

Extra-Ocular Sebaceous Carcinoma of the Skin: A Report of Five Cases and a Review of the Literature

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Received July 23, 2015; Revised August 05, 2015; Accepted August 24, 2015

Abstract *Background:* Extra ocular sebaceous carcinoma is a rare aggressive adnexal tumour. The diagnosis of this tumour is difficult due to the variety of its clinical and histopathological features. The prognosis is actually considered as aggressive as the ocular counterpart. *Methods and results:* We propose to discuss the clinical features, histopathological findings and aggressive potential of extra ocular sebaceous carcinoma. Therefore, five extra ocular sebaceous carcinoma cases, diagnosed at the Dermatology and Pathology departments of Farhat Hached Hospital, from January 1998 to December 2007, were reviewed. The diagnosis was based on a histopathological examination. Three of them developed locoregional and/or distant metastases. One patient died from metastatic disease. Surgery was the mainstay of treatment without any cutaneous recurrence after a mean follow-up of two years. *Conclusions:* Extra ocular sebaceous carcinoma has an unpredictable prognosis. It can be highly aggressive and cause death. Surgery remains the mainstay of treatment.

Keywords: sebaceous adenocarcinoma, extra ocular sebaceous carcinoma, skin cancer, prognosis, surgery

Cite This Article: Mariem MOHAMED, Lobna BOUSSOFARA, Abdlefaddeh SLAMA, Mohamed DENGUEZLI, Colandane BELAJOUZA, Bedreddine SRIHA, Najet GHARIANI, and Rafiaa NOUIRA, "Extra-Ocular Sebaceous Carcinoma of the Skin: A Report of Five Cases and a Review of the Literature." *American Journal of Medical Case Reports*, vol. 3, no. 9 (2015): 291-296. doi: 10.12691/ajmcr-3-9-8.

1. Introduction

Sebaceous carcinoma (SC) is a rare, aggressive cutaneous appendageal tumour that may be one of the cutaneous diagnostic markers of Muir-Torre syndrome, a genetic disease that is associated with visceral neoplasms or that occurs sporadically [1]. The great majority of SCs (75%) occur in the periocular region, commonly in the eyelid. Extra ocular SC (ESC) accounts for only 25% of all reported cases of SC [1]. SC commonly takes varied clinical and histological appearance, leading to delayed diagnosis or misdiagnosis. It is usually considered to be less aggressive than the ocular counterpart [1]. However, recent reports have shown that ESC can also be highly aggressive often causing metastasis [2,3,4].

We report here 5 additional ESC cases. These cases illustrate the varied clinical and histological patterns as well as unpredictable prognosis of this aggressive neoplasm.

2. Patients and Methods

Five ESC cases were retrospectively collected at the Dermatology and the Pathology Departments of Farhat

Hached Hospital, from January 1998 to December 2007. The diagnosis was based on histopathological examination. A database was developed in the five cases, in order to record the following information: demographic features (sex, age, personal and family history), clinical manifestations, histological and immunohistochemical findings, treatment and outcome. The clinical behaviour of these neoplasias was followed for a minimum period of 1 month (because of patient demise) and a maximum of 36 months (average follow-up of 19 months).

3. Results

Five patients were identified with the diagnosis of ESC between January 1998 and December 2007. They were 3 men and 2 women, with a mean age of 64.5 years (range: 33-80 years). High solar ultraviolet exposure was detected in all cases and heavy smoking was noted in one case (Case 1). None of the patients gave a family or personal medical history of internal malignancy. The average time of tumour course before diagnosis was 11.5 months (range: 1-36 months). The clinical features of these cases were diverse (Figure 1 (a-e)). Four cases occurred on the face: nose (Case 1), forehead (Case 2), lower lip (Case 3) and cheek (Case 5). The tumour aroused on the left side of the

chest in Case 4. SC of oral mucosa was seen in a 70-year-old female without a history of Fordyce granules. Squamous cell carcinoma and melanoma were the main suspected clinical diagnoses, but, the histological and the immunohistochemical findings confirmed the diagnosis of SC in all cases. In fact, a histological examination revealed an infiltrative poorly circumscribed neoplasm involving the dermis in the five cases. Tumour cells showed varying degree of sebaceous differentiation: well-differentiated in Cases 1 and 5 (Figure 2 (a,b) and Figure 6), moderately well-differentiated in Cases 2 and 4 (Figure 3(a,b) and Figure 5) and poorly differentiated SC in Case 3 (Figure 4 (a,b)).



Figure 1. A: Exophytic, irregular and violaceous tumour in the right wing of the nose. Case 1



Figure 1. B: Firm and ulcerated tumour in the forehead. Case 2



Figure 1. C: Markedly ulcerated, irregular and indurate mass in the lower lip. Case 3



Figure 1. D: Yellowish colored, firm and ulcerated tumour in the left side of the chest. Case 4



Figure 1. E: Nodular and keratotic tumour in the right cheek. Case 5.

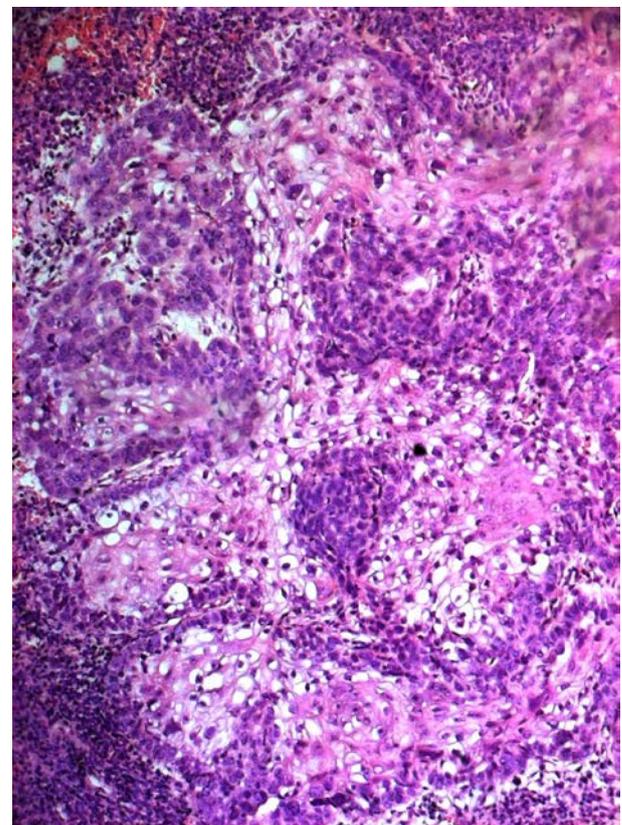


Figure 2. A: Well-differentiated sebaceous carcinoma (HE, magnification x 100). Case 1

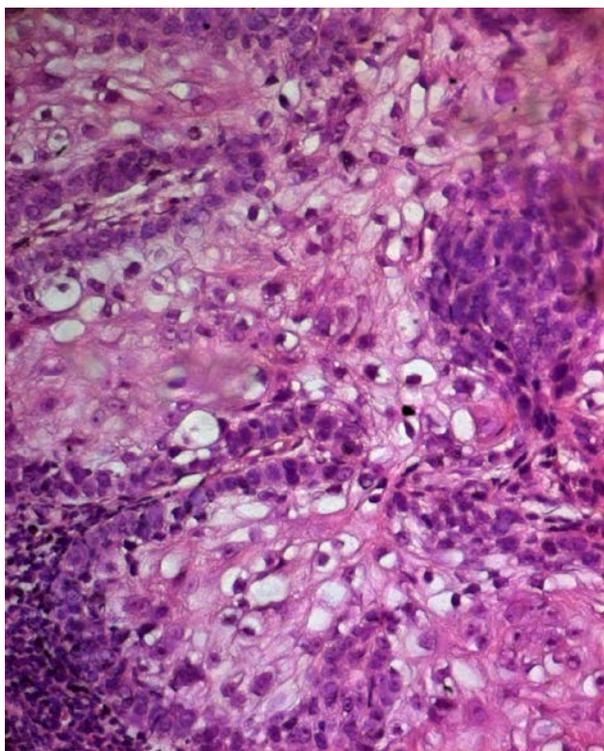


Figure 2. B: Well-differentiated sebaceous carcinoma (HE, original magnification x 200). Case 1

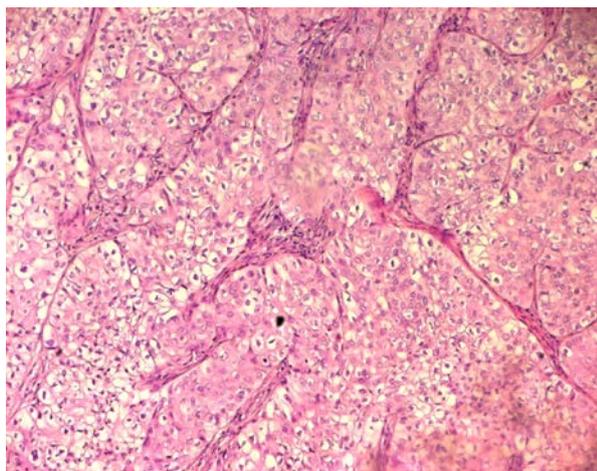


Figure 3. A: Moderately well-differentiated sebaceous carcinoma (HE, magnification x 100). Case 2

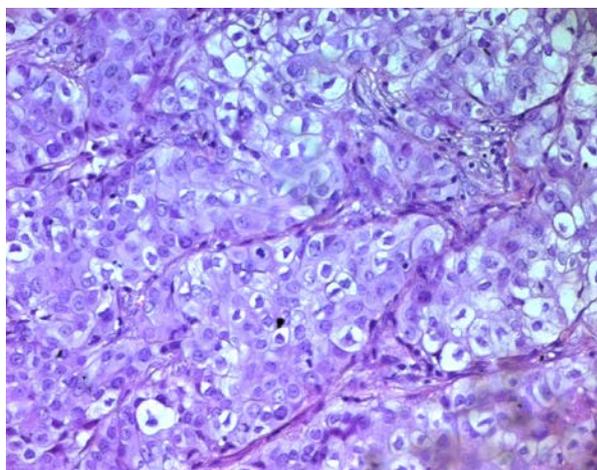


Figure 3. B: Moderately well-differentiated sebaceous carcinoma (HE, magnification x 200). Case 2

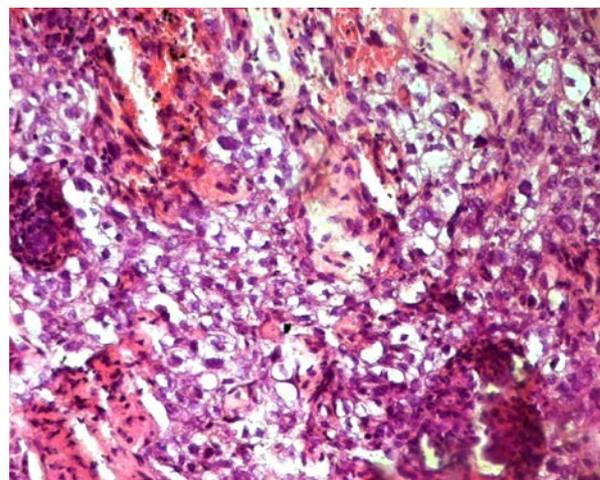


Figure 4. A: poorly differentiated sebaceous carcinoma (HE, magnification x 100). Case 3

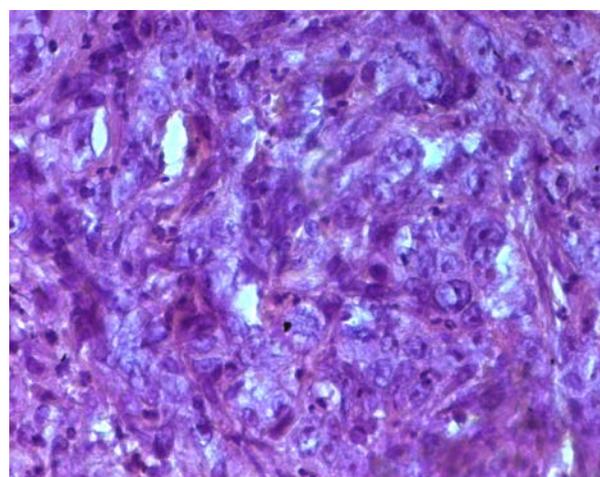


Figure 4. B: poorly differentiated sebaceous carcinoma (HE, magnification x 200). Case 3

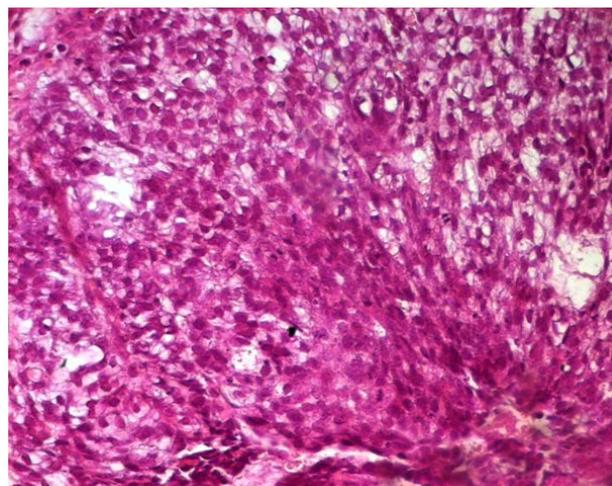


Figure 5: Moderately well-differentiated sebaceous carcinoma (HE, magnification x 200). Case 4

On immunohistochemical study, the tumour cells showed a positive reaction to epithelial membrane antigen (EMA) in all cases (Figure 7) and they were negative for carcinoembryonic antigen (CEA), S100 protein, Melan-A, Vimentin, HMB45, and Specific Neural Enolase (SNE). Cytokeratin 7 (CK7) was demonstrated positive in Cases 2 and 4 (Figure 8).

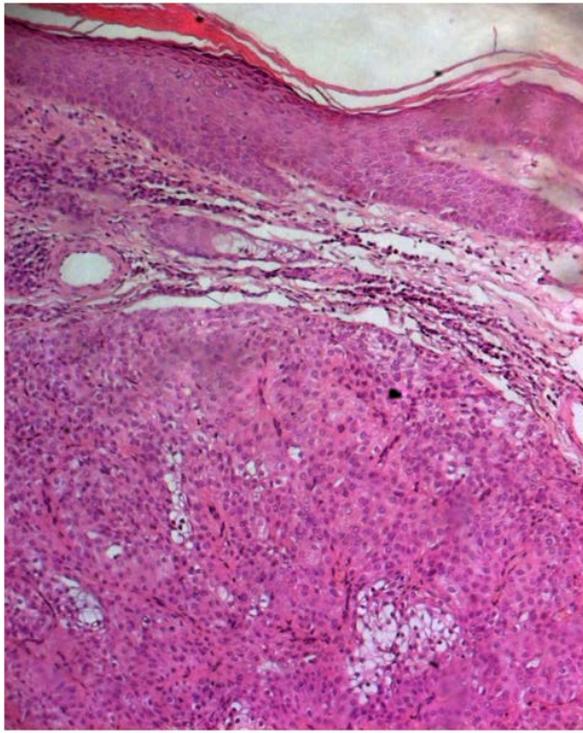


Figure 6: Well-differentiated sebaceous carcinoma (HE, magnification x 100). Case 5

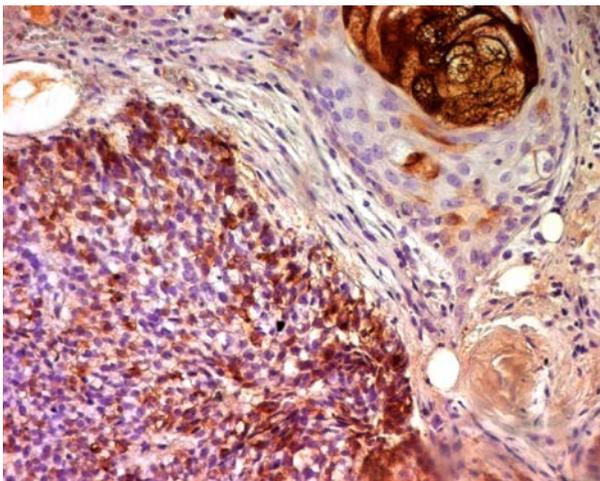


Figure 7. Tumour cells showed strong positive reaction for EMA (original magnification x 200). Case 1

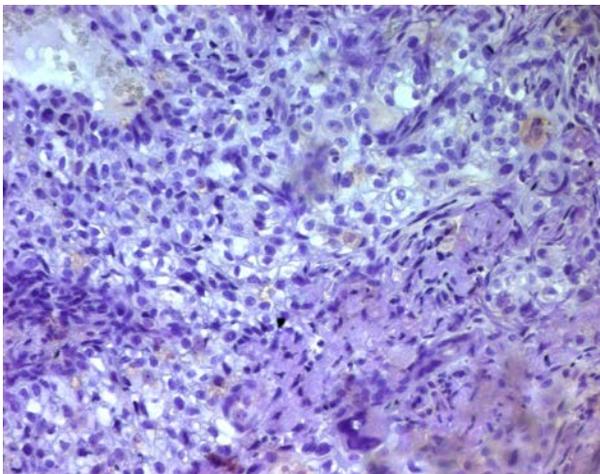


Figure 8. Tumour cells showed weak positive reaction for CK7 (original magnification x 200). Case 2

All patients underwent instrumental examinations (chest x-ray, CT scan, cervical and abdominal ultrasound examination) and had a blood test. Two patients (Cases 1 and 3) had metastasis at the time of presentation: cervical lymph node in the two cases, extensive local invasion to the mandible bone in Case 3 and distant metastasis to the lungs and bone in Case 1. Case 4 developed subcutaneous soft tissue metastasis in his right arm three months after the diagnosis of his primary ESC.

Further investigation revealed all patients did not give any family history of visceral neoplastic disease or skin tumours of the sebaceous type. No additional tests like colonoscopy, upper gastrointestinal endoscopy, mammography, and endometrial biopsy were performed to rule out other MTS-associated internal tumours in any of our cases. A study of MSH2 and MLH1 expression and microsatellite instability was not possible.

Excision with wide surgical margins was performed on four cases (Cases 2, 3, 4 and 5), followed by bilateral cervical lymphadenectomy in Case 3 and surgical removal of subcutaneous metastasis in Case 4. Case 1 rapidly died because of multiple visceral metastases and Case 5 died two years later because of ageing. Three patients (Cases 2, 3 and 4) were still alive with neither recurrence nor metastasis after a mean follow-up of 2 years (range: 1-3 years).

The results are summarised in [Table 1](#).

4. Discussion

SC is a rare adnexal tumour arising in any anatomical site that contains sebaceous glands. The general frequency of this tumour varies from 0.2% to 4.6% of all malignant cutaneous neoplasms [5]. Three-quarters of cases occur in the periocular region, particularly on the eyelids, arising especially from the Meibomian glands [1,2]. ESC is less common than its periocular counterpart [2]. The most common extraocular sites are the head and the neck in approximately 70% [2], as in four of our cases, followed by other hairy regions of the body including the trunk in approximately 15% of cases, as in our Case 4, or on the limbs in less than 10% of cases [2,6].

Primary malignant sebaceous tumours of the oral mucosa are extremely rare. At the best of our Knowledge, only seven cases of oral mucosa SC have previously been reported [7,8]. Our patient (Case 3) seems to be the eighth one. None of these cases has been reported to be associated with Muir-Torre syndrome [7,8]. Two of them were reported to have developed SC in an area that contains Fordyce granules [7,9].

Sebaceous carcinoma, as observed in the current cases, is most common in elderly individuals with a mean age of 70 years [2,5]. Our patients were aged between 33 and 80 years (mean age: 64.5 years). The sex distribution of this tumour appears to be equal for male and female patients [2,3].

Clinically, ESC presents as a pink to red-yellow slowly enlarging firm dermal or subcutaneous nodule [1]. In one-third of the cases, there is a tendency for ulceration and spontaneous bleeding [1]. The tumour can range from 6 mm to 20 cm in size [10]. The mean size in our cases was 2.5 cm.

Table 1. Characteristics of SC patients

Case	Age (yEARS)	Sex	Average time of diagnosis (months)	Site	Clinical presentation
1	68	M	1	Right wing of the nose	Exophytic, irregular, violaceous, obstructive, and 4x4 cm in diameter tumour (fig 1A)
2	33	F	36	Forehead	1.5 cm in diameter, firm and ulcerated tumour (fig 1B)
3	70	F	3	Lower lip	5x4 cm in diameter, markedly ulcerated, irregularly shaped, and indurate mass (fig 1C)
4	72	M	6	Left side of the chest	1x1 cm in diameter, yellowish colored, firm and ulcerated tumour (fig 1D).
5	80	M	11	Right cheek	1x1 cm in diameter, nodular tumour with keratotic surface (fig 1E)

Case	Histological IHC findings	Metastasis	Treatment	Follow up
1	Well-differentiated SC EMA (+)	- Cervical lymph node - Bone: maxilla, collar-bone, vertebra, ribs. - Lung	none	Died one month later (general metastasis)
2	Moderately Well-differentiated SC EMA (+) CK7 (+)	none	Surgical excision	No recurrence after 3 years of follow-up
3	Poorly differentiated SC EMA (+)	- Mandible - Cervical lymph node	Wide surgical excision and bilateral cervical lymphadenectomy	No recurrence after 2 years of follow-up
4	Moderately Well-differentiated SC EMA (+) CK7 (+)	Subcutaneous right arm metastasis, 3 months after surgical removal of primary tumour	Wide surgical excision of primary tumour and metastasis	No recurrence after 1 year of follow-up
5	Well-differentiated SC EMA (+)	none	Wide surgical excision	Died for other causes at 2 years

M: male; F: female; SC: sebaceous carcinoma; EMA: epithelial membrane antigen; CK7: cytokeratin 7

Histologically, ESC is usually, as observed in our cases, located in the dermis [1]. It is composed by an asymmetric, poorly circumscribed aggregation of irregularly sized and shaped cells. The cells exhibit varying degrees of sebaceous differentiation and manifest as finely vacuolated or foamy rather than clear cytoplasm [4]. Well-differentiated SC, as observed in Cases 1 and 5, is characterized by a prominent sebaceous differentiation which is often toward the center of tumour lobules. Moderately well-differentiated, as seen in 2 of our cases (Cases 2 and 4), is characterized by only a few areas of highly differentiated sebaceous cells. In poorly differentiated SC, as observed in Case 3, the majority of neoplastic cells exhibit pleomorphic nuclei, prominent nucleoli, a scanty cytoplasm and a moderate increase in the mitotic activity [1].

The clinical and histological findings for ESC may resemble those of other tumours such as basal cell carcinoma, squamous cell carcinoma, melanoma, or other less common glandular or adnexal tumours, thereby leading to delay in diagnosis, inappropriate treatment, and an increase in morbidity and mortality [1].

Lipid stains as Oil-Red-O or Sudan IV and electron microscopic examination [1] may show intracytoplasmic lipid droplets in the neoplastic cells. Immunohistochemical studies may reveal some positive reactions for epithelial membrane antigen (EMA), and androgen receptor (AR), but not for carcinoembryonic antigen (CEA), S100 protein, or gross cystic disease fluid protein 15 (GCDFP) [11]. In the present work, all cases were positive for EMA, and negative for mesenchymal, neural and melanocystic markers. Two of our cases were positive for CK (Cases 2 and 4).

The etiology of SC is not known. A higher frequency of SC in the Asian population without documented causes was reported [1]. Other factors are also incriminated in the histogenesis of sebaceous tumours: Older age and female sex [12]; ultraviolet exposure, as noted in all our cases, which may explain SC predilection for the head and neck

[1], previous radiation therapy in the tumour site [1]; and immunosuppression [12]. Most SCs arise de novo, but some tumours have been shown to originate from already existing benign tumours such as actinic keratosis [13], nevus sebaceous [14], mature cystic teratoma [15] or pleomorphic adenoma [16]. Genetic factors are also involved in SC pathogenesis. In fact, SC can be sporadic or associated with Muir-Torre syndrome. Muir-Torre syndrome is a hereditary disease of autosomal dominant transmission characterized by the association of at least a skin tumour of sebaceous lineage (sebaceous adenoma, sebaceoma, sebaceous epithelioma, sebaceous carcinoma, or basal cell carcinoma with sebaceous differentiation), with or without a keratoacanthoma associated with one or more visceral neoplasms, commonly colon cancer [12]. Lesions associated with Muir-Torre syndrome often have unstable microsatellites due to inheritance of defective genes encoding DNA mismatch repair proteins MLH1 or MSH2 and, less commonly, MSH6, MSH3, MLH3, PMS1 and PMS2 [17].

Regardless of the anatomical site involved, SC is an aggressive neoplasm, [1]. ESC has been traditionally claimed to have a better prognosis than the ocular forms [4]. However, review of the recent literature has revealed that ESC has a tendency to be locally aggressive, to develop cutaneous recurrence and to metastasize widely [3,4]. In addition, the risk of metastasis from sporadic SC seems to be higher than that from SC associated with MTS [18]. The most common site of metastasis is in the draining lymph node [4,19]. Distant metastases have been reported in less than 10% of all ESC cases [3] and may occur in the abdomen [5], lung [5], brain [5], bone [20] and subcutaneous soft tissue [4]. In the current series of 5 patients, there were two regional metastases (40%) to the draining lymph node, one extensive local invasion (20%) and two distant metastases (40%) to the bone, lungs, and soft subcutaneous tissue. To the best of our knowledge, a subcutaneous soft tissue metastasis, as observed in Case 4, has been reported in only one case so far [4].

Calculation of ESC survival rate is difficult because of the relatively low number of cases with sufficient follow-up. In fact, a tumour-related mortality of 20% and of 36% was reported, respectively by Bailet et al. [3] in a series of 91 ESC cases and by Moreno et al. [4] in a review of 22 metastatic ESC cases. In our series of 5 patients there was no recurrence, one tumour-related death (20%) and one unrelated tumour death (20%) after an average follow up of 2 years.

Surgical removal of tumours with a wide local excision (5- 6 mm margins) or with Mohs micrographic surgery remains the mainstay of treatment [1,5,7,21]. On any suspicious lymph nodes, surgical removal of the tumours must be undertaken by regional lymphadenectomy for confirmed nodal metastasis. Radiation therapy in the management of ESC is considered largely palliative and for post surgical management of metastatic disease [22]. Chemotherapeutic regimen for SC consists of individual trials of case reports [23]. Metastatic disease may be treated by excision and/or radiation and/or chemotherapy [1]. In our series, surgery was the mainstay of treatment without any recurrence after a mean follow-up of 2 years.

Our series illustrate the high variety of ESC clinical and histological features. Due to the association of SC with MTS, a systemic approach is warranted in a patient suspected of having this malignancy. ESC is an aggressive tumour and may cause death. Early surgical therapy remains the best treatment and may improve the prognosis. However, long-term follow-up is strongly recommended because of the propensity of the tumour for local recurrence, regional and distant metastases.

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