Review

Mucosal melanoma of the nasal cavity and paranasal sinuses

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A B S T R A C T

Mucosal melanoma of the nasal cavity and paranasal sinuses is a rare disease, but its incidence appears to be increasing. The mean age at diagnosis is between 65 and 70 years. Unilateral nasal obstruction and epistaxis are the most common presenting complaints. Melanoma arises in the septum or lateral wall of the nasal cavity in the great majority of cases. The histological diagnosis is based on specific immunohistochemical labelling and is usually established at an advanced stage of disease: stage T3 or T4 tumours according to the 7th edition of the American Joint Committee on Cancer (AJCC) classification of tumours. First-line treatment consists of surgery. The place of intranasal endoscopic surgery remains controversial due to the difficulty of controlling surgical margins and should be reserved for experienced teams. Adjuvant radiotherapy is usually performed due to its efficacy on local and regional disease control. Five-year overall survival of mucosal melanoma of the nasal cavity and paranasal sinuses in the most recent series does not exceed 40%. Local recurrence is observed in about 50% of cases and metastatic disease is common. The quality of initial tumour resection with negative surgical margins is the most important prognostic factor for tumours confined to the nasal cavity. Hopes for improvement of survival are based on early diagnosis, progress in radiotherapy techniques and cell and gene therapy that are currently under evaluation.

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1. Introduction

Primary mucosal melanoma of the nasal cavity and paranasal sinuses is a rare tumour [1,2]. Positive diagnosis of this tumour is made difficult by the non-specific presenting complaints [3,4]. This tumour has a poor prognosis due to its aggressive nature and the frequently delayed diagnosis. It mainly occurs in the elderly and the presence of comorbidities can limit the extent of treatment [4]. Treatment options essentially consist of radical surgery and radiotherapy, while chemotherapy is reserved for advanced forms. Despite a better knowledge of this tumour, the 5-year overall survival remains poor and does not exceed 40% in any of the published studies [5–8].

2. Pathogenesis and epidemiology

2.1. Pathogenesis

Melanocytes are dendritic cells arising in the neural tube and located at the dermo-epidermal junction of all mucous membranes.

The presence of melanocytes in the mucosa of the nasal cavity and paranasal sinuses has been known for a long time. Melanocytes are detected under normal conditions in about 21% of individuals [3]. Mucosal melanoma is a neuroectodermal tumour arising from these melanocytes [3,9]. A higher density of melanocytes in the mucosa of the nasal cavity and paranasal sinuses compared to other sites could explain the relative frequency of primary mucosal melanomas in this site [5]. No risk factor has been clearly identified to explain the development of these tumours. In contrast with melanoma of the skin, in which sun exposure is known to be the major risk factor, the risk factors for mucosal melanomas have not been identified. No link has been demonstrated between Human Papilloma Virus (HPV) or Herpes virus in the aetiologypathogenesis of mucosal melanoma [3]. Exposure to formaldehyde has been suspected but not confirmed in several studies [3,10]. Smoking may constitute a predisposing factor essentially for mucosal melanoma of the oral cavity [3,11]. Several genetic studies have demonstrated gene mutations affecting the tyrosine kinase receptor [3,12]. Some authors have suspected the role of heredity and environment in the pathogenesis of mucosal melanoma in order to explain the different prevalence rates of these tumours between Caucasian (1% of melanomas) and Asian populations (7.5% of melanomas) [1,5].

Casiraghi and Lefèvre considered that mucosal melanomas of the nasal cavity and paranasal sinuses were histologically related to the group of malignant round cell tumours [13]. They suggested
a morphological continuum of these tumours between the two extremes of life, with sarcomas in children and young adults and mucosal melanoma in the elderly [13].

2.2. Epidemiology

Primary mucosal melanoma of the nasal cavity and paranasal sinuses is a rare tumour, representing between 0.7 and 1% of all melanomas in Caucasian populations and between 4 and 8% of malignant tumours of the nasal cavity and paranasal sinuses [3,14]. The incidence of mucosal melanoma appears to be increasing, especially in the nasal cavity and paranasal sinuses [2,15]. This increasing incidence appears to be significant in women [2,14,15]. Despite this increase, the prevalence currently remains identical in the two sexes [4]. The patient’s age at the time of diagnosis is between 60 and 80 years with a mean age between 65 and 70 years [5,16]. Primary mucosal melanoma can arise in various anatomical sites, but it predominantly (55% of cases) involves the head and neck [5], in which the nasal cavity and paranasal sinuses is the most frequent site, representing 70% of cases (50% in the nasal cavity, 20% in the paranasal sinuses) followed by the oral cavity in about 17% of cases [2].

3. Diagnosis and assessment

3.1. Clinical features

The most common presenting complaints are nasal obstruction and epistaxis. Nasal obstruction is unilateral, permanent and progressive, either isolated or associated with other symptoms. Epistaxis can be abundant or minimal with the presence of streaks of blood when blowing the nose [4,17]. Some patients have reported epistaxis to be the most common presenting complaint [6]. These non-specific symptoms are often considered to be responsible for the long interval between first symptoms and diagnosis of melanoma. This is particularly true when the tumour arises in the paranasal sinuses [7]. Other symptoms include rhinorrhea which can be purulent in the case of superinfection, pain and lacrimation in the case of invasion of the inferior meatus and lacrimal duct. More advanced tumours may present in the form of malar swelling, nasal deformity or exophthalmos.

3.2. Clinical examination

Unilateral symptoms must be considered to be suspicious and justify thorough fibroscopic or endoscopic investigation of the nasal cavity. Intranasal examination defines the appearance of the tumour (sessile, nodular, polypoid or granulating), its size and implantation. It may be slate-coloured, reddish, crimson, brownish or black, which is highly suggestive of the diagnosis. The tumour surface can be homogeneous or heterogeneous, with a friable consistency and the tumour may be covered by a greasy exudate. An ulcerated appearance is frequently observed [3,13]. One-third of melanomas are achromic [4]. The exact origin of the tumour is sometimes difficult to determine and the tumour is often already extensive at the time of diagnosis with a mean diameter ranging between 2 and 3 cm [14]. Tumours of the nasal cavity predominantly involve the septum and lateral wall, while tumours of the paranasal sinuses predominantly involve the maxillary sinus followed by the ethmoid, frontal and sphenoidal sinuses [4,5]. The cranial nerves must be systematically examined looking for oculomotor disorders and sensory loss of the face. Complete clinical staging assessment must include palpation of regional lymph nodes. At the time of diagnosis of the primary tumour, cervical lymph node metastases are detected in 10 to 20% of patients [1,13,17] and haematogenous metastases are detected in 6% of patients (lungs, brain, bone, liver) [13]. A complete dermatological and ophthalmological examination must be performed to detect a possible primary tumour in order to confirm the primary or secondary nature of the tumour of the nasal cavity and paranasal sinuses.

3.3. Histology

The diagnosis is based on histological examination of tumour biopsies. Histological examination is difficult due to marked cytoligical and architectural polymorphism [4]. The presence of intracytoplasmic melanin pigment can be detected by the affinity for Fontana stain [13,17] (Figs. 1 and 2). Several parameters are evaluated on histological examination: morphology and cellular architecture, pigmentation, presence of ulceration, percentage of necrosis, number of mitoses, inflammation and bone, perineural, lymphatic and vascular invasion. Confirmation of the diagnosis is based on immunohistochemistry using a panel of markers: protein S100 and melanocytic markers (HMB45, Melan-A, tyrosinase, MITF) [13]. Epithelial cell markers are negative but several aberrant cases have been reported [13].

3.4. Imaging

An imaging assessment comprising computed tomography (CT) of the facial bones and magnetic resonance imaging (MRI) is an
essential part of the local staging of the tumour. Computed tomography of the facial bones and skull base is performed with axial and coronal sections, with contiguous 1 mm thick (spiral acquisition) or a maximum of 3 mm thick slices and dual window settings (bone and soft tissues). Intravenous iodinated contrast agent injection allows enhancement of the tumour with respect to surrounding tissues. Three-dimensional (3D) reconstruction is particularly useful when facial reconstruction is planned. The usual appearance is that of an aggressive osteolytic tumour. Brain and facial MRI provides three-dimensional sections and usually comprises three sequences: T1, T1 post-gadolinium and T2. Malignant melanoma is characterized by heterogeneous contrast enhancement. According to some authors, a spontaneous high-intensity signal on T1 with a low-intensity signal on T2 would be characteristic of melanoma. This unusual appearance, sometimes observed with other types of tumours (angiosarcoma, cylindroma and aesthesioneuroblastoma) appears to be related to the high melanin content and/or bleeding inside the tumour [18,19]. T2-weighted MRI can distinguish tumour invasion from paranasal sinus fluid retention. Finally, MRI is essential to define the anatomical relations of the tumour with the orbit and skull base and to detect any brain metastases (Figs. 3 and 4). Distant staging is based on chest, abdomen and pelvis CT and positron emission tomography (PET). This staging assessment looking for metastases can be decisive in the choice of treatment and to assess the value of certain cosmetically and functionally destructive forms of radical surgery (orbital exenteration).

3.5. Classification

The clinical and imaging assessment allows staging of the melanoma in order to propose adapted treatment and to assess the prognosis. Ballantyne’s classification is the oldest classification, but does not take tumour size, tumour histology and local extension into account [20], as stage I is defined as tumour confined to the original site, stage II is defined as tumour with regional lymph node metastases and stage III is defined as tumour with distant metastases. Use of this old classification allows comparison of various series [1], but it is now preferable to refer to the classification established by the American Joint Committee on Cancer (AJCC) [21,22]. The 7th edition of the AJCC classification does not comprise stage T1 and T2 in view of the systematically aggressive nature of these melanomas. The proposed classification comprising stage T3 and T4 tumours is more consistent with the local extension and the poor prognosis of this disease (Table 1).

4. Treatment

4.1. Surgical treatment

A general consensus has been reached to consider surgery as first-line treatment [1,5,23]. The indication for surgery must take into account the patient’s quality of life, due to the poor global prognosis of these tumours. The treatment decision is generally taken by an oncology multidisciplinary consultation based on the staging assessment. Surgery is indicated as first-line treatment and in the case of local recurrence. The choice between an external or an intranasal incision depends on the tumour size and site. The choice of intranasal endoscopic surgery remains controversial due to the difficulty of controlling surgical margins and should be reserved for experienced teams [16]. It is indicated for strictly intranasal tumours and under conditions of tumour resection that are able to achieve the same cancer control results as via an external approach. Craniofacial resection is the reference technique for tumours situated in contact with or invading the skull base [16]. The tumour must be widely resected with 1.5 to 2 cm negative surgical
margins [17]. Margins are considered to be negative when they are greater than or equal to 5 mm on definitive histological examination of the operative specimen. Systematic lymph node dissection is not part of conventional surgical management and is only performed in the presence of clinically or radiologically pathological lymph nodes [1]. The sentinel lymph node biopsy technique, used in cutaneous melanoma, is currently under evaluation in mucosal melanoma.

4.2. Radiotherapy

Mucosal melanomas are generally considered to be poorly radiosensitive. Melanomas are composed of cells with a high post-irradiation regenerative capacity. Radiotherapy is classically indicated in the presence of positive surgical margins, local recurrence, locally advanced tumour, or sometimes for palliative purposes or when the patient refuses surgery. The majority of authors consider that adjuvant radiotherapy increases local and regional control without increasing survival independently of tumour stage [8,24–27]. There does not appear to be any significant survival difference between patients treated by surgery alone and patients treated by surgery and adjuvant radiotherapy [3,28]. However, the findings of these studies are controversial, as other teams have demonstrated the efficacy of surgery and adjuvant radiotherapy on survival [1].

In particular, the development of new radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) has improved the results obtained with conventional radiotherapy especially on local and regional control with good local safety and low morbidity [29–31]. As a result of this progress, radiotherapy is increasingly proposed systematically as part of the initial phase of treatment as an adjuvant to surgery whether or not the surgical margins are invaded [29,31].

4.3. Chemotherapy

Chemotherapy is classically indicated for palliative treatment or in metastatic patients [7]. However, some authors have proposed multimodal first-line treatment comprising chemotherapy and/or immunotherapy for the management of locally aggressive forms [28,32]. A recent study highlighted the value of selective intraarterial chemotherapy [33]. Immunotherapy by interleukin 2 or interferon alpha (IFNα) either alone or in combination with chemotherapy and vaccination is currently under evaluation [34,35]. In metastatic disease or unresectable forms of cutaneous melanoma, the chemotherapy strategy is designed according to the presence or absence of V600 mutation [31,36]. Vemurafenib, a BRAF protein kinase inhibitor, is therefore reserved for the treatment of advanced melanoma associated with BRAF V600 mutation [31,37]. Trials of vemurafenib and ipilimumab combination therapy are currently underway in patients with BRAF mutation. In the absence of BRAF V600 mutation, treatment of these advanced, treatment-refractory forms is based on the use of ipilimumab either alone or in combination with standard chemotherapy (dacarbazine). The transposition of these recent data to the management of stage 4 mucosal melanoma of the nasal cavity and paranasal sinuses must be considered in the light of progress of oncogenetics in these mucosal forms.

However, the adverse effects of these treatments represent a considerable limiting factor for the management of patients with mucosal melanoma of the nasal cavity and paranasal sinuses, who are generally elderly with comorbidities contraindicating any form of chemotherapy or immunotherapy.

5. Survival and prognosis

The 5-year overall survival of mucosal melanoma of the nasal cavity and paranasal sinuses in the most recent series does not exceed 40% (20%–40%) [5–8] and mean survival does not exceed 28 months (17–28 months) [4,27]. Local recurrences occur in about 50% of cases [3,27]. This high recurrence rate appears to be due to the multifocal nature of the lesions, submucosal lymphatic spread and the high rate of vascular invasion. Local recurrences are also related to inadequate first-line surgical resection. Local recurrences are predictive of the presence of distant metastases [3,27]. The most common metastatic sites are lungs, liver, bone and, more rarely, brain and adrenal glands. Metastases are found in about 50% of cases, sometimes during the course of the disease [27], while lymph node metastases are found in 20 to 40% of cases [13,27].

Prognostic factors have been extensively studied in the literature by means of multivariate analyses. The quality of the initial tumour resection with negative resection margins is the most important prognostic criterion for tumours confined to the nasal cavity [6,17].

An advanced age at the time of diagnosis is a factor of poor prognosis. The unfavourable age limit has been estimated to be 70 years according to some authors [38] and 60 years according to others [1,3], while age less than 50 years appears to be associated with a better prognosis [3]. Tumour size greater than 3–4 cm is considered to be a factor of poor prognosis [13,38]. An isolated sepal tumour is associated with good prognosis [6] in contrast with tumours of the paranasal sinuses that have a very poor prognosis.

Ballantyne’s stage I has a better prognosis [1]. A high mitotic index and a pseudopapillary and sarcomatoid architecture on histological examination are factors of poor prognosis [4,13,39]. Some authors consider the presence of melanin and the level of pigmentation to be factors of poor prognosis [4], while achromic melanomas are usually considered to be associated with a poorer prognosis [40].

6. Conclusion

Early diagnosis of mucosal melanoma of the nasal cavity is an essential prognostic factor. The presence of unilateral symptoms, such as epistaxis or nasal obstruction, in a patient over the age of 60 years must be considered to be suspicious. The diagnosis is based on histological and immunohistochemical examination of a biopsy. First-line treatment is based on wide surgical resection, possibly completed by adjuvant radiotherapy. An initial complete resection with healthy margins is a decisive factor for survival. The overall prognosis of these tumours is very poor. Hopes for improvement of survival are based on progress in radiotherapy techniques and cell and gene therapy that are currently under evaluation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References
