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Primary Nasal Mucosal Melanoma: A Case Report

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Abstract **Case Report**

Nasal mucocal melanoma is a rare and aggressive neoplasm. In most cases, it arises in the lateral wall of the nasal cavity. As it shows nonspecific clinical symptoms and risk factors, anterior nasofibroscopy and imaging plays a crucial role in the diagnosis. The final diagnosis is based on histological and immunohistochemical findings. The wide surgical excision is the mainstay of the treatment and the adjuvant radiotherapy is often used to prevent local recurrence and metastasis. We report a case of a 61 years old female patient with obstruction and epsistaxis. The first facial magnetic resonance imaging was suggestive of an inverted papilloma misleading the diagnosis. The patient had undergone nasal endoscopy with a biopsy. The histological and immunohistochemical were consistent with the diagnosis of a mucosal melanoma. A facial computed tomography revealed a solid mass filling the entire right nasal cavity with extension to the homolateral ethmoidal cells and the maxillary sinus and erosion of the middle and lower turbinates and the nasal septum. A second facial magnetic resonance imaging showed a neoformation of the right nasal cavity. The lesion was initially removed using and endonasal endoscopic approach. Local recurrence occurred one month later, which leaded to perform a lateral rhinotomy approach. The histopathological aspect was consistent with the diagnosis of malignant melanoma and the patient received a postoperative 3D radiation therapy. The diagnosis is based on histological and IHC studies. Wide surgical excision with negative margins is the cornerstone of any treatment regimen for sinonasal mucosal melanoma followed by adjuvant radiotherapy even if there is no clear consensus. In spite of a well conducted treatment, the melanoma of the nasal cavity remains an aggressive tumor with a non-negligent risk of local recurrence, with a poor prognosis and a survival rate not exceeding 35% after 5 years.

Keywords: Nasal melanoma, Imaging, MRI, Treatment, Surgery, Radiation Therapy.

INTRODUCTION

Melanoma is a malignant tumor that develops from melanocytes which are derived from the neuro ectoderm [1]. This entity can develop in the skin, as well as in the different mucous membranes, especially those of the oral, and sino-nasal cavities, the gastrointestinal tract and the genito-urinary system [2].

Mucosal melanoma is a rare neoplasia, representing less than 1% of all melanomas [3], and is located in 50% of cases in the head and neck region, of which more than 72% are found in the sino-nasal cavity [4]. The nasal fossa is the most frequent site, more particularly the lateral wall [5].

The most frequent symptoms are unilateral nasal obstruction and epistaxis, however they are not specific [6]. The diagnosis is based on histopathological and immunohistological findings.

The radiological diagnosis and local staging are based on facial computed tomography (CT) and magnetic resonance imaging (MRI) [7], while the distant extension assessment is based on the positron emission tomography (PET) scan [8].

The wide surgical excision is the mainstay of the treatment. And the adjuvant radiotherapy is often used to prevent local recurrence and metastasis [9].

In spite of a well conducted treatment, the melanoma of the nasal cavity remains an aggressive tumor with a poor prognosis and a survival rate of 20 to 35% after 5 years [10].

We report a case of primary nasal cavity melanoma in a 61 years old female patient, initially misdiagnosed as an inverted papilloma.

CASE PRESENTATION

A 61-year-old woman presented with a 6 months history of a right-sided permanent nasal obstruction and mucopurulent rhinorrhea associated to a recurrent spontaneous anterior epistaxis. She had no particular medical or family history, nor significant occupational exposure to any particular substance.

On examination, we noticed a painful large swelling on the right side of the nose and of the right maxillary area. Nasal endoscopy showed a unilateral polypoid easily bleeding mass in the right nasal fossa with bloody crusts.

Then a facial MRI was performed, showing a neoformation measuring 30 x 22 x 16 mm, focused on the area of the middle right nasal meatus, with an iso-signal intensity in T1 and T2 weighted sequences. The mass showed high signal intensity on diffusion-weighted image and a moderate enhancement on gadolinium-enhanced MRI. It was responsible for a bulging of the papyraceous lamina, an obstruction of the frontonasal and ostio-infundibular ducts, without orbital invasion. It involved the middle and inferior turbinates, and was suggestive of an inverted papilloma.

The patient had undergone nasal endoscopy with a biopsy under local anesthetic where a lesion of 5 mm was removed.

Histopathology showed a necrotic and hemorrhagic tumor with malignant cells and focal melanin pigment (Figure 1). The immunohistochemistry (IHC) demonstrated positive stains for S-100 and Melan-A which is consistent with the diagnosis of a mucosal melanoma. There was no evidence of BRAF mutation.

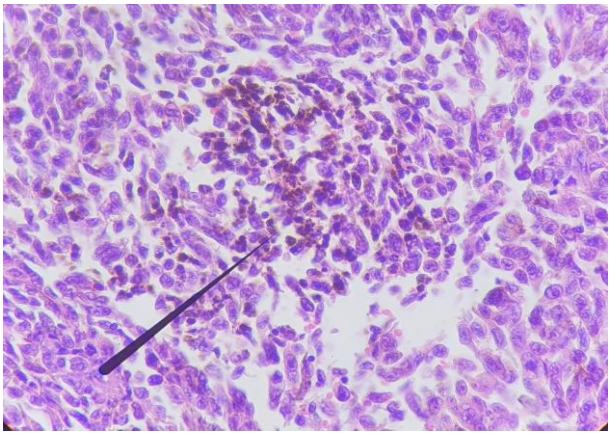

Figure 1: Section showing malignant cells with melanin pigment (H&E x200)

A complete ophthalmological and dermatological examination was performed, revealing no abnormalities. A facial CT revealed a solid mass filling the entire right nasal cavity, measuring 32 x 15 mm, heterogeneously enhanced after the injection of an intravenous contrast agent. It was responsible for its enlargement with subtotal destruction of the middle and lower turbinates and contralateral deviation and erosion of the nasal septum. The mass extended to the homolateral ethmoidal cells and the maxillary sinus causing erosions of its medial wall (Figure 2 and 3).

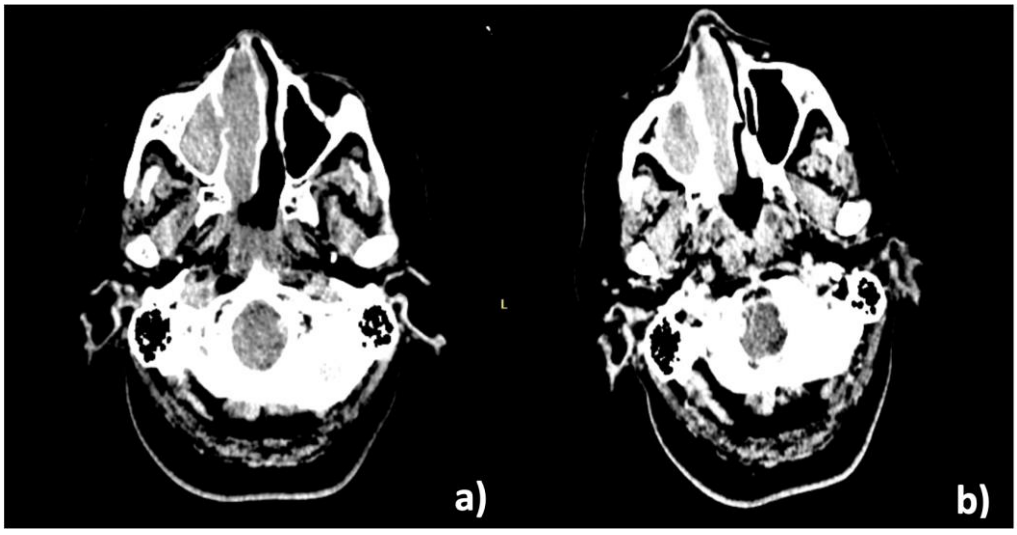

Figure 2: Facial CT without (a) and with contrast (b), soft-tissue window, axial sequences: solid mass filling the entire right nasal cavity with extension to the homolateral maxillary sinus, heterogeneously enhanced after the injection of an intravenous contrast agent

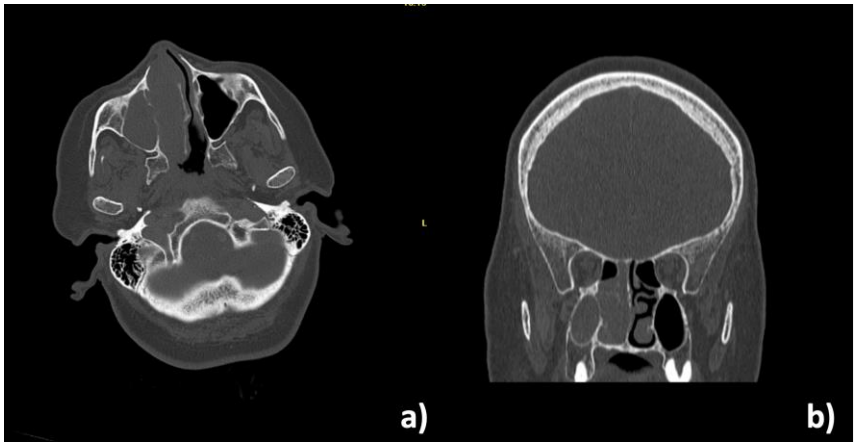

Figure 3: Facial CT, bone window, axial (a) and coronal (b) sequences: the mass is responsible of subtotal destruction of the middle and lower turbinates, controlateral deviation and erosion of the nasal septum and the medial wall of the homolateral maxillary sinus

A second facial MRI was performed showing a neoformation of the right nasal cavity measuring 33 x16 mm, with an iso-signal intensity in T1 and T2 weighted sequences, a high signal intensity on diffusion-weighted image and an intense enhancement on gadolinium-enhanced sequences. The mass was responsible for a displacement of the nasal septum and an invasion of the anterior ethmoidal cells and it extended towards the maxillary sinus, filled of a thick fluid retention (Figure 4 & 5).

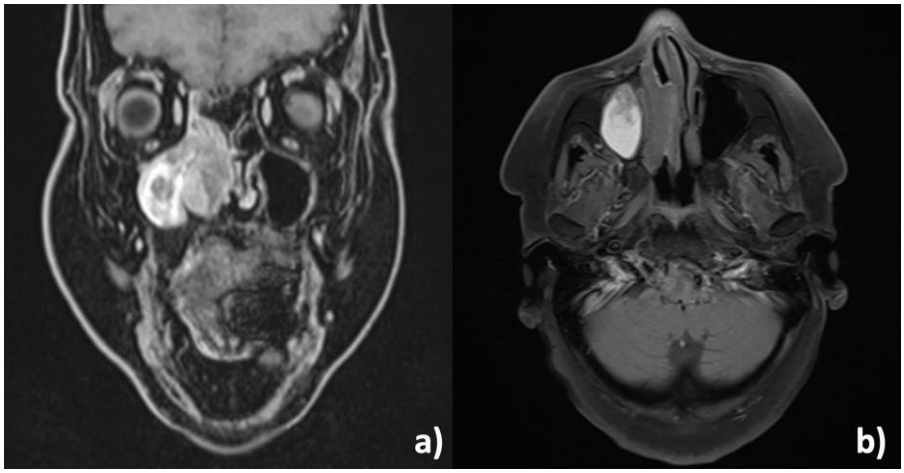

Figure 4: Facial MRI, T1 and T1 Fat-Suppressed weighted sequences, coronal (a) and axial (b) sections: a neoformation of the right nasal cavity with an iso-signal intensity, responsible of a deviation of the nasal septum, an invasion of the anterior ethmoidal cells and the maxillary sinus

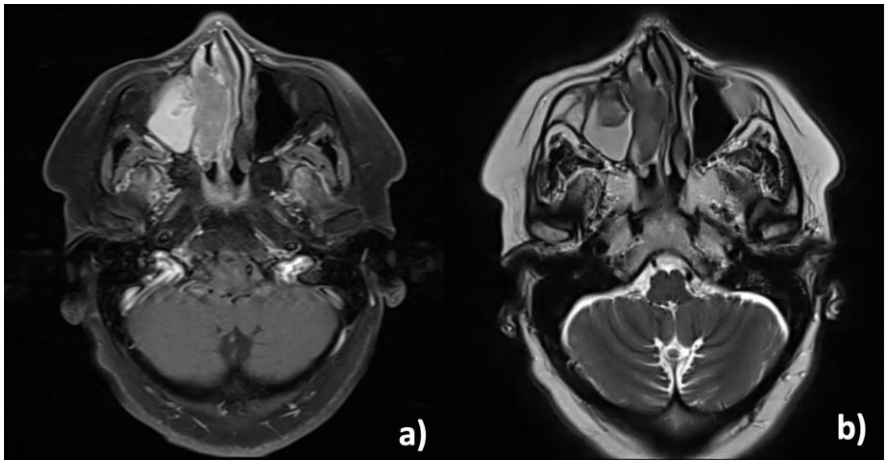

Figure 5: Facial MRI, T2 and T1 Fat-Suppressed gadolinium-enhanced weighted sequences, axial sections: a neoformation of the right nasal cavity with an iso-signal intensity (a) and intense enhancement of the tumor (b)

CT studies of the central nervous system, the chest, the neck, the abdomen and the pelvis didn't identify any lymph nodes or distant metastasis.

The tumor was classified stage I according to the Ballantyne staging system, and stage III (cT3N0M0) according to American Joint Committee on Cancer (AJCC) classification of mucosal melanoma (7th edition). The lesion was initially removed using endoscopic surgery (Figure 6).

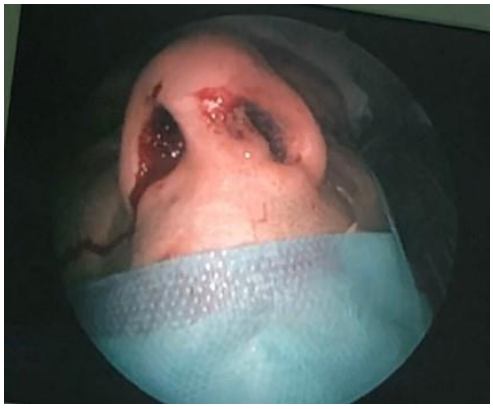

Figure 6: Endoscopic approach via endonasal route

An Endonasal Endoscopic Approach (EEA) was performed with a total middle and inferior turbinate resection (MTR and ITR), ethmoidectomy and a wide middle meatal antrostomy (MMA) (Figure 7).

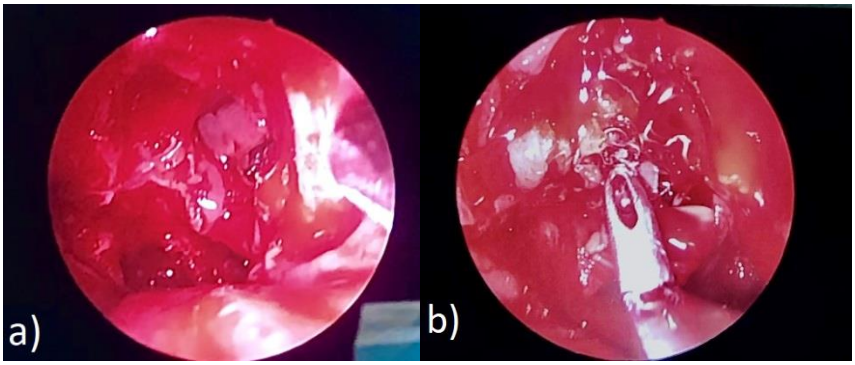

Figure 7: Endoscopic images with a 0°, 4-mm telescope. a) Tumor extended to the posterior ethmoidal air after middle and inferior Turbinectomy. b) Debulking the tumor with the piecemeal removal technique

One month later, the patient presented with one sided nasal obstruction and recurrent nasal bleeding that was confirmed to be related to a local recurrence after endoscopic examination. This time, we decided to perform a lateral rhinotomy approach. A transfacial subtotal maxillectomy and resection of vomer bone was also executed which allowed radical ablation of the controlateral extension of the tumor as well.

The histopathological aspect was consistent with the diagnosis of malignant melanoma with positive macroscopic margins.

The patient received a postoperative 3D radiation therapy (RT) of 60 Grays (Gy), 3 Gy per fraction, 5 days a week with a good tolerance.

DISCUSSION

The primary nasal melanoma (NM) presents a rare and aggressive tumor. It mainly affects individuals over 60 years of age and rarely young people [11]. The male-to-female ratio is 2/1 [12].

No specific risk factors were demonstrated to have an impact on the incidence of NM. Although cigarette-smoking and occupational exposure to particular substances seems to be a possible risk factor [13-15]. The International Agency for Research on Cancer has defined formaldehyde, leather dust, wood dust, nickel, chromium VI and mineral oils as definite human carcinogens for sinonasal cancer [6]. Our patient didn't present any particular exposure to any of these factors.

The lateral wall presents the initially mostly affected area, followed by the nasal septum, middle and inferior nasal conchaes. The maxillary sinus is the most frequent paranasal sinus secondary affected [16].

It is important to note that it's often difficult to distinguish the exact origin of the sinonasal melanomas

because they are frequently discovered at an advanced state [5]. Symptoms of NM are not specific, and are often absent in the initial stage. The most common complaints are represented by progressive unilateral nasal obstruction and recurrent epistaxis. Other symptoms can be associated such as rhinorrea, headache, diplopia and hyposmia [6].

Clinical examination by an anterior nasofibroscopy can show a pigmented, pale-yellow lesion or translucent polypoid mass which can be mistaken for a benign lesion [17, 18], as in our case.

The diagnosis is based on histological and IHC studies, because their microscopic characteristics overlap with other malignant tumors especially in the case of amelanotic melanomas. Histologically, the cells of mucosal melanomas can be round, fusiform or microcytic. Their size is variable, from medium to large and their mitotic activity is important [19]. They are positive to S-100 protein and melanocytic markers, such as melanoma-associated antigen recognized by T-cells MART-1/Melan-A, tyrosinase and microphthalmia transcription factor (MITF) and HMB-45 [20].

Radiologically, imaging plays a crucial role in the diagnosis, local-regional extension assessment, preoperative planning and monitoring of NM.

The CT of the facial bones and skull base reveals an aggressive mass lesion with strongly contrast enhancement responsible for adjacent bone destruction [21].

Brain and facial MRI is a useful tool for the diagnosis of NM. The MRI appearance differs according to the histological features of the lesion: melanotic or amelanotic [22], with up to one-third of cases being amelanotic [23].

Melanotic melanomas are characterized by heterogeneous contrast enhancement. They typically show high signal intensity on T1, low signal intensity signal on T2-weighted sequences. On the other hand, amelanotic melanomas exhibit T1 hypo-intensity and T2-weighted hyperintensity. On gadolinium-enhanced MRI, they demonstrate mild to moderate enhancement [22].

The typical MRI appearance of melanotic melanomas may be explained by the high melanin content or the presence of haemorrhage within the lesion [24]. A study published by SG Crich and Al., suggested that the intensity of the MRI signal is correlated with the amount of melanin in the tumor. Thus, the more the melanin the tumor contained, the higher the signal on T1-Weighted and the lower signal on T2-weighted it showed in MRI [25].

In typical cases, MRI can help within differential diagnosis of melanoma. It can distinguish between solid lesions and inflammatory mucosal lesions. Also, MRI findings enable to distinguish melanoma from other types of tumors such as inverted papillomas which demonstrate a convoluted cerebriform pattern seen on T2 and/or contrast-enhanced T1 weighted MRI images [26].

It should also be noted that the atypical MRI appearance of melanomas is not uncommon and may be associated with a poor prognosis [27], as in the case of our patient.

In addition to the evaluation and characterization of the primary site of the disease, MRI can also be used to delineate the local extent of the disease to the skull base and the orbits and the regional lymph node involvement. However, evaluation of lymphatic extension is usually done by CT or PET scan.

Lymph node metastases are less frequent in NM than in oral mucosal melanomas. They are found in 25% of cases in the early stages of the disease [28], and they often involve the submandibular and upper internal jugular groups [29].

The radiological factors of poor prognosis are tumor thickness greater than 5 mm, vascular invasion and distant metastases [28].

Finally, the study of distant metastases is performed by chest, abdomen and pelvis CT and positron emission tomography (PET) and assessment of response to treatment is based on CT and/or PET/ CT.

The imaging assessment enables staging of the head and neck melanomas, which was originally based on the Ballantyne staging system [30].

The 7th edition of the AJCC classification is preferred and is a specific TNM staging system for head and neck mucosal melanoma which can be used prior to any treatment (cTNM), after surgical resection (pTNM), and at recurrence (rTNM) [31].

This classification takes into account the aggressiveness and the poor prognosis of the melanomas, thus it classifies the tumors in stage T3 and T4 with T3 defined as the disease confined to the mucosa ,T4a refers to moderately advanced disease and T4b to very advanced disease [31].

The diversity, rarity, and discovery of new therapeutic modalities require a multidisciplinary approach to the choice of the optimal therapeutic strategy [32].

Wide surgical excision with negative margins is the cornerstone of any treatment regimen for sinonasal mucosal melanoma. The complex anatomy of

the sinonasal cavity makes oncologically sound resection challenging and not uncommonly impossible.

The approach of the tumor can either be done with endoscopic excision or open surgery. A myrid of studies has proven similar efficacy and oncological outcome of both techniques. In one series of sinonasal melanoma patients treated at MD Anderson Cancer Center [33], endoscopically assisted approaches resulted in a significantly higher 2-year overall survival rate than open procedures did [32].

Endonasal Endoscopic Approach (EEA) is an innovative surgical technique used to remove carcinoma occupying the nasal cavities, using the nose and sinuses as natural corridors to access tumors.

The operation is usually started by debulking the tumor with powered instrumentation to more clearly defining the possible site of origin of the lesion [34]. This technique is performed using two important procedures. The first one is the piecemeal removal of the lesion and surrounding anatomic structures into a smaller fragment that could be removed from the nasal fossae [35]. These fragments are then submitted (anatomically oriented) to histopathologic examination. The second procedure requires lesion central debulking by micro-debrider with control of tumor margins and subsequent removal of bony structures surrounding the lesion. With this technique, it is possible to remove a surgical box, leaving margins free from disease [35].

As for External Surgery, it includes two types of techniques: transfacial approach and craniofacial approach [36]. Only the first procedure will be briefely discussed in our article. This surgical modality, when indicated for malignant tumors with invasion of the midface and mesostructure, involves both an ablative and a reconstructive time. The ablative time should be ideally radical with clear margins while the reconstructive time has to minimize aesthetic and functional damages [37].

In mesostructure malignant tumors, we use lateral nasal rhinotomies, such as Sebileau-Moure, Hautant, Weber-Ferguson Dieffenbach and sub-labial rhinotomies like Denker Rouge and midfacial degloving. Each of these approaches offers a special access point to the tumor and depends on the tumor size, location and extension, as well as on the surgeon experience to choose an approach over another [37].

The lateral rhinotomy is considered one of the most commonly used techniques for exploration of the difficult sinonasal masses, in order to control the lesion in its entirety [38].

Considering the low incidence of nodal disease in the NM, therapeutic neck dissection is not systematically performed, and based on the existence of clinically or radiologically detected nodes involvement [40]. Some authors have adopted the sentinel lymph node technique in order to select patients requiring cervical lymph node dissection [41, 42]. The status of lymph node disease is not correlated with the risk of local recurrence nor with the risk of distant metastasis [28, 40, 43, 44]. In our case, no lymph node dissection was performed.

In patients with local recurrence, without distant metastasis, as in our patient's case, a second surgery is considered the best therapeutic option when the tumor is resectable [45].

In terms of primary nasal cavity melanoma (NM), surgery has been shown not to affect overall survival, therefore the main aim of both procedures is to allow a minimally invasive radical approach and improve the quality of life. The two methods have similar oncological efficacy, however, the endoscopic approach has a lower risk of morbidity and acceptable aesthetic results [40]. The choice of the right surgical approach depends on the tumors characteristics and the surgeons experience [3].

As for radiotherapy, although malignant melanoma has been considered as a radioresistant tumor, its response to radiotherapy has been well proven through several studies [46]. It can be used as adjuvant or definitive treatment of NM.

There is no clear consensus regarding the indications for adjuvant radiotherapy in NM. According to the National Comprehensive Cancer Network (NCCN), it is indicated for patients with high-risk nodal disease. It is also recommended for patients with positive or close margins when a second surgery is not feasible [47]. Adjuvant radiotherapy improves local control, but has no significant effect on survival outcome [48]. While definitive radiotherapy is reserved for patients with unresectable disease or with a poor performance status [49].

Although the radiation dose and the fractionation regimen are still unclear in the management of NM, doses of adjuvant radiotherapy higher than 50 Gy have been recommended for local control in many series [40]. Some studies have shown that hypofractionation may improve local control and overall survival [50, 51], while others revealed no superiority of the hypofractionated regimen over the conventional one [46].

The immune checkpoint inhibitors and targeted therapies against BRAF and MEK have increased overall survival in cutaneous melanoma, while a limited number of series showed a lower response rate in mucosal melanoma [52]. They are recommended for unresectable and metastatic cases [45].

CONCLUSION

Primary nasal mucosal melanoma is an aggressive and rare entity with non-specific symptoms, different histological presentations, frequent local recurrence and poor prognosis.

The presence of unilateral nasal symptoms in patients over 60 years old must be considered as suspicious signs and the individualization of any nasal mass and pigmentation must make the clinicians think of mucosal melanoma as potential diagnosis.

On imaging, the typical appearance of mucosal melanoma is that of a mass with hyposignal and hypersignal intensity on T1 and T2-weighted sequences, respectively and with heterogeneous contrast enhancement. The diagnosis is based on histological and immunohistochemical findings.

First-line treatment is based on surgical resection, possibly performed by an open or an endoscopic technique followed by adjuvant radiotherapy even if there is no clear consensus.

Despite the overall poor prognosis of these tumors, early-stage identification may lead to a better prognosis and the development of more efficient therapies in radiotherapy techniques and cell and gene therapy can improve the survival outcomes.

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