CASE REPORT

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Malignant melanoma of nasal cavity

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Abstract

Introduction: Malignant melanoma rarely develops in the mucous membranes. Statistical data indicate that rhinosinusal mucosal melanoma was reported in less than 1% of all melanic tumors and in 2–8% of all cancers developed in the nasal fossae and sinuses. Due to reduce and non-specific symptoms and a high degree of invasion away, patients come for a medical expertise in advanced stages of the disease, which is leading to a poor prognosis. The average five-year survival is 20–30%. *Patient and Methods*: We present the case of a 65-year-old female patient coming from a rural environment, hospitalized for unilateral nasal obstruction and nasal mucosal changes of a blackish appearance on all of the walls. *Results*: The endoscopic examination revealed a matter and of a blackish appearance nasal mucosa along the whole length of the left nasal cavity (septum, turbinates, floor, ceiling). Presumptive diagnosis of melanoma led to the excision of inferior and middle turbinate mucosa, floor and ceiling mucosa and the excision of the nasal septum, keeping the columella and the posterior portion. Histopathological and mostly immunohistochemical exams confirmed the diagnosis of malignant melanoma. To determine the phenotype of tumor cells, it was evaluated their immunostaining for HMB-45, Melan-A, S-100, vimentin, cyclin D1 and CD44 markers. The patient followed oncologic treatment and radiochemotherapy, presenting a favorable evolution with the absence of loco-regional recurrence or distant metastasis 24 months postoperatively.

Keywords: malignant melanoma, nasal cavity, rhinosinusal mucosa, immunohistochemical markers.

Introduction

The first case of melanoma developed at the level of the rhinosinusal mucosa was reported by Lucke in 1869 and has since been reported in less than 1% of the total melanic tumors and in 2–8% of all neoplasms developed in the nasal fossae and sinuses [1].

Melanomas developing in the nasal cavity or paranasal sinuses are rare and have a poor prognosis [2]. Primary melanoma of the head and neck represents 25–30% of all melanomas [3]. The incidence of melanoma that develops in the aerodigestive tract mucosal surface varies between 0.4–4%, most of them in the nasal cavity or paranasal sinuses [4, 5]. Nasal cavity is more frequently affected than the paranasal sinuses and the maxillary sinuses are more frequently involved than the ethmoid sinuses. Peak incidence is between the fifth and eighth decade and is slightly more common in men than in women. Age and sex do not affect prognosis [6, 7]. The average five-year survival is 20–30% [1].

Patient and Methods

We report the case of a 65-year-old patient, which was admitted in the ENT Clinic of Emergency County Hospital, Craiova, in December 2008, for left nasal obstruction, recurrent microepistaxis, physical fatigue, loss of appetite and unsystematic headache with approximately two months evolution. Patient history revealed no systemic diseases and the fact that the patient had not undergone any surgery. Of rural origin, the patient worked in agriculture, being much time exposed to solar radiation. She did not smoke and drank alcohol only occasionally (Figure 1).

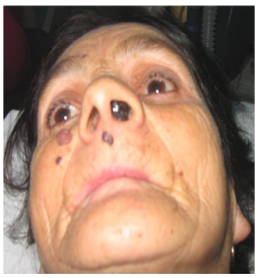

Figure 1 – ***Melanic pigmentation disseminated lesions on the face.***

Inspection of head and neck region showed multiple pigmented melanic lesions, especially in the areas exposed to direct sunlight. Inspection and palpation did not reveal the presence of adenopathies in the lymph node chains of the face and neck area.

ENT examination, made during rhinoscopy, viewed at the level of the vestibule and the left nasal fossa a tumor with blackish appearance, smooth surface, soft,

depressed, which obstructed the lumen quasi-completely.

Mucosa of the septum, the left inferior turbinate, the left nasal fossa's floor and ceiling, had a dull, blackish appearance.

The rest of the ENT examination showed no pathological changes.

Biological tests, cervical ultrasound, chest X-ray and abdominal ultrasonography were normal.

Computer-tomography examination (CT) revealed a tissue mass in the left nasal fossa of 31.5/13 mm axially, with heterogeneous contrast capture that deformed the nasal fossa and produced its obstruction, without osteolysis and excluded the presence of any processes of replacement of space at the cerebral level. The neck CT scan did not reveal the presence of lymph nodes.

Before surgery a panendoscopy was performed, with a thorough examination of the cavum, the hypopharynx, larynx, esophagus and tracheo-bronchial tree, thus invalidating the existence of synchronous tumors or other pathological lesions in the ENT area.

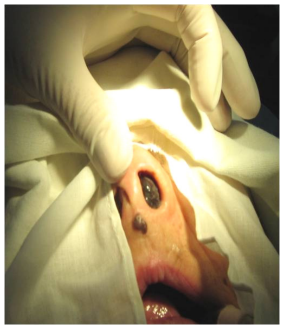

Figure 2 – ***Nasal cavity tumor: intraoperative image.***

The presumptive diagnosis of malignant melanoma, corresponding to stage I (primary tumor without metastases), determined a surgical intervention, being practiced the excision of the tumor formation and the mucosa of the inferior and middle turbinates, the mucosa of the floor, the ceiling and the excision of the nasal septum, with the preservation of the columella and the posterior portion of vomer.

Intra-operative, the black color of the tumor formation extending to the mucosa of all the walls of the nasal fossa impressed.

The resection piece, consisting of several fragments, was fixed in formalin 10% diluted, for 48 hours, then it was sent to the pathology laboratory for histo-pathological diagnosis. Of each of the sent pieces was taken one fragment, which was processed by conventional histological techniques of inclusion in paraffin, and paraffin blocks thus obtained were sectioned in the microtome at 3 μm, obtaining fine sections which were displayed on both albumin leaf for the usual Hematoxylin–Eosin staining, and poly-lysine blades for immunohistochemical examination (IHC).

For IHC, the preparations were processed by the Streptavidin–Biotin complex method (sABC). The tumoral immunophenotype was assessed by evaluating the immunostainig of markers, using specific antibodies: anti-HMB-45 (clone HMB-45, dilution 1:50, DAKO), anti-S-100 protein (polyclonal, 1:250 dilution, DAKO), anti-vimentin (clone V9, dilution 1:50, DAKO), anti-Melan A (clone 103, dilution 1:50, DAKO), anti-CD44 (clone DF 1485, dilution 1:50, DAKO) and anti-cyclin D1 (clone DCS-6, dilution 1:40, DAKO). For each anti-body were used appropriate positive external controls.

Results

Macroscopic evaluation

The macroscopic evaluation of the resection revealed multiple tumor fragments, of varying sizes from 0.4 to 1 cm, some black, others brown-blackish, with soft consistency (Figure 3).

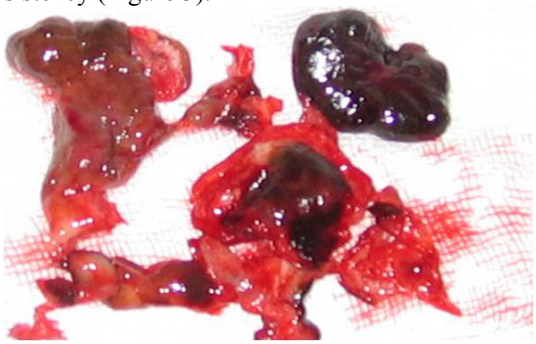

Figure 3 – ***Macroscopic appearance of the resection piece.***

On the microscopic examination of the sections of tumoral fragments, it was observed, subepithelial, both in the superficial chorion and the deep one, a diffuse proliferation of round cells, small, non-cohesive, with severe nuclear and nucleolar atypia (Figure 4).

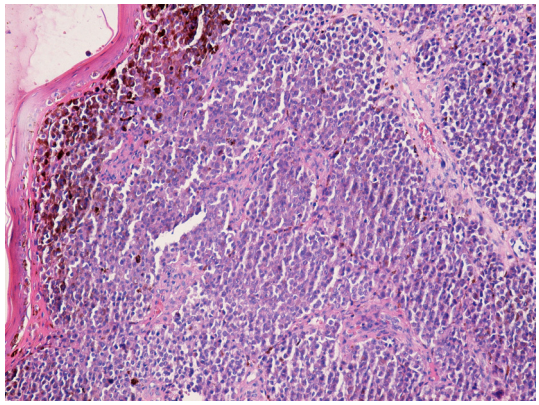

Figure 4 – ***Malignant melanoma: diffuse proliferation of round cells, non-cohesive, with intracytoplasmic melanic pigment, both in the superficial chorion and the deep one (HE stain, 40×).***

Also, stretched areas of cells subepithelial located showed intracytoplasmic melanic pigment (Figure 5), this being highlighted and isolated also in the tumor cells isolated from the tumor. The tumor cells had an epithelioid appearance, with eccentric nuclei and cytoplasm weakly eosinophilia. Although at first glance the tumor proliferation appeared to be diffuse, however, on closer examination, it was ascertained the presence of intratumoral very thin conjunctive septas, delimiting islands of tumor cells under the form of lobules.

Although the tumor was located at the junction of the nasal fossa skin and nasal mucosa, microscopic examination showed no invasion of respiratory epithelium, which showed only ulcerated areas and subjacent loose stroma with seromucous glands, not invaded by the tumor.

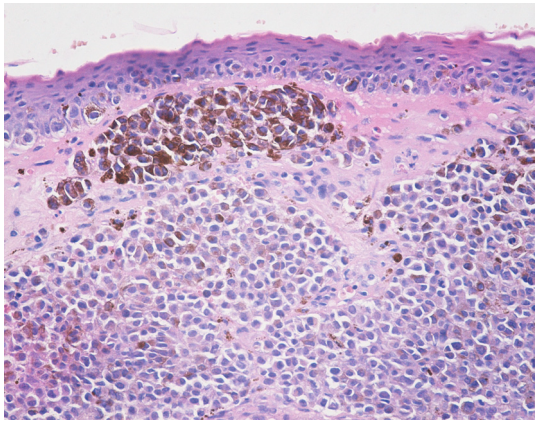

Figure 5 – ***Malignant melanocytes arranged in clusters and sheets within the dermis (HE stain, 100×).***

Immunohistochemical examination

Immunohistochemical examination confirmed the melanocytic origin of the proliferate tumor cells. Thus, the main marker of melanocyte cells, namely, HMB-45, showed a diffuse positive cytoplasmic immunostaining in the tumor cells. The intensity of the immunostaining was different in different parts of the tumor, emphasizing moderate-intensity areas (Figure 6), alternating with areas where intense HMB-45 was positive in tumor cells (Figure 7).

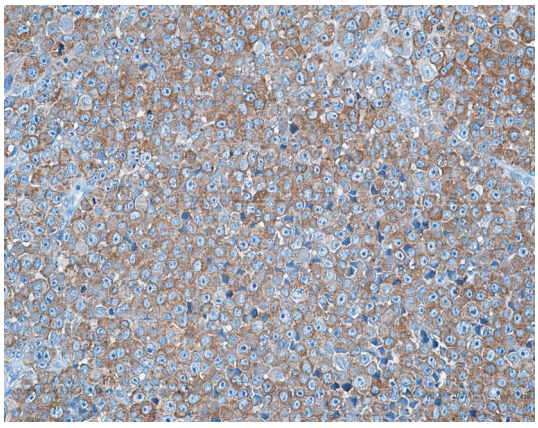

Figure 6 – ***Moderate-intensity positive immunostaining within tumoral cells for HMB-45, LSAB technique, 200×.***

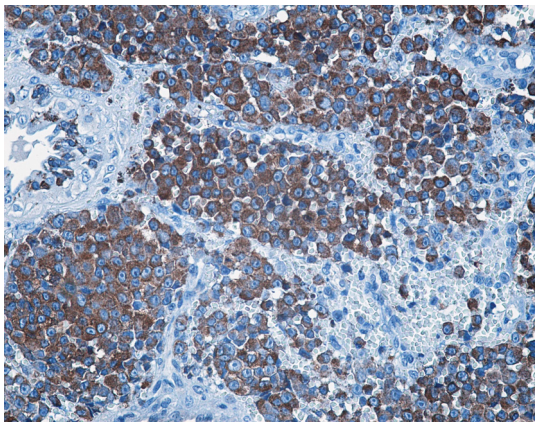

Figure 7 – ***Intense positive immunostaining within tumoral cells for HMB-45, in different parts of the tumor, LSAB technique, 400×.***

Also, vimentin mesenchymal markers and S-100 protein showed diffuse positive cytoplasmic staining in the tumor (Figures 8 and 9). Unlike them, the cytoplasmic immunostaining for Melan-A was focally positive in the tumor (Figure 10).

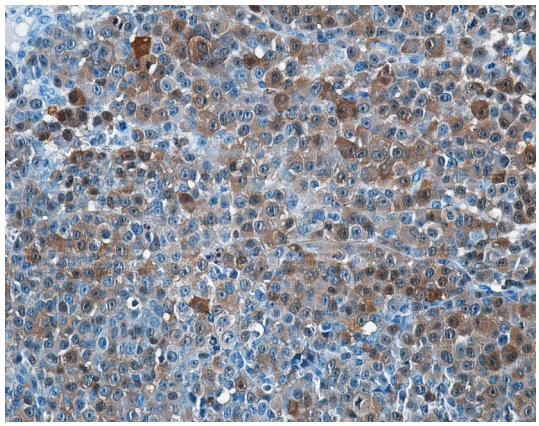

Figure 8 – ***Diffuse positive cytoplasmatic staining in the tumor for vimentin, LSAB technique, 400×.***

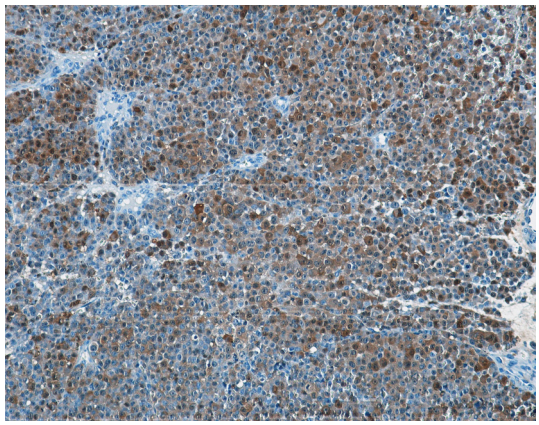

Figure 9 – ***Intense and diffuse positive immunostaining within the tumor for S-100, LSAB technique, 200×.***

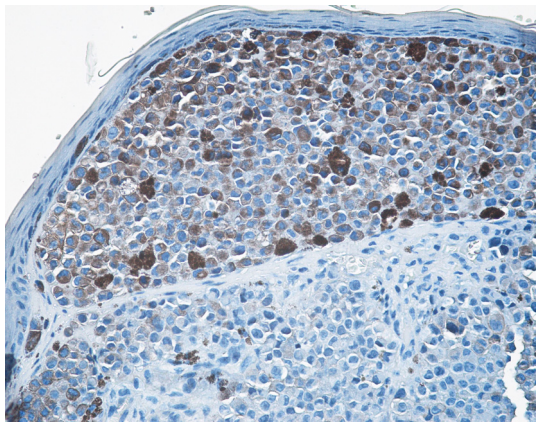

Figure 10 – ***Focally positive immunostaining within the tumor for Melan-A, LSAB technique, 200×.***

In assessing the prognosis of this tumor, it was evaluated the immunostaining for cyclin D1 and for the presence of adhesion molecule CD44. The immunoreaction for cyclin D1 was intensely focal positive in the nuclei of tumor cells (Figure 11), while CD44 marker was revealed diffuse into the tumor (Figure 12).

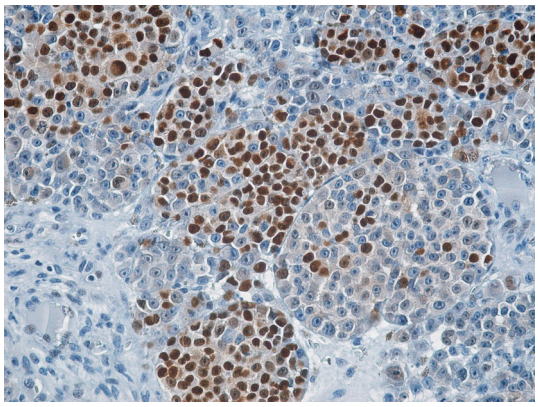

Figure 11 – ***Nuclear positive immunostaining within the tumor for cyclin D1, LSAB technique, 400×.***

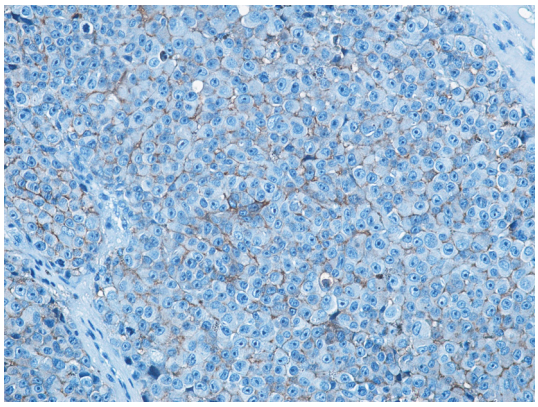

Figure 12 – ***Membrane positive immunostaining within the tumor for CD44, LSAB technique, 200×.***

Postoperative evolution

Patient's postoperative evolution was favorable, with *per primam* surgical cure. She followed a post-operative radiochemotherapy sequence in the territorial medical oncology center. The patient presented at regular intervals, every three month for ENT reexaminations, being evaluated both clinical, endoscopic and imagistic with CT examinations. At 24 months, the outcome was favorable, with no evidence of loco-regional recurrence or distant metastasis (Figures 13 and 14).

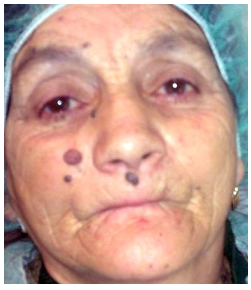

Figure 13 – ***Follow-up 18 months: without lymph node metastases.***

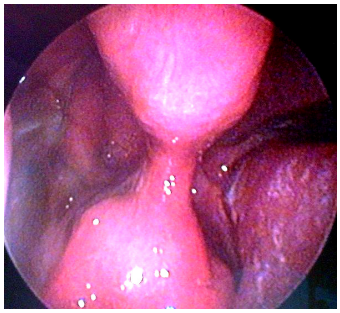

Figure 14 – ***Follow-up 18 months: urging rhino-sinusal mucosa.***

Discussion

Melanomas are tumors arising from melanocytes, derived from neuroectodermal cells located in the basal layers of the skin, annexes and some mucosa. Malignant melanoma often occurs based on pigmentation abnormalities, but it can develop on upright tissue. The vast majority of melanomas grow at skin level and only 20% of them in the head and neck region.

Common sites for melanoma are the head, neck and limbs. These areas are exposed to sunlight, one of the predisposing factors. Less common sites are the oral and genital mucosa, nail bed, conjunctiva, orbit, esophagus, nasal or nasopharyngeal mucosa and leptomeninges.

The cause of melanoma appearing in area of mucosa hidden to sun exposure is unclear. Smoking may play a role in the activation of preexisting melanocytes, leading to melanogenic metaplasia [6].

Mucosal melanoma of the nasal cavity and paranasal sinuses is rarely encountered in routine ENT practice – 1.3% of all malignant melanomas [8]. One's own statistics for 10 years, we reported only two cases of mucosal melanoma: the presented one and another localized in the hypopharynx.

This tumor has a poor prognosis due to higher rates of loco-regional recurrence and remote metastasis. It presents an invasive character and great metastatic power, on both lymphatic and sanguine pathways.

The incidence of regional lymph node metastasis at presentation is approximately 5–15% [9]. The group of submandibular lymph nodes is the most frequently involved. There is no universally accepted staging system for rhinosinusal melanoma in the TNM standard system, largely because of the rarity of mucosal melanomas.

According to the clinical form developed, a three stages classification is recognized:

- stage I: primary tumor without metastases;
- stage II: primary tumor with loco-regional node metastasis;
- stage III: primary tumor with distant metastases.

Researchers from the *American Armed Forces Institute of Pathology* proposed in 2003 a staging system for nasosinusal and nasopharynx melanoma, where T1 represents a primary tumor in one anatomic site, T2 is a primary tumor at two or more sites, N1 is any lymph node metastasis, and M1 represents any distant metastasis [10].

In our case, only one anatomical site was involved (the nasal cavity) and the CT scan invalidated the presence of lymph nodes or distant metastases, indicating stage I according to this system.

Time of presentation to the doctor depends on the size and location of the lesion. Most patients experience epistaxis and progressive nasal obstruction [2], as it was in our case.

In the moment of initial appearance, these tumors are usually well advanced. Natural evolution of malignant melanoma is marked by local recurrences, extensions and frequent metastasis to lymph nodes and viscera, thus becoming one of the most dangerous forms of nasosinusal cancer. A high index of suspicion is necessary to make an early diagnosis.

Among cancers arising in the nasal cavity and paranasal sinuses, mucosal melanomas are rare in comparison with squamous cells carcinomas.

The differential diagnosis of a nasosinusal tumor includes various round cell tumors, which may be benign, intermediate and malignant [11]. Benign tumors include nasal polyps, osteoma, chondroma, schwannoma and neurofibroma, cementoma [11]. Tumors classified as intermediate include inverted papillomas, meningiomas, hemangiomas and hemangiopericytomas [11, 12], and of the malignant one, squamous cell carcinoma is the most common, followed by adenoid cystic carcinoma, adenocarcinoma, neuroblastoma, "rotund-cell" sarcoma, lymphoma and undifferentiated carcinoma with small cells.

Histological diagnosis of melanoma presents several challenges. A study published in 2002 showed that the analysis of sections stained with Hematoxylin–Eosin (HE) had a specificity of 100% and a sensitivity of 59% [13]. After the appearance of tumor cells, malignant melanoma may have several histological patterns, namely round cellular, with spindle and mixed cells, so a differential diagnosis of all types of round or spindle cell tumors is necessary. Sometimes, just examining HE stained sections is not sufficient for differential diagnosis, the immunohistochemical exam being necessary in these cases to determine the phenotype of proliferate tumor cells. Because melanocyte cells have embryo origin in both ectoderm and mesoderm, they will express melanocytic and mesenchymal markers.

Malignant melanoma show strong cytoplasmic positivity for HMB-45 in the majority of cases (65–95%), with the proportion of positive tumor cells ranging from a few to 100%. When the expression of the antigen is weak, staining may appear as a fine granularity similar to that seen in cytologic preparations [14].

The positivity for HMB-45 is seen in almost all types of primary and metastatic melanoma including amelanotic melanoma, spindle cell melanoma and acral lentiginous melanoma. Attesting to the specificity of the antigen, HMB-45 reactivity has been demonstrated in malignant melanomas of diverse morphology such as signet ring melanoma, myxoid melanoma, small cell melanoma, balloon cell melanoma and in melanomas of different anatomic sites such as the gallbladder, urinary bladder, anorectal region, vulva, sinonasal region, uterine cervix, other mucosal sites and bone [14]

Melanomas and melanocytic proliferations occurring in complex tumors such as pulmonary blastoma have also been HMB-45+ [15, 16].

As HMB-45 immunoreactivity is melanocyte-specific, positivity can be encountered in lesions with melanin production such as adrenal pheochromocytoma, melanotic neuroectodermal tumor of infancy (prognoma), melanin-containing hepatoblastoma, malignant epithelioid schwannoma of the skin, pigmented carcinoid tumor and esthesioneuroblastoma. More recently, HMB-45 positivity has been reported in a variety of lesions, which may have implications for their differentiation or histogenesis [14].

S-100 is a sensitive protein in melanomas, but non-specific, while HMB-45, monoclonal antibody derived from extracts of melanoma, is more specific, but can occasionally be detected in carcinoma cells [17].

For cases in which staining for these two markers give ambiguous results, specific melanoma markers, known as Melan-A is usually used.

Melan-A has proven to be very specific in differentiating melanoma from other malignancies with which it can be confused on optical microscopy, such as sarcomas, plasmacytomas and carcinomas.

There is a recent report on the use of rapid intraoperative immunohistochemistry for S-100, HMB-45, and a 'melanoma cocktail' consisting between 71% and 86%, while maintaining high specificity [18]. However, because of its unavailability, of HMB-45, Melan-A, and tyrosine [18]. The results had high sensitivities, ranging rapid immunohistochemistry is not frequently used.

It is generally accepted that the cornerstone of treatment is surgical resection of the tumor with not invaded tumor safety margin [19].

Compared with squamous cell carcinoma, nasosinusal melanoma uncommonly metastasize in lymph nodes, but most frequently in the lungs and brain [12]. Therefore, a radical neck dissection is not recommended for patients without clinical or radiological evidence of cervical metastases [20].

Historically, melanoma has been characterized as a radio resisting mucosal disease, but recent observations suggest that radiotherapy has an important role. The literature shows overall initial response rate of 50–75% for the radiotherapy alone being used to treat localized mucosal melanomas. However, long-term survival remains a major problem [21, 22].

Bonner demonstrated the usefulness of concomitant chemotherapy in squamous cell carcinoma of head and neck region, indicating the possible role of concomitant chemotherapy *per primam* in mucosal melanomas [23]. Chemotherapy may play a role in the postoperative period as well. A number of questions and controversies still remain.

Currently, the most accepted treatment of malignant melanoma is surgery and postoperative radiotherapy. Consequently, that was the treatment in our case.

Mucosal melanomas tend to be more aggressive and have a worse prognosis than the cutaneous ones: only 10–15% survival rate at five years [10, 24].

The prognosis may be influenced by clinical stage at presentation, tumor thickness, presence or absence of vascular invasion on histologic examination, the appearance of local recurrence and distant metastases.

Our patient, diagnosed with stage I disease, with a thin layer of malignant cells (<5 mm), no report of vascular invasion and without the presence of distant metastases appears to have a relatively good prognosis.

Conclusions

A high index of suspicion has been considered in evaluating a rhinosinusal tumor, especially when it was associated with epistaxis or unilateral nasal obstruction.

ENT examination, completed with endoscopic examination and CT scan explore raised the suspicion of malignant melanoma of the nasal cavity.

Correct diagnosis was made by histopathology and immunohistochemistry examinations. Markers of high specificity for malignant melanoma of the rhinosinusal mucosa proved to be S-100, HMB-45 and Melan-A.

The absence of adenopathy and distant metastases constituted an important factor in prognosis and treatment, and thus the patient diagnosed with localized stage I disease (primary tumor without metastases) undergone radical surgery, followed by postoperative radiotherapy.

Removal of nasal tumor with wide surgical excision of the entire tumoral transformed mucosa, completed with oncological treatment led to a favorable evolution.

Acknowledgements

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