanoma of the head and neck, consistent with the eighth edition of the TNM classification prepared by the AJCC is presented in Tab. I.–III. [15]. It coincides with the TNM Classification according to UICC [16].

Treatment of mucosal melanoma of the nasal cavity and paranasal sinuses is based on radical tumor resection. In retrospective studies comparing endoscopic-guided surgery with intranasal access and extranasal approach, there were no significant differences in local recurrence, relapse-free survival and overall survival. The advantages of intranasal access include a shorter time of surgery (and hospitalization), less intraoperative blood loss, a better cosmetic effect, and better quality of life after surgery [8, 17]. External approaches include: lateral rhinotomy (Moure's incision), Weber-Ferguson incision and Denker operation [17, 18]. Obtaining free surgical margins in the head and neck region can be difficult, which results in a high rate of local recurrences estimated at 38–46.6% and distant recurrences of 34.6–66% [19]. Most authors recommend adjuvant radiotherapy for the tumor area and regional lymph nodes IMRT (Intensity Modulated Radiation Therapy) [3, 8] and VMAT (Volumetric Modulated Arc Therapy) [14]. Radiation

therapy is associated with better local control despite the initially higher stage of disease and positive surgical margins [19, 14]. Further clinical studies of mucosal melanoma should focus on molecular diagnostics, assessment of regional metastases and multifocality, followed by vascular invasion, tumor polymorphism, population factors and necrosis assessment [20].

Studies show that in 16–25% of cases of mucosal melanoma, there occurs aberration of c-KIT receptor (CD117), a similar phenomenon occurs in acral melanoma; these types of melanoma are not associated with UV exposure. In skin melanoma, c-KIT mutations are observed only in 5–10% of cases [5, 21]. BRAF gene mutations are also observed; in mucosal melanoma they are described in about 10% of cases, while in melanoma of the skin they are found in about 50% of cases; NRAS mutations are reported in 25% of cases of mucosal melanoma [21]. Prinzen et al. found overexpression of PD-L1 in only 13% of subjects with MM; however, in patients without a confirmed mutation, therapy with the PD-L1/PD-1 inhibitor may still be considered, as patients with skin melanoma without confirmation of the above-mentioned mutations also benefited from its use [14]. Based on a study of a group of 75 patients with mucosal melanoma, Shaefer et al. found the highest response rate and the longest progression-free survival when using pembrolizumab (PD-1 inhibitor) in combination with ipilimumab (anti-CTLA-4 drug) [22]. Nivolumab in combination with ipilimumab has been shown to be more effective than either of these medicines alone [6].

A clinical trial currently available in Poland for treatment melanomas of the skin or mucosa includes immunomodulatory drugs – ipilimumab, pembrolizumab and nivolumab. The eligibility criterion is histological confirmation of melanoma of the skin or mucosa in stage III (inoperable) or IV.

CONCLUSIONS

1. Mucosal melanoma of the head and neck is usually diagnosed at an advanced stage;

2. The late diagnosis and aggressive course of the disease impedes the radical nature of surgical treatment; adjuvant radiotherapy is used;

3. For people over 65 years of age, the Comprehensive Geriatric Assessment should be considered for appropriate qualification for oncological treatment;

4. Research is ongoing on the treatment of mucosal melanoma using immunomodulating therapy.

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