Multifocal Metastasizing Extra-Ocular Facial Sebaceous Carcinoma as Diagnostic Challenge: Case Report and Systematic Review

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Abstract

Purpose Sebaceous carcinoma (SC) is a rare adnexal tumor. Extra-ocular, facial SC is very uncommon and local metastases are an extreme rare finding. A respective case is presented and discussed together with the current literature. **Case and Review** A tumor of the left ear of an 87-old male was primary excised together with multiple suspicious lesions of the head and neck. Most specimens were histopathologically rated as squamous cell carcinomas (SCC). Despite the *in-sano* resection, additional new suspicious retro-auricular and temporal lesions were detected. Successive resections were diagnosed as basal cell carcinomas (BCC) and, because of a *non-in-sano* resection in a third approach, as SC. After reappraisal and immunohistochemical staining [epithelial membrane antigen (EMA), CK 5–6 and CD 15], most of the former specimens turned out to be SC as well. A literature search showed 3 reported cases of extra-ocular head and neck SC with cutaneous local metastases. In another review, in a total of 168 cases, SC was diagnosed after wrong initial histological diagnosis (SCC n = 56, BCC n = 44; other entity or precursors of carcinomas n = 68).

Conclusion Due to inconsistent histologic patterns, histopathological misdiagnosis of the uncommon facial SC and its metastases may complicate further therapy, prolong treatment and may lead to a worse prognosis of this neoplasm. A close interdisciplinary collaboration of clinician, surgeon and pathologist is of most relevance for the right diagnosis.

Keywords Sebaceous gland carcinoma · Cutaneous metastases · Subcutaneous metastases · Satellite metastases · Histology · Immunohistochemistry

Introduction

Sebaceous carcinoma (SC) is a rare adnexal tumor which represents 0.2–4.6 % of all malignant neoplastic cutaneous lesions [1]. With an equal gender distribution, the peak incidence is bimodal in the third and between the seventh and eighth decades of life [2, 3]. Further risk factors are white race as well as genetic predisposition. For example, Muir–Torre syndrome, an autosomal dominant condition with variable penetrance, consists of sebaceous carcinoma together with colon cancer, sebaceous adenomas and epitheliomas as well as multiple or early-onset keratoacanthomas [4].

SC originates from adnexal skin structures and develops most frequently in association with the Meibomian or Zeiss glands of the eyelids. Accordingly, it is found most often in the periocular area [5]. Approximately 25 % of sebaceous carcinomas occur in extra-orbital sites, in 15 % of these cases the torso and in 10 % the extremities are affected [2, 5, 6]. The most common extra-ocular localization is the parotid area, followed by nose, scalp, neck, external auditory canal, retro-auricular and submandibular region [3]. Extra-ocular facial SC presents as a pink, red or yellow-

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gray, well or less circumscribed mass. Its clinical appearance may vary and is not pathognomonic [2, 3, 7, 8]. It may also mimic benign conditions such as keratoacanthomas [9]. Typically, the local margins are infiltrated. The aggressive potential of SC is also demonstrated by its tendency towards local regional as well as distant spread [2]. Early lymphogenous and haematogenous metastases are documented in up to 25 % of cases [2, 3]. This probability has shown to be less in extra-ocular sites [10]. Accordingly, extra-ocular multifocal facial metastasizing SC is nearly unknown. Therapy of SC consists in surgical removal with wide margins. Sentinel lymph node biopsy has been described to be favorable for ocular SC; in positive cases, a lymphadenectomy is advocated [7, 11, 12]. In extra-ocular head and neck SC a sole observation of regional lymphatic nodes may be reasonable [10].

Diagnosis of SC is confirmed when sebaceous neoplastic cells can be seen [13]. Differentiation between SC, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) has been shown to be difficult with routine staining methods [14]. As the treatment of SC differs from the treatment of SCC and BCC [15, 16], discrimination remains important and special staining methods are recommended [9, 14, 17].

In summary, SC exhibits a variety of clinical presentations and histological growth patterns that the diagnosis is often delayed for months to years [9]. A case of such a diagnostic challenge with a very rare extra-ocular facial SC together with local cutaneous metastases is presented and discussed together with the current literature.

Case Report

An 87-year-old white male came to the Department of Cranio-Maxillo-Facial and Plastic Surgery with a reddish, partial hyperkeratotic lesion of the upper 2/3 left ear, measuring approximately 6×4 cm (Fig. 1). Additionally, multiple hyperkeratotic lesions of the head and neck region were seen. Initial surgical biopsy of the ear showed a moderately differentiated SCC. Due to the patient's cardiovascular morbidity, the following operations were carried out under local anesthesia. The upper pinna was removed with surgical safe resection margins (Fig. 2). Following pathohistological findings gave evidence of a wide spread carcinoma in situ transferring to a moderately differentiated SCC. The coincidental lesions of the skin were excised and diagnosed as SCCs as well. After 2 months, additional new retro-auricular as well as temporal tumor nodules were detected (Fig. 3) and a second resection with wide safety margins was conducted. Out of the respective specimen, a metatypical basal cell carcinoma with moderate invasive squamous carcinoma-like growth was diagnosed. Because of a *non-in-sano* resection in

Fig. 1 Suspicious, ulcerating lesion of the upper 2/3 of the left pinna at the day of the first admission

Fig. 2 Specimen of the upper left ear after initial resection

the depth of the retro auricular area, a third follow-up resection had to be conducted. Pathohistological evaluation now proved a moderate differentiated SC with angiolymphatic invasion and pagetoid intraepidermal tumor-spread (Fig. 4a–c). Immunohistochemistry confirmed the diagnosis with a strong positive reaction on Anti-EMA (epithelial membrane antigen [17] (Fig. 5) and a strong staining of most of the tumor cells with anti-CK5/6. Anti-CK7 presented a faint, central reaction in the tumor-aggregates. Anti-vimentin staining showed a strong reaction in the subepithelial

Fig. 3 New tumor growth in the retro auricular area as well as super-auricular temporal

stroma without staining the tumor cells. Anti-CD15 was positive in the center of the tumor-aggregates, where the cells showed an abortive sebaceous differentiation (Fig. 6). Staining with Anti-CD10 was negative, staining with podoplanin showed a positive reaction of the lympho-epithelium, giving evidence for lymphangiosis (angiolymphatic invasion). Because of this new diagnosis the former specimens were reappraised and immunohistochemically stained. It could be concluded that all of the former resections of the ear, retro auricular and temporal area as well as most of the other lesions were also SC. Finally, the diagnosis of multifocal metastasizing extra-ocular SC was made. In the following staging examinations (computed tomography, ultrasound) Muir–Torre syndrome could be ruled out; however, as no clinical evidence of Muir–Torre was seen, the tissue was not evaluated for mismatch repair defects using immunohistochemistry. In the following radiological evaluation, metastasis-suspicious ipsilateral cervical lymph nodes and lung coin lesions were seen. After extensive education of the patient about his diagnostic findings he deprecated further diagnostics and therapy. In a total follow-up time of 1.5 years, no other metastasis occurred and the patient did not show any signs of recurrence.

Systematic Review

A systematic literature review for case reports with extra-ocular cutaneous, multifocal metastasizing SC in the time between 1960 and 2011 was conducted. In a second review,

Fig. 4 Nest-like, solid atypical epithelial complexes with central comedonecrosis (5a, x10, HE-staining). The tumor-cells display high-grade features and a high frequency of mitotic figures, with a wide, partly bright, partly finely granulated cytoplasm (5b, x20, HE-staining). Close to the tumor-nests, angiolymphatic invasion is evident (5c, x40, HE-staining)

reports of SC with an initial histologic misdiagnosis—like in this case—were collected for the same period.

Results

Local cutaneous/subcutaneous metastases were described in the course of disease in 3 cases of extra-ocular facial SC (Table 1). Extra-facial SC with multifocal metastases is described in 4 cases (Table 2). Further literature research

Fig. 5 Immunohistochemical staining with Anti-EMA (epithelial membrane antigen), showing a strong positive reaction (x10) (Strong staining reaction of the tumor cells against EMA)

Fig. 6 Positive staining reaction for CD15 (x20) in the centers of the tumor-nest

provided 168 SC-cases with a wrong initial histological diagnosis. The most frequent misdiagnosis was SCC (n = 56) followed by BCC (n = 44). Altogether there were 68 cases of misdiagnoses of non-SCC and non-BCC carcinomas.

There were 3 cases of SC with two initial consecutive pathohistological misdiagnoses in the course of the disease. A lot of cases of non-malignant, non-tumorous entities like inflammation, chalazia and chronic blepharoconjunctivitis as initial diagnoses prior the diagnosis of SC were reported as well.

Discussion

SC represents the second most common malignant tumor of the eyelid after basal cell carcinoma [3, 5, 11] and counts 1–5.5 % of all eyelid malignancies [2, 3, 7, 18]. In other studies, SC is representing the third and fourth most frequent eyelid malignancy [2, 19]. Extra-ocular facial SC is a rather uncommon phenomenon. It is suggested that extra ocular SC has a better prognosis than ocular SC [3, 10, 15]. Local cutaneous or subcutaneous metastases like in this case report are very uncommon. Together with this case, only 3 documented reports of facial extra-ocular SC could be found. In cases of extra-facial SC, another 4 such cases were reported. In 7 of 8 cases with cutaneous metastases, male patients were affected; the mean age was 63 years. In 6 cases, lymphogenous metastases were described [20–24]. In 3 cases pulmonary metastases were present [20, 22], in one case hepatic [22] and in another one skeletal metastases was described

Table 1 Cases with cutaneous metastases of the facial extra-ocular SC

	Murphy et al. [25]	Moura et al. [20]	Melletie et al. [21]
Sex	M	M	M
Age	71	71	63
Symptoms	Epistaxis, enlarging firm smooth lesions in the right nostril	Multiple rapidly growing hemorrhagic tumors	nod
Localization	Right nostril	Forehead	Nose
Metastasis	Left nostril	Local cutaneous metastases Lymphogenous metastasis Lung/skeletal metastasis	Local cutaneous metastases of face and neck Parotid lymph node metastasis
Treatment	Surgical removal	1. Classic surgery 2. Local radiation therapy $\geq$ recurrence 3. Chemo-and cryosurgery 4. Systemic chemotherapy + radiation for the skeletal metastases	1. Curettage/desiccation/surgical excision 2. Lat. parotidectomy, radical neck dissection 3. Radiation
Recurrence	Left nostril	Local cutaneous metastasis	3 $\times$ local recurrence and parotid metastasis
Prognosis	18 months without recurrence	Died $\sim$ 4 years later, due to metastatic colon-carcinoma without recurrence of the SC	nod

nod not described

Table 2 Cases with extra-facial SC leading to cutaneous metastases

	Bhat et al. [9]	Swick and Lang [22]	Khan et al. [23]	Moreno et al. [24]
Sex	M	M	F	M
Age	32	83	49	45
Symptoms	Spreading yellowish firm papules of the left lower limb	10 × 8 cm solid red tumor Satellite-lesions	Vaginal bleeding 5 mm lesion on the right labium major	3 × 2 cm subcutaneous nodule of the axilla
Localization	Left feet/shank	Right flank	Vulva	Left axilla
Metastasis	Primary multifocal cutaneous metastasis	Subcutan, lymphogenous, pulmonic, hepatic	Subcutan, lymphogenous	Subcutan, lymphogenous
Treatment	1. Amputation 2. Chemotherapy	Palliative radiotherapy	1. Surgery/inguinal lymphadenectomy 2. Radiation therapy ≥ recurrence 3. Palliative chemotherapy	Surgery
Recurrence	nod	nod	Right vulva/inguinal skin	Multiple subcutaneous nodules
Prognosis	nod	nod	nod	Died 6 month after first presentation

nod not described

[20]. Only in one case the death of a patient 6 months after diagnosis due to SC was seen [24]. In another case the patient died approximately 4 years after first diagnosis, but due to another metastatic tumor [20]. In one case, 18 months free of recurrence was described [25]. In four cases the prognosis was not mentioned. In most of the cases, multimodal therapies like irradiation and chemotherapy after surgery were employed. Though, due to missing follow-up data, the effects of these treatments cannot be evaluated. Multimodality is frequent in ocular SC, especially in extended diseases and recurrent tumors [26]. About 18 % of advanced periocular SC are multicentric [5, 26]. Khan et al. described dissemination via intraepithelial pagetoid spread or free-floating cancer cells within tear fluid (lacrimal oncorrhea) [5, 27]. In our case, the mechanism may be angiolymphatic invasion with lymph- and hemangiotic tumor spread, as well as pagetoid intraepidermal tumor spread. Another possibility is haematogenous drift of circulating tumor cells with subsequent interaction of the circulation cells with the host cells and creation of in-transit metastasis like in melanoma [28]. Multifocal cutaneous SC could also be found in cases of Muir–Torre syndrome. This autosomal-dominant syndrome is characterized by multifocal appearance of sebaceous lesions associated with other, especially colorectal and visceral carcinomas [29]. The patient in this case had no visceral malignancy and there was no cancer anamnesis. Therefore, Muir–Torre was ruled out.

The diagnostic difficulty of SC is highlighted by several wrong initial clinical diagnoses of SC documented in the literature [27]. Clinical misinterpretation in cases of extra-ocular SC leads to diagnoses of BCC, SCC, ceratoacanthoma,

cornu cutaneum and Bowen's disease as well a numerous other malign and benign lesions [11, 19, 30, 31]. Likewise, histopathological evaluation of SC is also difficult. Accordingly, 168 other reported cases of initial histological misdiagnosis with final diagnosis of SC were found. This shows the dilemma of the pathologist facing the notorious “masquerader” [1, 5, 32]. The most frequent misdiagnoses are SCC and BCC [27]. Pereira et al. [32] and other authors described the resemblance of the histologic patterns between SCC, BCC and SC. The poorly differentiated SC can show squamous differentiation with foci of keratinization. These may lead to the misdiagnosis of SCC. SC can be confounded with BCC, because of the basaloid aspect and the palisade-like configuration of tumor cells at the invasion front. But the typical BCC shows no sebaceous differentiation and has subordinate pleomorphisms [5, 19, 32]. The rare case of a BCC with sebaceous differentiation can thus be misdiagnosed as primary sebaceous carcinoma [33]. SC typically consists of roundish nests of tumor-cells with central comedo-necrosis, in vicinity to regularly structured sebaceous glands. These tumor-nests are smaller than the nodules of BCC, about the size of the surrounding sebaceous glands. Well-differentiated SC shows overt sebaceous differentiation and is to be discerned from sebaceous adenoma and from sebaceoma. The tumor cells of not well-differentiated SC may display high-grade features with a high frequency of mitotic figures and sometimes only abortive sebaceous differentiation within the centers of the tumor-nodules, which is, nevertheless, detectable in most cases. Angiolymphatic invasion is a consistent finding in SC, as well as intraepidermal pagetoid tumor-spread, which should not be misinterpreted as in situ SCC.

Immunohistochemistry is helpful in the diagnosis of SC, since SC consistently expresses EMA (which is absent in SCC and BCC) and, in the centers of the tumor-nests, CD15. Surrounding sebaceous glands serve as a positive internal control for CD15. CD 10 is usually absent in SC, which helps in distinguishing it from BCC. Ansai et al. [14] showed that positivity for adipophilin is most useful in the diagnosis of sebaceous neoplasms. Anti-AR (androgen receptor) is described as the best marker to differentiate between SC and SCC.

Because of the rarity of this tumour, no therapy standard exists. Resection with wide safety margins and selective use of radiotherapy remains the treatment of choice [34]. Sentinel-lymphnode biopsy is an established diagnostic method [12]. Otherwise the role of chemotherapy is in the focus of current research [35]. In the case of an extraocular SC in the metastatic stadium, interdisciplinary therapy concepts with surgeons and oncologists need to be discussed.

Conclusions

Cutaneous metastases and the multifocal appearance of SC are very uncommon features. The masquerading behavior in clinical and histopathological appearance as well as the rareness of SC may lead to misdiagnosis and mistreatment. This may impair the prognosis. One has to be aware of the varying histologic patterns and the varying degree of differentiation in SC. Immunohistochemistry is helpful in the diagnosis of SC. A close interdisciplinary collaboration of clinician, surgeon and pathologist is of most relevance for the right diagnosis.

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