Sinonasal Mucosal Melanomas. Review of 17 Cases

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Introduction: Mucosal melanomas (MM) represent 1.3% of all melanomas; 55% of them are located in the head and neck region mainly in the sinonasal and oropharyngeal cavity. Sinonasal mucosal melanomas have a high rate of local recurrence and a high risk of developing metastases, 2 reasons explaining the low survival rate.
Material and method: We present 17 cases of sinonasal mucosal melanomas that were diagnosed and treated in our department from 1984 to July, 2008. The patients were studied by age, gender, site of presentation of the tumour, symptoms, radiology findings, treatment, and course.
Results: Seventeen patients with sinonasal mucosal melanomas were studied. Of these 64.7% were females and the mean age at presentation was 74 (range, 48 to 93 years). Twelve cases developed in the nasal cavity and 5 in the paranasal sinuses. The most frequent site of presentation was the septum (35%), and the most common symptom was epistaxis (77%). Three patients rejected any treatment, 12 of the patients were treated surgically, 1 received chemotherapy, and another chemotherapy plus radiation therapy. The 5 year disease-specific survival rate was 35.7%.
Discussion and conclusions: Sinonasal mucosal melanomas are rare tumours with a high mortality. The treatment of choice is still surgical resection with wide surgical margins. Even so, the main cause of treatment failure is local recurrence, followed by the development of metastases. Because of the poor prognosis with this tumour, new treatment strategies are necessary.

Key words: Sinonasal melanomas. Paranasal tumours. Lateral rhinotomy.

Melanomas mucosos rinosinusales. Revisión de 17 casos

Introducción: Los melanomas mucosos (MM) representan el 1,3% del total de melanomas. El 55% de ellos se encuentra en la región de la cabeza y el cuello, principalmente en el área rinosinusal y la orofaringe. Los MM rinosinusales tienen una alta tasa de recurrencias locales y una gran capacidad para desarrollar metástasis, lo que se traduce en una supervivencia muy corta.
Material y método: Se presentan los MM rinosinusales diagnosticados y tratados en nuestro servicio desde 1984 a julio de 2008. Se recogieron datos clinicopatológicos que incluyen edad, sexo, sitio y síntomas de presentación, hallazgos radiológicos, tratamiento y evolución.
Resultados: Se realiza una revisión de 17 pacientes. El 65% eran mujeres. La media (intervalo) de la edad a la presentación fue 74 (48-93) años. Los melanomas se originaron en la cavidad nasal en 12 pacientes y en los senos paranasales en 5. El lugar de presentación más frecuente fue el septum (67%), y el síntoma de presentación fue la epistaxis (77%). Tres pacientes rehusaron recibir tratamiento, 12 fueron tratados quirúrgicamente, 1 con quimioterapia y 1 con quimioterapia y radioterapia. La supervivencia específica a 5 años fue del 35,7%.
Discusión y conclusiones: Los melanomas rinosinusales son tumores raros pero con una elevada mortalidad. El tratamiento de elección sigue siendo la resección quirúrgica con amplios márgenes quirúrgicos. A pesar de ello, la principal causa de fracaso del tratamiento son las recidivas locales y el desarrollo de metástasis. Dado el mal pronóstico de este tumor, parecen necesarias nuevas estrategias terapéuticas.

Palabras clave: Melanoma rinosinusal. Rinotomía paralateronasal. Tumores paranasales.

INTRODUCTION

Melanocytes are dendritic cells originating from the neural crest, located in the dermo-epidermal junction and in the mucosa, which, when malignant, lead to the formation of malignant melanomas. Mucosal melanomas are neoplasias with a more aggressive and often different behaviour than that of cutaneous melanomas.[1] Mucosal melanomas have a neuroectodermal origin, thus their impact on tissues with endodermal origin such as the oesophagus, larynx, and nasopharynx, among others, is scarce.[2,3]

Mucosal melanomas are a rare form of neoplasia, and therefore only 1.3% of melanomas have their origin in the mucosa; 55% of mucosal melanomas are located in the region

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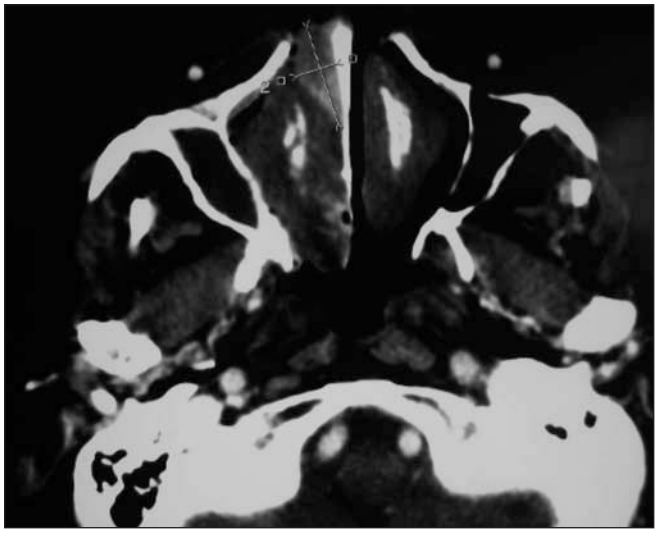

Figure 1. CT scan showing a tumour formation originating from the right septal region diagnosed as sinosinusal melanoma.

of the head and neck.[2] In this region the most frequent locations are the upper respiratory tract (56%) and the oral cavity (44%).[4] The exponential increase in the incidence of cutaneous melanomas in recent years has not been observed in mucosal melanomas, which is probably related to their lack of exposure to ultraviolet radiation.[2] Unfortunately, the increased survival which has been achieved in cutaneous melanomas has not been observed in the mucosal variety, for which the survival at 5 years remains very low at between 15% and 20%.[4]

In this paper, we studied mucosal melanomas arising in the nasal cavity and paranasal sinuses treated at our hospital to determine their clinicopathologic characteristics and potential prognostic factors.

METHOD

Rhinosinusal melanomas diagnosed and treated in our hospital between January 1984 and July 2008 were reviewed. Patients were studied by age, gender, place of presentation, principal symptoms, characteristics of imaging studies, treatment, and evolution. Survival was calculated using the Kaplan-Meier method, with the aid of the SPSS 12.0 software package.

RESULTS

During the study period, 17 rhinosinusal melanomas were diagnosed, corresponding to approximately 5% of all malignant tumours of the nasal cavity diagnosed at our hospital during this period. The patient characteristics are listed in Table.

We observed a predominance of females: 11 (65%) of 17 patients were women. The average age (range) of patients was 74 years (48-93). The female patients presented a higher average age (82 [55-86] years) than the male (72 [48-93] years).

The melanomas originated in the nasal cavity in 12 (70%) of the 17 patients and in the paranasal sinuses in the remaining 5 (3 had originated in the mucosa of the ethmoid, 1 in the maxillary sinus, and 1 in both). Of the tumours located in the nasal fossa, 8 (67%) originated in the septum (Figure 1) and 4 (33%) in the region of the turbines, 10 of these cases were confined to the fossa, while 2 had extended to the paranasal sinuses.

The most common symptom was epistaxis, found as the presenting symptom in 13 patients (77%); 8 patients (47%) reported nasal obstruction, always accompanied by epistaxis; 3 patients referred visual disturbances. Symptoms that were present in only 1 patient were facial deformity, pain, headache, tinnitus, and nasal scabs.

Of the 17 patients, 3 (18%) refused treatment; 12 patients (71%) were surgically treated, and 11 of these (65%) received surgery with curative intent, whereas 1 (6%) received surgical resection as a palliative measure. Palliative surgery was performed in a 93-year-old patient with extensive co-morbidity, facial deformity and repeated epistaxis, who also presented cervical lymph node metastases; this patient received endoscopic surgery with tumourectomy, which was repeated 3 times and it was also necessary to apply flash radiation therapy to control the epistaxis.

Immunotherapy was applied after curative surgery to 4 patients (24%), 3 of them with bacillus Calmette-Guerin and 1 with interferon alpha-2-beta. Treatment with complementary radiation therapy following surgery was carried out in 1 patient (6%).

Isolated chemotherapy was applied to 1 (6%) patient and chemotherapy in combination with radiation therapy to 1 (6%). Surgery was ruled out as a treatment of choice in both patients due to advanced age and extensive co-morbidity in 1 case; the other patient presented invasion of the anterior cranial fossa.

In 3 patients it was not possible to perform appropriate follow-up, thus they were eliminated from the analysis. The average (range) follow-up for the remaining patients was 25 months (15-72). Of these, 5 died from the tumour and 1 for different causes (he was free of disease at the time of death). Four patients are alive with tumour at the time of last review and 4 are free of the disease. The 5-year survival calculated by Kaplan-Meier excluding the 3 patients without follow-up was 35.71% (Figure 2).

Of the 11 patients who were treated surgically with curative intent, 1 (9%) was lost during follow-up, 4 (36%) are disease-free; 7 of the 11 patients had tumour recurrence at 4, 6, 9, 10, 15, 44, and 52 months, respectively. Salvage surgery was carried out in 5 of the 7 patients; 2 of them are disease-free. One of the patients had tumour recurrence 3 months after performing salvage surgery, which was considered unresectable, while another patient presented bone metastases 5 months after the salvage surgery. Tumour recurrence took place in 1 patient 9 months after surgery and, due to its extension, it was considered unresectable. One patient developed brain metastases 4 months after surgery.

Table 1. Clinicopathologic Characteristics of Patients With Rhinosinusal Melanomas

Case	*Age*	*Gender*	*Place of Presentation*	*Symptoms*	*Treatment*	*Evolution (mo)*
1	83	Female	R ethmoid	Visual alterations	Chemotherapy	No follow-up
2	84	Female	R middle turbine	Epistaxis	No treatment	Alive with tumour (30)
3	84	Female	R middle and lower turbine	Epistaxis, nasal obstruction	Surgery (PR) + BCG	Deceased due to other causes (27)
4	70	Female	R septum	Epistaxis	Surgery (PR) + BCG	Alive without tumour (60)
5	74	Female	L septum	Epistaxis, nasal obstruction	Surgery (PR) + BCG	Alive without tumour (72)
6	73	Male	R middle turbine	Epistaxis, nasal obstruction	No treatment	No follow-up
7	67	Female	R septum	Epistaxis, nasal obstruction	Surgery (PR)	Alive with tumour (20)
8	48	Male	L septum and ethmoidal sinus	Epistaxis, nasal obstruction	Surgery (PR)	Alive with tumour (15)
9	86	Female	R septum and ethmoidal sinus	Epistaxis	No treatment	Deceased (9)
10	69	Female	R ethmoidal sinus	Epistaxis, visual alterations	Chemotherapy and radiation therapy	Deceased (7)
11	75	Female	L maxillary sinus	Visual alterations and facial deformity	Surgery (PR)	No follow-up
12	93	Male	Septum and top of L NF	Epistaxis	Palliative surgery and radiation therapy	Deceased (16)
13	65	Male	Septum and bottom of L NF	Epistaxis and nasal obstruction	Surgery (PR)	Alive without tumour (15)
14	77	Female	L ethmoidal sinus	Cephalea and visual alterations	Surgery (CA) + radiation therapy	Alive with tumour (5)
15	55	Female	R septum	Facial pain and nasal scabs	Surgery (PR) + immunotherapy ($IFN_{\alpha 2\beta}$)	Alive without tumour (52)
16	80	Male	R maxillary and ethmoidal sinus	Epistaxis, nasal obstruction, and tinnitus	Surgery (PR)	Deceased (4)
17	78	Female	L lower turbine	Epistaxis, nasal obstruction	Surgery (PR)	Deceased (16)

CA indicates craniofacial approach; IFN, interferon; L, left; NF, nasal fossa; PR, paralateronasal rhinotomy; R, right.

With regard to patients treated with curative intent, 16 surgical procedures were performed on 11 patients, equivalent to 1.5 procedures per patient. Distant metastases developed in 5 of our patients, preceded in most cases by local recurrences.

Of the 3 patients who could not be followed, 1 refused any form of treatment, 1 belonged to the surgical group, and 1 was treated with chemotherapy. One of the patients who refused treatment was alive 30 months after diagnosis.

DISCUSSION

Rhinosinusal mucosal melanomas are usually diagnosed at advanced ages (between the sixth and eighth decade of life), and in both genders equally, although some authors indicate a slight predominance in males,[1,2,5,6] which is consistent with our data, except for a slight predominance of females (65%). It occupies the third place in types of cancer of the nasal cavity (12% of the total) and are among those with the worst prognosis (approximately 20% survival at 5 years).[7]

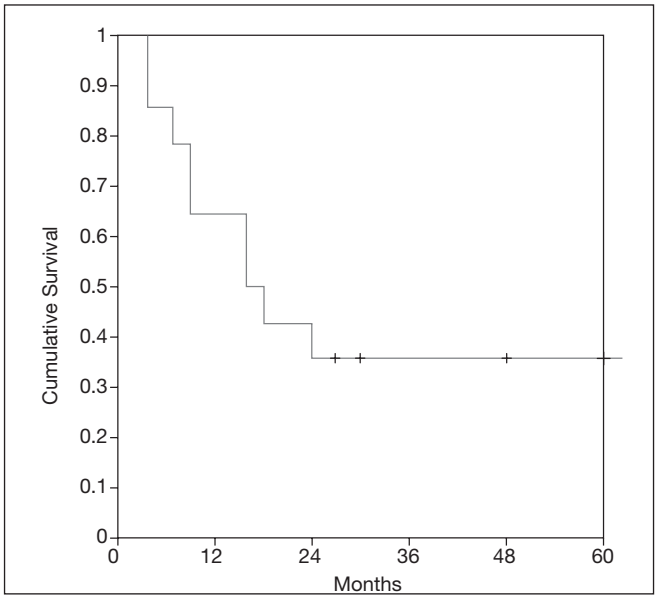

Figure 2. Cumulative survival of patients with rhinosinusal melanomas treated in our department.

The rhinosinusal location is the most frequent in mucosal melanomas of the head and neck. Of these, approximately 80% are in the nasal cavity and 18% in the sinuses. In the present series, 70% were located at the level of the nasal cavity and 30% in the paranasal sinuses.[1,8]

At the level of the nasal cavity, the most common sites of presentation are the septum (41% of cases), the middle turbine (29%), the inferior turbine (23%), the lateral nasal wall (7%), and the bottom of the nasal fossa (1%).[9,10] This preference for the septum was also observed in our series, as it affected 67% of the cases; in half these patients the tumour was confined to the septum, while in the other half it extended from the septum to surrounding regions.

Mucosal melanomas are also characterized by being multiple, having satellite formations and having an early angiolymphatic invasion, resulting in advanced locoregional stages and spreading at a distance with a high mortality rate for the disease.[2] This fact was evident in 1 of our patients who at the time of diagnosis showed rhinosinusal involvement in 3 different anatomical sites.

The symptoms of presentation in mucosal melanomas depend on the anatomical site of initiation. Patients with melanomas of the nasal cavity usually present epistaxis and obstruction of the nostril. Symptoms such as proptosis, diplopia, facial pain, and facial asymmetry are more frequent in those arising in the paranasal sinuses and are usually associated with advanced stages of the disease.[1,2,11] In the current study, epistaxis was the most common symptom (76% of cases), whilst 47% of patients also presented nasal obstruction at the time of diagnosis. Three patients presented visual alterations and the sites of origin in these cases were the paranasal sinuses.

In rhinosinusal melanomas, the regional metastasis or the depth of the tumour invasion have not been shown as important factors in prognosis.[1,12] At the time of diagnosis, most patients present a disease localized at the site of origin, which does not necessarily confer a better prognosis, since local recurrence is the major cause of failures in treatment. In 50% of patients local recurrences take place, usually during the 12 months following treatment.[1,2] In accordance with these data, in this series there was local recurrence in 7 (64%) of 11 patients. Dauer et al[13] recommended a close monitoring of operated patients, since the early resection of the tumour recurrences may increase survival. Thus, 3 of our patients could be salvaged surgically, and are free of disease.

There is no system of TNM type staging for rhinosinusal melanomas, so comparing different treatments with one another is very difficult. So far, the most commonly used system is Ballantyne's system, which divides them into 3 stages: stage I, tumours confined to the site of origin; stage II, tumours with regional lymph node metastases; and stage III, tumours with systemic metastases.[9]

Other authors believe that stage I (localized disease) should be subdivided into histological parameters and suggest level I for in situ melanomas, level II for tumours with invasion of the lamina, and level III for tumours with in-depth invasion.[14]

Unlike nasal melanomas, mostly diagnosed (75%) at stage I, melanomas of the paranasal sinuses are diagnosed in more advanced stages.[15,16] In the current series, 2 of the 5 patients with melanomas of the paranasal sinuses died at 4 and 7 months, 1 is alive with tumour 5 months after surgery, and the other 2 were lost during follow-up. One of these patients presented invasion of the anterior cranial fossa at the time of diagnosis. The experience with this type of patients suggests that patients with melanomas of the paranasal sinuses have a worse prognosis than those with tumours in the nasal cavity, which is probably due to a delayed diagnosis.

In contrast to squamous cell carcinoma, rhinosinusal melanomas metastasize with less frequency to cervical lymph nodes, but tend to develop a greater number of distant metastases, especially in the lungs and brain.[16] Lymph node metastases are evident at the time of diagnosis. In our series only 1 of the 17 patients had them, and no treatment of the cervical metastases was carried out due to the advanced state of the disease at diagnosis.

Surgery is the treatment of choice in localized rhinosinusal melanomas. The need to preserve vital structures leaves the surgical margins positive in some cases.[2] Surgery was carried out with curative intent in 11 of the 17 patients in our series, of which 4 (36%) were free of disease at the last review with an average follow-up of 28 months. Thus, the specific survival of patients at 5 years was 35.71%, indicating a poor prognosis for this disease, although similar to other tumours in the same location (adenocarcinomas, squamous cell carcinomas) and better than that of undifferentiated carcinomas. It should be mentioned that in our series the 5-year survival is slightly better than in other similar studies.[13]

Surgical procedures depend on the location of the tumour and its extension. The most commonly used approaches are paralateronasal rhinotomy, craniofacial resections, and endoscopic surgery.[8] The most commonly used approach in this series was paralateronasal rhinotomy, which was performed in 10 of the 11 cases treated with curative intent. In the remaining case a craniofacial resection was carried out on a patient with melanoma at the level of the ethmoidal sinus with extension to the orbit. Endoscopic surgery was performed in a patient with palliative intent.

Given the frequency of distant metastases, in patients requiring radical surgery with approaches such as craniofacial surgery, or orbital exenteration, a positron emission tomography should be considered in order to find them.[16] Magnetic resonance studies may find perineural spread, and in those patients in whom it is detected, the therapeutic attitude may change and palliative measures could be considered.[17]

Prophylactic resection of lymph nodes is not recommended.[2] Lymph nodes should be treated only if the presence of palpable tumours is demonstrated, if a positive biopsy is obtained by FNA or if radiological criteria for malignancy are met.[9] In the present series, prophylactic lymph node dissection was never carried out.

The role of radiation therapy in melanomas is not clearly defined.[2,18] Radiation therapy is mainly applied to patients with positive surgical margins, those presenting local recurrence or as a palliative measure. Dauer et al[13] published a higher specific survival when complementary radiation therapy was applied. As in the case of surgical dissection,

prophylactic irradiation of the lymph nodes is not recommended.[2,9]

Immunotherapy and chemotherapy have been used as adjuvant or palliative therapies. Immunotherapy is effective only in a small group of patients.[2,9] In our series, chemotherapy was applied to 2 patients who were not considered for surgical treatment due to their advanced stages and co-morbidities. It was not possible to monitor one of the patients and one died 7 months after diagnosis. Immunotherapy was administered as a complementary treatment to 4 of the patients; in 3 it was carried out with BCG, and in 1 case with interferon alpha-2-beta. All 4 patients presented a normal course, but 3 of them presented localized lesions in the septum, which have recently been reported to have a better prognosis.[13]

Dauer et al[13] have recently published a clinicopathologic review of 61 cases with a 5-year survival of 22%. They found a better prognosis for lesions located at the level of the septum and a worse prognosis for lesions at the level of the maxillary sinus, a view which we share, after observing the evolution of our patients. A third of patients had cervical metastases, which preceded distant metastasis. Distant metastases rapidly led to death. Local recurrences usually precede the development of distant metastases, thus making the control of the primary tumour a strategy to follow in order to attempt to increase survival. This is a view we share with these authors, as in the present study 5 patients developed distant metastases, which were preceded by local recurrence in 4 of them.[19]

In conclusion, rhinosinusal melanomas are rare tumours that mainly affect elderly patients. Surgical resection with wide surgical margins remains the treatment of choice. Despite this, the main cause of treatment failure is local recurrence, and distant metastasis is frequent. Given the poor prognosis of this tumour, it seems necessary to carry out studies aimed at developing new therapeutic strategies to improve the prognosis of patients suffering from this disease.

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