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CASE REPORT

Merkel cell carcinoma of the forehead area: a literature review and case report

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Abstract

Background Merkel cell carcinoma (MCC) is an uncommon, aggressive malignancy of the skin, mostly affecting head and neck area in elderly white patients. Between head/neck sites, face accounts for 61% and forehead accounts for 17% of all face MCCs.

Purpose We here present a literature review MCC cases arising in the forehead area, published in the English literature in the period 1987–2018, and report a personal observation with a late diagnosis and a treatment out of the current recommendations. The aims of this paper are to provide an up-to-date on MCC arising in the forehead area and to raise awareness about misdiagnosis of this type of lesion mimicking arteriovenous malformations (AVM).

Material and method Literature review was performed on PubMed and Medline database and "Merkel cell carcinoma (MCC)," "forehead" and "MCC forehead location" were the terms the authors searched for. Patients' data have been drawn from descriptions of single cases and of short case series reports. For each case, data were collected about clinical characteristics, treatment modalities and outcomes. The study has been limited to the clinical features of the disease, excluding etiologic/pathogenic aspects.

Results Twenty-five patients with forehead MCC have been identified, coming from 20 sources. Nineteen presented a locoregional disease and 6 had an advanced pathology. TNM classification was reported in only two cases lacking for the other available data. Patients presented at mean age of 66 years with solitary or multiple nodules or dome-shaped/hemispherical mass, rarely ulcerated. Mean size of tumors was 1.13 cm of max diameter. Previous or concurrent malignancies or immune-hematologic disorders (AIDS) were often associated. At first investigation, lesion was often mistaken for other malignant or benign processes and, then, diagnosis was generally late. Some type of preoperative biopsy was performed in 3 patients, while the others had only a postoperative microscopic study of specimen. Initial treatment consisted in 6 cases (24%) in a not further specified about extent and width of margins local excision of the primary lesion, while a wide resection was reported in only 3 cases (12%). Surgical treatment of involved lymph-nodes was performed in 3 cases (12%). Six patients underwent radiotherapy for locoregional or distant recurrences. Mortality and overall survival rate at five years were 28% and 24%, respectively. Spontaneous regression was observed in 3 patients (12%).

Case report Personal observation concerned an 82-year-old woman presenting with a forehead periorbital 5 × 5 cm red-bluish mass. The erythematous lesion was erroneously diagnosed as hemangioma on the base of color, the absence of any signs of malignancy, an angio CT indicating a hypervascular tissue and a FNA cytology (FNAC) lacking of malignant cells. The mass was excised as a benign lesion with about 1 cm margins extent without searching larger edges. Postoperative radiotherapy was

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offered to the patient after histology report, but she refused. After 4 months from surgery, she had a parotid metastasis and died from the illness in spite of platinum-based chemotherapy.

Conclusions This study confirms the aggressiveness of forehead MCC, comparable with that of other face similar tumors. Personal case suggests that the deceitful benign feature of lesion may mimic an AVM and that FNAC may be misleading and diagnostic failure worsen prognosis. Our experience suggests that in the face smaller than 2–3 cm margins resection may increase the risk of locoregional recurrence. Therefore, postoperative wide-field irradiation should be ever delivered, after forehead MCC surgery, not only when clear margins are unattainable or involved with tumor, but also when negative microscopic edges are documented and residual cancer is thought not persist in the tumor bed. Orbit irradiation seems to be not dangerous for the eye.

Keywords Merkel cell carcinoma (MCC) · Head and neck tumor · Face tumor · Forehead tumor

Introduction

Merkel cell carcinomas (MCCs) are uncommon, but increasing cancers of the skin [1–3] affecting mostly white elderly and immunosuppressed patients [4–6]. They are more aggressive than most of the other types of skin cancer, including melanoma [5, 6], being characterized by a frequent involvement of regional lymph nodes (80–83%) and of distant organs (20–75%) at presentation [7]. A wide local excision (WLE) with clear margins and adjuvant radiotherapy, together with a surgical or radiotherapy treatment of involved lymph nodes, is the mainstay of treatment for disease at early stages, but high rates of recurrence after surgery are still reported as local (12 to 50%), regional node (17 to 76%), and distant metastases (12 to 50%) [8, 9].

Head and neck region is the most common region of a primary MCC (48–53%) [4, 10] and it has been recognized to have an increased risk of local failure [11, 12], probably because of anatomical constraints that may preclude a WLE [13]. Sixty-one percent of head and neck tumors are located in the face [14], where cheeks have been found to be the most common subsite (29%), followed by eyelids (18%), forehead (17%), lips (9%), ears (7%), nose (5,4%), scalp (4%), and chin (2%) [10, 15]. Primary face MCCs can involve the face by various grades of tumor growth and local invasion producing aesthetic damages (from limited papule/nodule or dome-shaped mass up to complete hemiface disfiguration) and symptoms when involving nearby organs as eyes or ears (visus impairment or hearing loss).

Forehead is the third most frequent site [10, 15] of MCC. Periorbital or near-nose localization may have a surgical relevance because of the possible involvement of orbit, temple, eye, and nose root at the excision time and because of subsequent scar processes [16, 17]. In these cases, it may be a severe challenge to assure correct oncologic treatment and preserve essential structures [18, 19]. However, no significant damages to nearby organs have been reported in treatment the forehead primary MCC, while problems were encountered in some cases of tumor extension from cheek to the forehead area [20].

Material and method

A review of the current literature on MCC focusing to the forehead area and a retrospective analysis of published cases was performed. A personal case is presented separately in the paper and is included in the final discussion.

Literature review was performed on PubMed and Medline database and "Merkel cell carcinoma (MCC)," "forehead," and "MCC forehead location" were the terms the authors searched for. Patients' data have been drawn from descriptions of single cases and of short case series reports. For each case, data were collected about clinical characteristics, treatment modalities, and outcomes. Time search was limited from 1987 to 2018. Only single case and short case series reports were found.

Data were collected about the authors, year of publication, patients' age and sex, number of cases described, size of tumor, previous/concomitant diseases, staging with lymph-vascular spread, primary treatment, recurrences, secondary treatment, and outcomes. The study has been limited to the clinical features of the disease, excluding etiologic and pathogenic aspects. Clinical/pathological characteristics are reported in detail in Table 1 and summarized in Table 2.

Results

Twenty-five patients with forehead MCC have been found coming from 20 sources [21–38]. Eight females and 11 males were identified; in 6 cases, the sex has not been reported. The median age at time of diagnosis was 66 (range 27–93 years). The median tumor size (greatest diameter) was 1.13 cm (range 0.5–3 cm). The majority of patients (19 cases) presented a locoregional disease and the other 6 had an advanced pathology. Only 2 patients could be staged on the base of TNM staging system for MCC of the American Joint Cancer Committee (AJCC) [15] because of missing data (Table 1).

Patients presented with asymptomatic, solitary (13 cases) or multiple nodules (2 cases), flesh to red-bluish-colored

Table 1 Clinical/pathological data of 25 cases of forehead MCC published from 1987 to 2017, coming from 19 sources

Source/year	Age/sex	Number cases	Feature/size cm	Prev/conc disease	LN-vascular spread	Primary treatment	Recurrence	Secondary treatment	Outcome
Rocamora [21] 1987	82/	2	Nodule			WLE			
						WLE	Non-LR		
Kayashima [22] 1991	68/F	1	Nodule 1.6 × 1.6			biopsy			Sr aft 11 y
Connelly [23] 1997	85/M	1	Nodule 1.4		Parotid LN	Biopsy		WLE+LN adenectomy intraparotid	SR aft 50 m
Nghiem [4] 1998		1	Multiple nodules						
Lawenda [24] 2001	67/M	1	Nodule		T1 N1 Stage III	WLE; Parotidectomy; mRND; RT		CT	Responce to CT
Damborenea Tajada [25] 2001	72/F	1	Nodule			Excision	Parotid nodule; Jugulodigastric LN	Parotidectomy +RND + RT	No LR aft 3 y
Wang [26] 2004	51/M	1	Nodule	BCC		Incomplete excision	Paraspinal soft tissues of his lower back	Re-excision; RT	
Bensaleh [27] 2007	69/M	1	Nodule 2 × 1			WLE	Head; LN neck	RT; CT	Death 24 m aft surgery
Kukko [28] 2007	27/F pregnant	1	Nodule			Local excision	Ulcerate recurrence	WLE; RT	No LR alive 24 m aft surgery
Busse [29] 2008	63/M	1	Nodule 2.5 × 2.2	HIV BBC SCC	Pre-auricular and parotid mass; cervical LN	Biopsy; excision by Mohs surgery	Liver metastasis		Death 15 m aft diagnosis
Manten [30] 2009	87/F	1	Nodule		Intrapulmonal,mediastinal, axillary nodal and pelvic metastasis	Biopsy			Death aft 1 m
Gorjon [31] 2011	87/m	1	Nodule	Epidermoid carcinoma, larynx BCC		WLE+RT			
Enomoto [32] 2011	83/F	1	Nodule			Biopsy+RT			SR 1 m aft biopsy
Kressin [33] 2012	64/M	1	Nodule 1.6 cm	Plasma cell myeloma		Parotid; Bone marrow		WLE+RT	Death aft 6 m
Braclik [34] 2013	64/M	1	Ulcerated tumor			Incomplete excision	Temple recurrence	RT	
Ricard [3] 2015	82/M	3					LN		
	81/M								
	87/F						Visceral		Death
Turdean [35] 2015	67/M	1	Nodule 1.7 × 1.7 × 0.8			WLE			SR aft 2 y
Takagishi [36] 2016	76/M	3	0.5			Excision			Dead
	59/F		0.5			Excision			Alive
	73/M		1			Excision+RT			Alive
Doia Pedoia [37] 2017	66/F	1	Nodule						
Petrov [38] 2018	93	1	3			RT	LR		Alive, retroauricolar metastatis

Prev, previous; *conc*, concomitant; *WLE*, wide local excision; *LR*, local recurrence; *non-LR*, non-local recurrence; *aft*, after; *SR*, spontaneous regression; *y*, years; *LN*, lymph node; *cr*, carcinoma; *BCC*, basel cell carcinoma; *SCC*, squamous cell carcinoma; *mRND*, modified radical neck dissection; *RT*, radiotherapy; *unr*, unradical; *f*, forehead; *diss*, dissection; *m*, months; *preauric*, preauricular; *submand*, submandibular

Table 2 Results related to clinical features, treatment and outcomes of reported forehead MCCs

Previous/concomitants diseases	Number	Percent
Cutaneous malignancies (epidermoid, basal or squamous cell carcinoma)	4	16.0
Other organ cancer (plasma cell myeloma)	1	4.0
Immuno-hematologic disorders (AIDS)	2	8.0
Clinical features		
Single nodule	12	48.0
Multiple nodules	2	8.0
Dome-shaped or hemispherical mass	4	16.0
Ulcerated lesion	1	4.0
Regional node involvement	7	28.0
Distant metastasis	2	8.0
Diagnostic methods		
Nodule biopsy		
Incisional	1	4.0
Excisional	1	4.0
Sentinel lymph node biopsy (SNLB)	1	4.0
FNA cytology**		
Surgical extemporaneous biopsy**		
Specimen postoperative study	11	44.0
TNM classification***		
Stage IA	1	4.0
Stage III (T1 N1)	1	4.0
Primary treatment		
Local excision not further specified	6	24.0
Wide local excision (WLE)	3	12.0
Mohs surgery	2	8.0
Lymphadenectomy	3	12.0
Adjuvant radiotherapy	5	20.0
Palliative radiotherapy (regional nodes)	1	4.0
Chemotherapy	1	4.0
Radiotherapy alone	1	
Recurrence		
Local	1	4.0
Regional	1	4.0
Distant metastasis	4	16.0
Secondary treatment		
Re-excision	3	12.0
Functional neck dissection (elective lymph node dissection?)	2	8.0
Sentinel node biopsy (SLNB)	1	4.0
Nodal biopsy	2	8.0
Intraparotid lymphadenectomy	2	8.0
Parotidectomy	2	8.0
Outcome		
Mortality	7	28.0
Survival	6	24.0
Spontaneous regression	3	12.0
LR recurrence	1	

dome-shaped or hemispherical mass (4 cases), sometime having telangiectasias and rarely ulceration (2 cases). They were often associated with previous or concurrent malignancies (5 cases) or immune-hematologic disorders (AIDS) (2 cases).

The case of a young (27 years) pregnant woman (reference 28) has been considered an exceptional occurrence (only two similar cases have been published).

At first investigation lesions were generally mistaken with a benign process (lipoma, epidermal cyst (reference 28), vessel changes as hemangioma (reference 38), or with other malignancy different from MCC (basocellular carcinoma, squamous cell carcinoma, skin metastases) and diagnosis was, therefore, late. Some type of preoperative biopsy was performed in 4 cases only, while diagnosis was based on the resection specimen microscopic study in the others. In 6 cases, initial treatment consisted in a not-further-specified extent and width of margin local excision, while a wide local excision (WLE) was declared in 3 cases only. Two patients had a micrographic surgical "Mohs" procedure. Radiotherapy alone was administered in only one case (reference 38). Three and one patients had, respectively, lymphadenectomy or a radiotherapy treatment of involved lymph nodes. After primary treatment, local recurrence rate was 4%, regional nodal recurrence rate was 4%, and distant metastatic recurrence rate was 16%. On the whole, locoregional and distant recurrences occurred in 24% of cases.

As secondary treatment, 3 patients required re-excision because of an incomplete primary excision. Two patients underwent functional neck dissection. A sentinel node biopsy was performed in one patient while two, presenting with clinical lymphadenopathy, underwent nodal biopsy. Two patients had an intraparotid lymphadenectomy and two had a parotidectomy. After secondary treatment, no recurrence was reported. Postoperative radiotherapy was administered in 5 cases and one patient had palliative radiotherapy for regional nodes. The rest of the patients refused adjuvant radiotherapy because of old age, poor health, or personal matters. Mortality and overall survival rate at 5 years were 28% and 24% respectively. Three cases (12%) underwent spontaneous regression, two of them after incisional and one after excisional biopsy.

Case report

An 82-year-old woman presented with a 2-month history of a bluish-purple painless mass on the left side of her forehead. The mass arose as a little papule over the eyebrow and enlarged suddenly following a fall. At presentation, the mass occupied the left periorbital region above the eyebrow and was hemispherical in shape and well circumscribed, red-bluish-colored, and measured 5 × 5 cm. Palpebral ptosis and visual field impairment were present. No fixity to the underlying structures was observable (Fig. 1). There were no neck or facial palpable nodes. A FNA biopsy formerly performed at another hospital was available and revealed normal blood cells only.

An angio CT scan demonstrated a hypervascular mass both at the venous and the arterial phase on the left side of the forehead, external to orbit and cranial cavity (Fig. 2). A provisional diagnosis of arteriovenous malformation like capillary hemangioma was postulated and a second FNA biopsy was not performed because of risk of hemorrhage. In the suspicion of a vascular lesion, the patient was then admitted for embolization of the afferent vessels by selective angiography of the left external carotid artery (Fig. 3) in order to reduce its volume. Successively, she underwent mass resection following surgical ligature of residual peduncle vessels (Fig. 4) under the eco-Doppler monitoring. In fact, control angiography did not confirm complete embolization of the lesion. A concomitant cutaneous plasty was performed for skin reconstruction of the supraorbital region in order to prevent scar retraction of the eyebrow (Fig. 5).

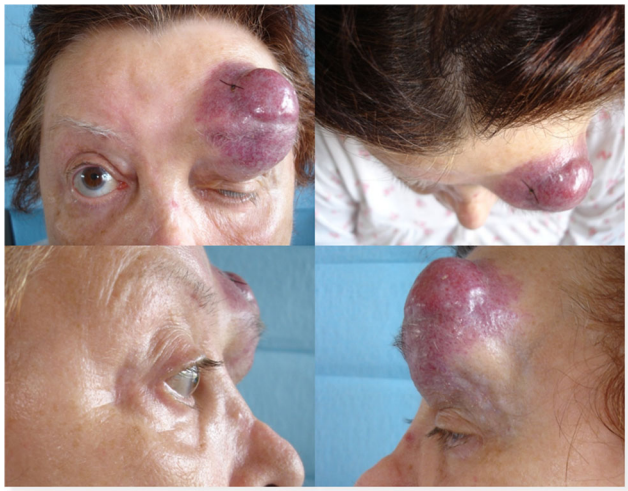

Fig. 1 Clinical preoperative view showing a circumscribed red-bluish hemispherical over the left side of forehead with palpebral ptosis

The resected lesion was 5 × 4 × 4 cm in dimensions and was characterized by an organized hematoma and a tumor mass of 2 × 2 × 1 cm (Fig. 6). Histological examination of the minor mass showed a Merkel cell carcinoma with neuroendocrine aspects (Fig. 7). Resection margins were free from disease with no doubts about residual neoplastic fragments in the surgical field. The tumor was classified as stage II (T2, N0, M0) according to MCC classification of American Joint Cancer Committee (AJCC) [11]. Adjuvant radiotherapy was proposed to the patient, but it was not performed because the patient refused it being afraid of potential eye damages.

Four months later, the patient presented with a hard, firm, and painless mass in the left parotid-masseteric region. A CT scan was performed and it showed an enlarged parotid gland with the presence of a nodal metastasis with skin, parotid, and masseteric muscle infiltration. Following a FNA biopsy, the cytologic results showed nodal malignant cells from primary MCC with high mitotic index. Patient underwent platinum-based chemotherapy but, after 4 months, she died for its illness.

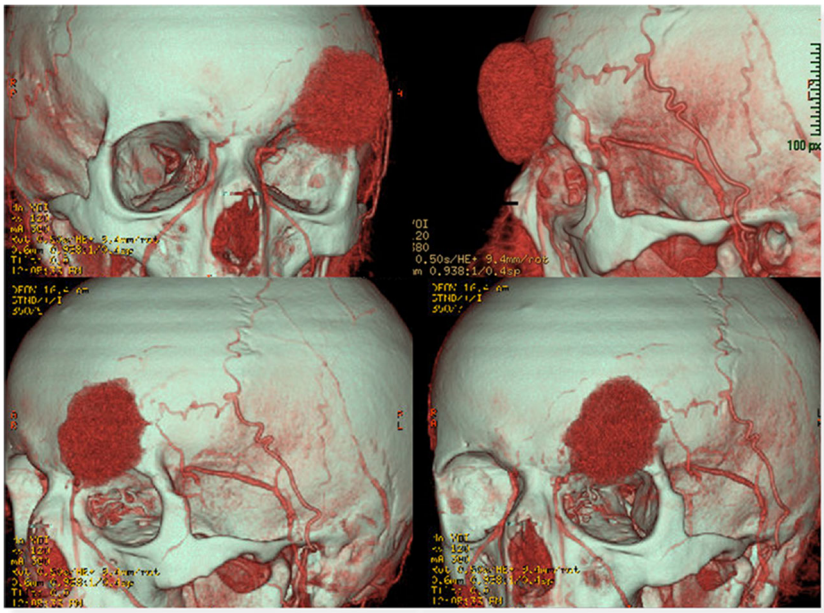

Fig. 2 Angio-CT three-dimensional reconstruction showing a hyper-vascular tissue both at the venous and the arterial phase

Discussion

As shown in Table 1, the clinical-pathologic data on forehead MCCs reported in the literature are largely incomplete. Lack of documentation is due to the fact that some cases come from a simple atlas photographic documentation (references 4, 38) or from a synthetic review table [9, 24, 31, 36], not provided with detailed case description. However, on the base of available data [3, 4, 21–37], 25 MCCs of the forehead area have been reported until now, accounting for 17% of all face MCCs [17, 18]. Compared with similar tumors occurring in the other anatomic subsites of the face, forehead localization follows in frequency an unknown number of cheeks, 112 lips, 114 eyelids, and 147 external ear cancer observations. They appear as a painless single (48%) or multiple nodule (8%), or dome-shaped/hemispherical, flesh-colored to red-bluish mass (16%), rarely ulcerated, sited in the left or right side or central part of forehead area.

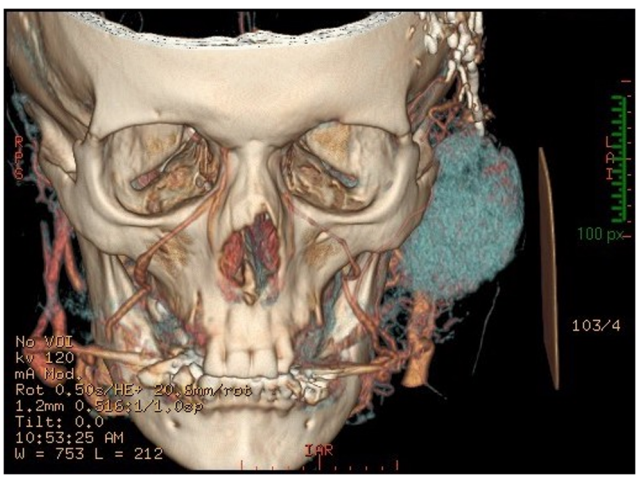

Fig. 3 Postoperative CT-three-dimensional reconstruction showing nodal metastasis into parotid gland

Compared with other face MCCs, forehead tumors present a similar incidence of previous or concomitant malignancies of the skin (epidermoid, basal cell, or squamous cell cancer) (16%) or of other organs (plasma cell myeloma) (4%) and an involvement of regional lymph nodes at presentation (28%) comparable with the 27% of nodal involvement of other MCCs (Table 2). They can be associated with other diseases as immune-hematologic disorders (8%). The majority of patients (72%) present a localized disease at diagnosis [21–38].

Having no specific feature, forehead tumors are often mistaken at first investigation as MCCs in other sites. Differential diagnosis should include epidermal cyst, lipoma, vessel changes between benign entities and basocellular/squamous cellular carcinomas or skin metastases between the malignancies. Diagnostic difficulties have been confirmed by our patient too, whose erythematous lesion was mistaken for an AVM at first investigation because of angio-CT characteristics and FNAC report.

Diagnosis of forehead, MCC is usually late, occurring from several days to some months from lesion occurrence (our patient too presented to us after 4 months) and it is based on incisional or excisional nodule biopsy, FNAC, or surgical specimen histopathologic study. Preoperative imaging may be misleading too on the base of the hypervascularity that may characterize the mass suggesting that it is more useful in evaluation of disease extent and surgical planning than in revealing the true nature of the disease. In our case, angio-CT scan well showed site and extent of the lesion that was external to orbit and cranial cavity, and vascular supply of the mass, pertinent to the external carotid artery, but did not showed any characteristic in order to suspect the true nature of the mass.

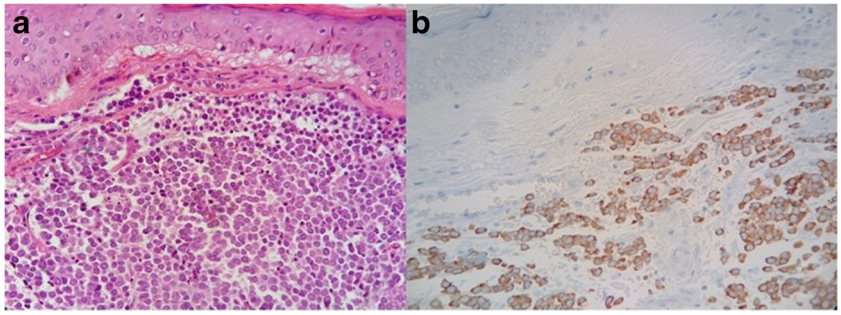

Fig. 4 Histological examination showed a Merkel cells carcinoma (MCC) marked keratin 20 **a** and chromogranin like neuroendocrine marker **b**

Previous FNAC (carried out elsewhere) failed to orient diagnosis to a malignant disease too. Having no specific feature, published forehead tumors rarely had an early preoperative suspicion for malignancy and were often undervalued at first investigation.

Generally Merkel cell carcinoma treatment depends on tumor staging at presentation and may consists in surgery, radiotherapy and/or chemotherapy in a multimodal approach. It has curative intent at stages I and II, palliative at advanced stages. Surgery has the major role for local or locoregional disease and consists in a WLE of the primary tumor and in dissection of involved regional lymph nodes. Tumor excision for MCC should include 2–3 cm of normal-appearing skin, or, at least, a minimum margin of 1.5 [39] or 1 cm [40], up to 5 mm when tumor affects the face. Because of anatomic constraints of this region, even these limited margins are not always possible to be obtained without important functional loss, worsening prognosis. In head and neck area, a surgical excision with 1 to 2 cm margins, followed by adjuvant radiotherapy of the primary site and of the primary areas of lymph node drainage, is then, generally, accepted [9].

As it can be expected, because of the small number of cases treated and the lack of the specifics of the most excisions reported (9 cases on 24 had a not further specified about extent and width of margins resection; rarely excision margins were indicated in the records), no standard of care has been established for the forehead MCC and existing recommendations are a result of individual experience on single patients.

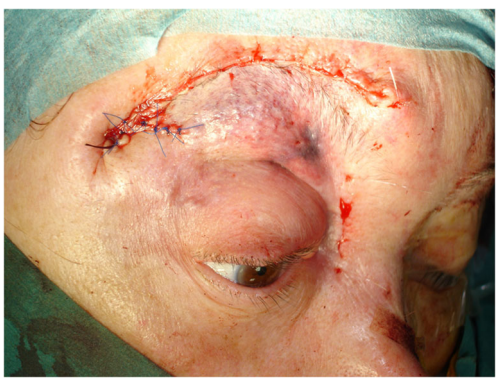

Fig. 5 Intraoperative view of concomitant cutaneous plasty of the supraorbital region in order to prevent scar retraction of the eyebrow

Also, if there is no formality according on the margins extent, the most European [9] and American authors [16] recommend for MCC a 1 to 2–3 cm margins extension surrounding the primary lesion, but others [19, 20], taking into account functional considerations in the head and neck region, consider smaller margins (≤ 1 cm) free from disease, can be accepted in the areas where more wide resection could not be performed without producing significant defects [9]. This minor margins acceptance contrasts with our experience as the poor outcome of our patient seems, instead, to confirm that smaller than 2–3 cm margin resections may effectively increase the risk of recurrence. So we now agree that the greatest possible margins should always be searched for in MCC treatment and adjuvant postoperative radiotherapy, for tumor site and regional lymph nodes area, should be always delivered, even after a wide excision with negative microscopic margins. As demonstrated by a recent case report [38], radiotherapy cannot be considered other than an adjuvant, complementary tool as a sudden recurrence is to be expected if surgery is not performed.

Moreover, risk for radiation damage to the eye due to the contiguity of radiation field to the orbit has been minimized in a recent study on the eyelids MCC management, where only one case of radiation eye damage (painful blind eye) has been reported in a series of 21 patients [41]. Also, another series of 18 periocular MCCs [42] did no show damages to the eye after radiotherapy. Therefore, today, we think orbit postoperative irradiation can be recommended in the periorbital Merkel tumor treatment, not only when wide surgical margins are

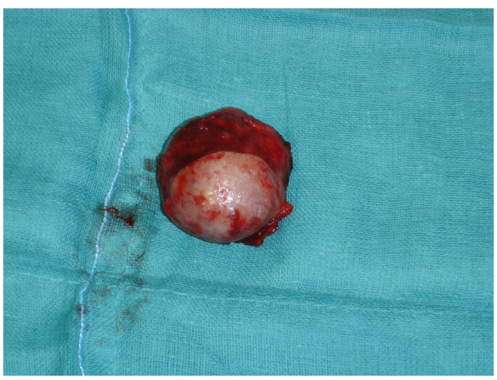

Fig. 6 Intraoperative view of the resected lesion

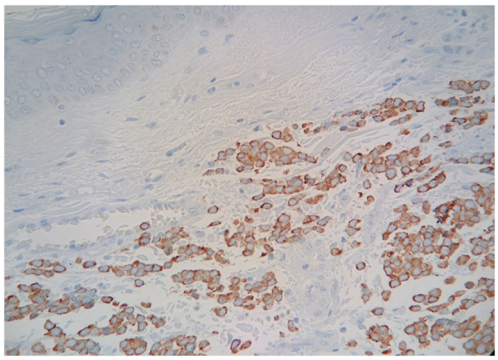

Fig. 7 Chromogranin stain showing neuroendocrine aspects

unattainable or are involved with tumor, but also when residual cancer is thought not to persist in the tumor bed.

Compared with other face MCCs, there are no differences in the recurrence-free or overall survival but, frequency of re-excision for the forehead tumor is higher (12%). A comparable mortality of 28% has been calculated for the different face localization while the overall mortality rate is 30–50% [38]. However, the overall 5-year survival rate of forehead MCC results to be 24%, highly below 5-year survival rate of the other face MCC localization (40%) [8].

Conclusions

This study provide additional evidence on some aspects of the forehead MCC behaviour and management that are still debated as the possible occurrence of early parotid metastasis and its meaning as a severe prognostic index; the difficulty of obtaining an early preoperative diagnosis; the only temporary effectiveness of radiotherapy alone; the orbit tissues tolerance to radiation. The deceitful benign feature of this malignancy together with a misleading FNAC may lead to a diagnostic failure and that AVM should be included in differential diagnosis.

In the face area, resection margins smaller than 2–3 cm may increase the risk of locoregional recurrence so postoperative adjuvant wide-field radiotherapy should be recommended after WLE even with negative microscopic margins.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval No ethical was requested for this kind of retrospective study.

Informed consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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