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Review

Mucosal melanoma of the nasal cavity and paranasal sinuses

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ABSTRACT

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.

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 aetiopathogenesis 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

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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 authors 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 rhinorrhoea 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 greyish 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.

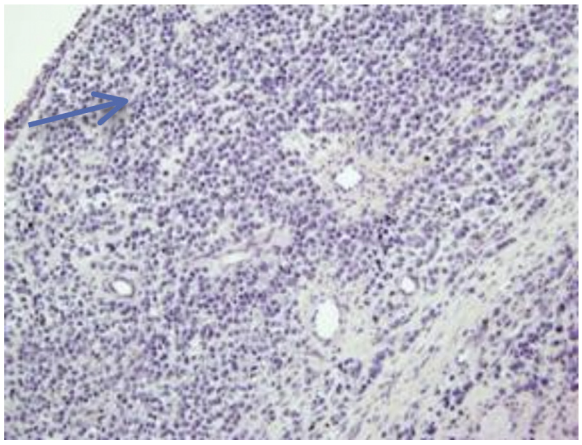

Fig. 1. Infiltration of the mucosa of the nasal cavity by melanoma. The arrow indicates the cellular proliferation invading the mucosa underneath an intact surface epithelium.

3.3. Histology

The diagnosis is based on histological examination of tumour biopsies. Histological examination is difficult due to marked cytological 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

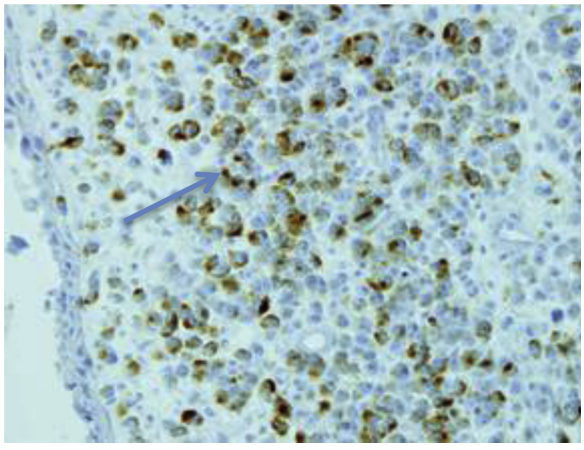

Fig. 2. Brown intracytoplasmic labelling of tumour cells with HMB45. The arrow indicates a zone of intense labelling in the form of small grains.