Fortuitous discovery of melanomas in the ENT Department – a histopathological and immunohistochemical study

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Abstract
The melanoma, having its origin in the melanocyte cells, is one of the most aggressive forms of skin cancer in the world with one of the highest rates of brain metastasis. The incidence of cutaneous melanoma in the Mediterranean countries varies from three to five cases/100 000 people/year. Its prognosis is based on an early diagnosis. Sinonasal mucosal melanoma (SNMM) is an extremely rare tumor, accounting for 0.3–2% of all melanomas. The non-specific symptomatology is often delaying the presentation of the patient at the hospital and therefore the diagnosis. The SNMM is a highly aggressive tumor, and the presence of metastasis at the diagnosis usually implies a poor prognosis. The management of the melanomas requires a precise pre-therapeutic assessment and a multidisciplinary approach for the diagnosis, with surgical treatment or radiotherapy required in order to ensure a better quality of life. In this paper, we retrospectively analyzed two cases of mucosal melanoma and one case of cutaneous melanoma of the nose.

Keywords: cutaneous melanoma, primary mucosal melanoma, immunotherapy.

Introduction
Melanoma is a rare malignancy arising from the melanocytes (cells of neuroectodermal origin), with or without melanin pigment. Due to the abundance of cells in the skin and its ultraviolet (UV) exposure, the melanoma is usually localized in the skin, but it is also found in areas that have not been exposed to sunlight.

Cutaneous melanomas are aggressive tumors with a large disparity between the incidence and prognosis ratio among the countries, with the mortality remaining high. Unlike for the mucosal melanoma, UV exposure is known as a related factor in the incidence of cutaneous melanoma in genetically predisposed patients.

The cutaneous melanoma is classified in four subtypes: the superficial spreading melanoma, the lentigo maligna melanoma, the acral lentiginous melanoma and the nodular melanoma [1]. Dermatoscopy can indicate the malignant potential of the lesion in an early stage, detecting the tendency of the melanomas to change with time [2]. A complete evaluation of the patients is mandatory, in order to identify the presence of metastasis.

The histological diagnosis follows the thickness of the lesion, the mitotic rates, the presence of necrosis and ulceration and contributes to the staging of the disease following the American Joint Committee on Cancer (AJCC) Classification [3]. A higher frequency of v-Raf murine sarcoma viral oncogene homolog B (BRAF) and neuroblastoma RAS viral oncogene homolog (NRAS) mutations have been found in some types of cutaneous melanomas [1]. The testing of these mutations should be considered in the patients with advanced disease.

The treatment of the cutaneous melanoma is based on the stage of the disease. The mainstay of treatment remains the surgical excision with wide margins, but treatment targeted algorithms with monoclonal antibodies are still evolving [2]. Radiotherapy can be used for better local control [4]. The patients with cutaneous melanoma have a risk of relapse, and the follow-up is mandatory.

The mucosal melanoma was first reported by Weber, in 1856 [5], followed by Lucke, in 1869 [6] and Viennois, in 1872 [7]. It is an extremely aggressive tumor, with unknown risk factors and great propensity to metastasize and recurrence.

Because of the highly variable clinical presentation and the rapid progression of the disease, the patients with melanomas of the paranasal sinuses are usually diagnosed at a more advanced stage. Metastases can be found in lungs, brain, lymph nodes, bone and liver [8]. The presence of the metastases carries a poor prognosis.
The most important factor in the diagnosis is represented by the excision-biopsy of the tumor and the immunohistochemical (IHC) exams revealing a high expression of S100 protein and melanoma antigen recognized by T-cells 1 (MART-1/Melan A), anti-human melanoma black 45 (HMB45) antibody, microphthalmia transcription factor (MITF) and neuron specific enolase. The literature suggests an elevated frequency of c-KIT mutations in 40% of mucosal melanomas [9].

The achromic melanoma is a diagnostic challenge for the clinicians. The presence of a non-pigmented lesion can lead the clinician to suspect other benign diseases, and to misdiagnose the achromic melanoma [10].

The radio-imagistic exams play an important role in staging and follow-up of the disease. The computed tomography (CT) identifies the expansion to the bone structures and the presence of the osteolysis. In order to finely identify the local expansion to the sinuses and cavities, magnetic resonance imaging (MRI) is used. For the extension to other structures in the body, a positron emission tomography (PET)–CT is recommended.

The treatment decision of melanomas of the nasal cavities is taken by a multidisciplinary team and is based on the staging of the disease. The two staging systems which can be used are: AJCC Classification and Ballantyne system. The complete surgical excision is the mainstay of the treatment in localized disease and in the case of local recurrence. When surgical treatment is unfeasible, the treatment of choice is radiotherapy for adjuvant or palliative intent, but it makes no improvement in survival rate [11, 12]. A representative feature of the melanomas of the nasal cavity and paranasal sinuses are the early and frequent relapses of the tumor.

**Aim**

The aim of this paper was to emphasize the necessity of early diagnosis of this disease, by using the description of two confirmed cases of mucosal melanoma and one case of cutaneous melanoma, allowing enhanced rates of early detection.

**Patients, Materials and Methods**

The current paper presented two cases of sinonasal mucosal melanoma (SNMM) and one case of cutaneous melanoma of skin nasal region which were diagnosed in Department of Ear, Nose & Throat (ENT), Emergency City Hospital, Timișoara, affiliated with the Victor Babes University of Medicine and Pharmacy, Timișoara, Romania. The eligible patients for this paper were selected from the database of the hospital and the following inclusion criteria were used: patients older than 18; available pathological report of the tumor with a diagnosis of melanoma, highlighted using morphological histological stains and sustained by immunohistochemistry.

The demographic data of the patients, their biological investigations and data related to their medical background were taken from the patient observation sheet.

The patients were biopsied in ENT Department of the Hospital between January 2015 and March 2019. The harvested specimens were fixed in 4% (v/v) neutral buffered formalin, sent to Service of Pathology and processed with usual histotechnical technique. The 4 μm-thick sections were cut using a semi-automated Leica RM2235 rotary microtome, displayed on SuperFrost™ microscope slides and stained with Hematoxylin–Eosin (HE). The histopathological (HP) diagnosis was completed using IHC reactions for further antibodies: anti-Ki67 (monoclonal mouse anti-human Ki67, clone MM1, 1/200 dilution, Novocastra™, Leica Biosystems), anti-S100 protein (polyclonal rabbit anti-human S100 protein, clone EP32, 1/100 dilution, Novocastra™, Leica Biosystems), anti-HMB45 (monoclonal mouse anti-human HMB45, clone HMB45, 1/60 dilution, Novocastra™, Leica Biosystems), anti-Melan A (monoclonal mouse anti-human Melan A, clone A103, 1/50 dilution, Novocastra™, Leica Biosystems), anti-CD117 (monoclonal mouse anti-human CD117, clone EP10, 1/200 dilution, Novocastra™, Leica Biosystems), anti-CD99 (monoclonal mouse anti-human CD99, clone PCB1, 1/50 dilution, Novocastra™, Leica Biosystems), anti-breast cancer-associated protein-1 (BAP-1) (polyclonal rabbit anti-human BAP-1, clone BAP-1, 1/100 dilution, Inviotrogen, Santa Cruz Biotechnology), anti-CD117 (monoclonal rabbit anti-human CD117, clone EP10, 1/200 dilution, Novocastra™, Leica Biosystems), anti-cytokeratin (CK) AE1/AE3 (monoclonal mouse anti-human CK AE1/AE3, clone AE1/AE3, 1/100 dilution, Novocastra™, Leica Biosystems), anti-protein gene product 9.5 (PGP9.5) (monoclonal mouse anti-human PGP9.5, clone 10A1, 1/40 dilution, Novocastra™, Leica Biosystems).

All the patients signed an informed consent to approve the participation in this study and signed the Patient Informed Consent and the Consent of Ethics Committee from Emergency City Hospital, Timișoara. The Ethics Committees of both Victor Babes University of Medicine and Pharmacy and of Emergency City Hospital, Timișoara, approved the study.

**Case presentations**

**Case No. 1**

An 81-year-old male patient was hospitalized in December 2015 after the appearance of a mass at the tip of the nose and the left nasal wing for about one year prior the hospitalization.

The physical examination showed a pigmented macular tumor formation, located at the tip of the nose and the left nasal wing, with dimensions of 4/5 mm, with a halo of brown, macular discoloration, painless and without inflammation signs. Lateral cervical lymphadenopathy was absent.

The patient was known with hypertension under medical treatment, without any other significant pathological personal history. He did not smoke and consumed alcohol occasionally.

Biological parameters of the patient comprised on: erythrocyte sedimentation rate (ESR) 20 mm/h, hemoglobin (Hb) 12.8 g/dL, hematocrit (Ht) 41.3%, serum creatinine 1.8 mg/dL, chest radiography – normal X-ray image. Exhaustive imaging was performed without revealing the presence of metastases.

Under local anesthesia, excision of the tumor was performed with oncological free tissue margins. The reconstruction of the nose was done using a skin graft from the ventral forearm.
The histological examination on HE-stained slides revealed a malignant tumor proliferation with mixed cellularity, composed of fusiform cells with heterochromatic nucleus and epithelioid cells with vesicular nucleus and eosinophilic macronucleoli. The tumor cells were disposed in nests and islands in the superficial dermis, with pagetoid spreading through the entire epidermis, from the basal cell layer to the granular layer, and affecting also the epithelial sheath of the hair follicle, descending in a continuous lentiginous manner alongside the basal membrane and basal cells. The tumor cells infiltrated the superficial dermis reaching the level of the superficial vascular plexus. The tumor was not ulcerated. The Clark level was III and the Breslow index was 1.2 mm. Associated extensive lesions of actinic elastosis were identified. The diagnosis of superficial spreading melanoma in the vertical growth phase was signed out. Excision was performed with free oncological margins.

The patient was advised against UV exposure, and the yearly follow-up revealed favorable evolution (Figures 1–4).

**Case No. 2**

A 70-year-old female patient was hospitalized in March 2016, with right unilateral nasal obstruction and mucopurulent nasal discharge from the right nasal fossa. The patient had no other pathological history and was not under any medical treatment. She did not consumed alcohol. Non-smoker. The general clinical exam was under normal limits. No palpable cervical lymphadenopathy was identified.

The anterior rhinoscopy showed a vegetative tumor mass that occupies the right fossa completely, painless spontaneously and on palpation, with bleeding on palpation.

Paraclinical exam showed: ESR 70 mm/h, Hb 10.9 g/dL, Ht 33%, serum creatinine 0.6 mg/dL, chest radiography – normal X-ray image.

The patient went through a complete imagistic examination without detecting any metastasis at that time.
Under local anesthesia, a biopsy of the tumor mass from the right nasal fossa was performed. HP examination of HE-stained slides revealed a sinonasal mucosa lined by ciliated columnar pseudostratified respiratory epithelium with area of squamous metaplasia with the connective tissue of lamina propria disclosed by islands and trabecula of a malignant tumor proliferation consisting of intense pleomorphic epithelioid cells with eosinophilic cytoplasm and vesicular nuclei, with prominent eosinophilic nucleolus. Some cells were bi- and multinucleated. A minimal amount of brown pigment was observed in the cytoplasm. The tumor showed extensive inflammatory necrosis. In the tumor stroma, many acute inflammatory cells were observed. The tumor was ulcerated. The diagnosis of achromic epithelioid cells mucosal melanoma was suspected. Due to the small amounts of cytoplasmic melanin content, IHC reactions were performed. The epithelioid cells were positive for S100 protein, HMB45 and Melan A. The Ki67 index was 30%.

Because the patient had no history of cutaneous melanoma, the primary site of the tumor was considered the sinonasal mucosa.

The final diagnosis of achromic epithelioid cell sinonasal melanoma (SNM) was signed out (Figures 5–10).

Case No. 3

A 58-year-old female patient was hospitalized in April 2017 in our Department of ENT with unilateral nasal obstruction on the left side for about six months with repeated episodes of bilateral minor epistaxis.

The anamnesis revealed a hypertension under treatment and hereditary background of cardiac diseases. The patient did not smoke and consumed alcohol occasionally.

Anterior rhinoscopy showed the presence of a vegetative, smooth, painless, spontaneous and on palpation bleeding mass in the left nasal fossa.

Under general anesthesia, the excision of the tumor from the left nasal fossa was performed.

HP examination of HE-stained slides revealed the presence of a malignant tumor proliferation in the connective tissue of lamina propria of sinonasal mucosa, consisting of nests of large polyhedral cells, with small quantity of eosinophilic cytoplasm and enlarged vesicular nuclei, with unequally distributed chromatin pattern and multiple eosinophilic macronucleoli. In order to phenotype the tumor cells, the IHC reactions were performed. The tumor cells were positive for S100 protein, Melan A, HMB45 and BAP-1, and negative for synaptophysin, CD99, PGP9.5, CK AE1/AE3 and CD117.
The final diagnosis of achromic SNM with epithelioid cells was signed out.

Following the result of the biopsy, the patient was referred to oncology for specialized treatment, but she refused the treatment.

Two years after the first surgical intervention, in March 2019, at regular follow-up, during the anterior rhinoscopy the patient presented a tumor mass, which occupied the middle and posterior third of the nasal fossa, infiltrating the upper third of the mucosa of the nasal septum, bleeding on palpation.

The paraclinical exam revealed: ESR 30 mm/h, Hb 13.4 g/dL, Ht 41.8%, serum creatinine 0.86 mg/dL, chest radiography – normal X-ray image. The imagistic examination showed no distant metastasis.

Under general anesthesia, the excision of the tumor from the left nasal fossa was practiced, consisting of a thickening of the mucosa at the level of the left anterior ethmoid and at the mucosa of the nasal septum. The mass was ablated without limits of oncological safety. The HP examination of HE-stained slides and IHC reactions confirmed the recurrence of an achromic SNM. After the surgical intervention, the patient was discharged without complications and is currently being monitored by her oncologist (Figures 11–16).

**Discussions**

The diagnosis of melanomas is sometimes a challenge, requiring significant skills of a combined team formed of a pathologist and clinician, who are analyzing the different manifestations, from the clinically, cytological, and pathological points of view.

Cutaneous melanoma is a distinct disease from mucosal melanoma, with a different etiology, incidence, prognosis, and treatment. Its incidence is rapidly increasing in some countries, due to the genetic predisposition but unfortunately also due to the lack of prevention. The mean age of diagnosis is 60 years [13, 14].

The skin phenotype I–III has an increased risk of melanoma suggesting the protective role of the melanin in the development of the disease [15, 16]. The presence of melanocytic nevi is associated with the development of melanoma [3]. The chemical exposure is also suspected to play a role in the carcinogenesis, but further study is needed.
Figure 13 – Intense Melan A positivity in tumor cells of cytoplasmic immunoreaction. Anti-Melan A antibody immunomarking, ×400.

Figure 14 – Cytoplasmic and nuclear immunoreaction in some tumor cell for S100 protein. Anti-S100 antibody immunomarking, ×400.

Figure 15 – Intensely and homogenous positive nuclear immunoreaction on tumor cell for BAP-1. Anti-BAP-1 antibody immunomarking, ×400. BAP-1: Breast cancer-associated protein-1.

Figure 16 – Cytoplasmic immunoreaction in a few tumor cells for HMB45. Anti-HMB45 antibody immunomarking, ×400.

Clinically, the cutaneous melanoma is an asymmetric lesion, with poorly defined borders, different colors and aspect. The dermoscopy has a high sensitivity and specificity and increases the diagnostics, but the “gold standard” in the diagnosis of this lesion remains the IHC reactions performed by an experienced pathologist [17].

The histological diagnosis follows the thickness of the lesion, the mitotic rates, the presence of necrosis and ulceration and contributes to the staging of the disease following the AJCC Classification [18].

Histologically, the tumor presents nests of melanocytes within the epidermis of various sizes, shape, spacing and displaying different architectural patterns and cytomorphological features [4]. Superficial spreading melanoma is the most common subtype of the cutaneous melanomas. Some histological risk factors that influence the prognosis are the thickness of the tumor and the mitotic rate [5].

The immunohistochemistry shows a high positivity of S100 protein and HMB45 staining. The Ki67 is helping distinguish the benign lesions from the malignancies [19]. Higher incidence of BRAF and NRAS mutations can be seen in some subtypes of melanoma (superficial spreading melanoma, nodular melanoma).

The higher incidence of BRAF oncogene mutation suggests a different genetic etiology from mucosal melanomas (higher incidence of KIT oncogene mutation). The mortality of the melanoma is associated with the tumor thickness of the lesion [20], early diagnosis having a vital importance.

The recommended treatment of the cutaneous melanoma is based on the stage of the disease. The mainstay of treatment remains the large surgical excision with safety margins, and the sentinel lymph node biopsy in case of a tumor thickness of >1 mm and the presence of some risk factors, for the correct staging of the disease [21]. The systemic treatment is evolving, many trials investigating the adjuvant treatment with interferon-alpha (IFN-α) showed an improvement of the survival rate [22]. The use of immunochemotherapy and BRAF inhibitors are still under trials [23].

Despite treatment, 8% of all melanoma patients develop a relapse within two years of the initial diagnosis [24]. Based on the mitochondrial redox ratio, a new tool for the diagnosis of the melanoma metastasis has been suggested, using an MRI method [25].

Primary sinonasal mucosal melanoma (SNMM) is a rare tumor, not entirely understood, representing 0.3–2% of all melanomas [26]. It is always associated with poor
prognosis, 5-year overall survival rate does not exceed 40%, having a high recurrence rate [27] and a high risk of metastasis [28].

The average age of presentation for SNMM is 65 years, slightly affecting more men than women (3:2 ratio). No risk factors have been identified, although tobacco smoking and the occupational exposure to formaldehyde have been suggested in the malignant transformation [29]. While a connection was suggested, there has not been a confirmation for the role of human papillomavirus (HPV) or herpesvirus in the outset of the mucosal melanoma.

Local recurrence can be seen in about 50% of patients due to the vascular invasion, rich lymphatic system and the multifocal nature of the lesions [30].

The overall prognosis is extremely poor; Monolidis & Donald reported in a study on 962 patients, a mean survival rate for SNMM at three years of 39.2% and at five years of 17.1% [31].

In the literature, metastases in the liver, lungs, bone and brain are seen in about 50% cases, while the metastases in the lymphatic system are found in up to 20–40% patients [32]. When the metastasis is isolated and completely removed, the survival rate has been found to be prolonged [33, 34].

Factors related to better prognosis have been largely studied in literature and are reported to be the absence of lymph node metastasis, and age under 50 years old at the diagnosis, and an isolated tumor with size lesser than <3 cm [16, 24, 25, 35]. Histologically, amelanotic melanomas are considered the most problematic to identify and to be associated with a poor prognosis [1], while the more pigmented ocular lesions have better prognosis [36, 37].

Clinically, the most common sites for mucosal melanomas of the nose and paranasal sinuses are the lateral nasal wall and nasal septum but mucosal melanoma can also involve the paranasal sinuses with predominance on the maxillary sinus followed by ethmoid, frontal or sphenoid sinuses [38–41]. The patients typically present non-specific symptoms, such as progressive nasal obstruction, facial pain, epistaxis epiphora and in some severe cases, facial deformaties. Most of the cases of nasal mucosal melanoma are diagnosed due to a clinically localized disease. In the literature, the most prevalent complaint is the epistaxis, followed by other non-specific symptomatology [42]. Lymphadenopathy is exceptionally encountered while metastases in the lungs, brain, bone or liver are encountered in only 6% of cases, in some studies, at the diagnosis [43].

The nasal endoscopy allows a topographic assessment of the tumor, its size and appearance, with an evaluation of the tumor extension. Sometimes, due to the wide extension of the mass, the exact implantation site is hard to determine [44]. As 40% of mucosal melanomas are supposedly lacking melanin, the diagnosis can be problematic and IHC techniques are indispenisible. As a result, these cells will test positive for S100 protein, Melan A, HMB45 and MITF, while remaining negative for CK AE1/AE3.

The pathophysiology of amelanosis is still unknown [45]. The pathological study makes it possible to establish the diagnosis.

Histologically, it is thought that the relocation of the melanocytes from aerodigestive tract in the endodermal or ectodermal mucosa is the fountainhead of the mucosal melanoma [46]. The confirmation of the diagnosis is made by IHC exam which highlights the markers of melanocyte differentiation (HMB45, Melan A, tyrosinase, MITF) and eliminate other differential diagnosis.

The imaging assessment is a fundamental element in the therapeutic decision. Cranial CT scan reveals the appearance of an aggressive osteolytic tumor. MRI shows a heterogenous contrast enhancement. In the literature, some studies are showing a spontaneous hypersignal on T1 with a low-intensity signal on T2 and determine the anatomical local extension and detection of brain metastases. A complete imaging assessment implies a chest radiography, an abdomen and pelvis CT and PET–CT for the staging of the melanoma.

The staging of the disease remains a challenge. The AJCC staging system can be used to stage the disease [47], but the Ballantyne staging system is still applied to the mucosal melanoma: stage I – localized disease, stage II – regional lymph node involvement, stage III – distant metastasis [48].

Histologically, the angioinvasion on light microscopy with a tumor thickness greater than 5 mm, having post-surgical positive margins, and more advanced disease at diagnosis have all been associated with worse prognosis [49].

The treatment of this disease implies a multidisciplinary team composed by a clinician, pathologist, radiologist and also oncologist which establish a personalized treatment. The mainstay of the treatment of localized disease with or without lymph node invasion is considered to be the complete resection with negative margins [50]. The choice of the surgical technique depends on the tumor extension and site of origin. Despite surgical treatment, local recurrence is observed in 50% to 90% cases with metastasis being common [51]. The benefit of postoperative radiotherapy remains unclear, but it can be used with palliative or adjuvant intent to enhance local control.

Chemotherapy is classically reserved as a palliative treatment for advanced forms with metastatic disease, having limited impact on survival [52]. Immunotherapy, in combination with chemotherapy, has been used in the treatment of certain isolated cases of SNMMs, but its effectiveness should be evaluated by larger studies [53, 54].

Most recently, in adjuvant therapy there has been seen better results with the use of intensity-modulated radiation therapy (IMRT) and charged particle therapy. Recently, the implication of genetics discoveries established new treatment strategies. While still in the phase of trial, on c-Kit positive mucosal melanoma there has been observed a complete tumoral dispersion at six weeks of treatment.

**Conclusions**

Mucosal melanoma of the nose and paranasal sinuses is a rare, very aggressive tumor with a high recurrence rate. Often diagnosed at an advanced stage due to the lack of specific signs, with local recurrences and metastases, it implies a poor prognosis. The “gold standard” of diagnosis of melanomas remains the pathological and IHC examination. Early detection and surgery excision with wide safety margins of resection are essential prognostic factors even though the overall prognosis...
remains very poor. More studies are under evaluation in order to improve the prognosis of this disease.

Conflict of interests
The authors declare that they have no conflict of interests.

Authors’ contribution
Cornelia Marina Trandafir and Alina Andreea Tischer equally contributed to the manuscript.

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