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CASE REPORT

Metatypical Carcinoma - A Continuous Challenge for the Clinician

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Introduction: Non-melanocytic skin cancers represent the most frequent type of cutaneous carcinomas. Also called basosquamous cell carcinoma and considered by some authors as a clinical form of basal cell carcinoma, metatypical carcinoma represents a controversial clinical entity. **Case presentation**: This paper aims to present the case of a 42-year-old female patient who presented to the doctor's office for the appearance of a painful cutaneous tumor located in the left submandibular region. Excisional biopsy was performed. The microscopic features were consistent with the diagnosis of metatypical carcinoma with the predominance of the squamous type. **Conclusions**: Taking into consideration its aggressive behavior, careful follow-up of patients diagnosed with this rare type of cutaneous tumor is mandatory for precocious identification of possible metastases and improvement of long and short term prognosis.

Keywords: metatypical, basosquamous, basal cell, squamatisation

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Introduction

Non-melanocytic skin cancers represent the most frequent type of cutaneous carcinomas. Basal and squamous cell carcinomas represent approximately 99% of non-melanocytic skin cancers, with basal cell carcinoma being 4 times more frequent than squamous cell carcinoma [1]. Risk factors for non-melanocytic skin cancers include solar exposure, skin phototype, premalignant lesions and certain oncogenic viruses [2].

Regarding the evolution, basal cell carcinoma grows slowly, does not metastasize and may be associated with local invasion , while squamous cell carcinoma presents with a more rapid growth and has the ability to metastasize. Therefore, a careful anamnesis and clinical examination of all non-melanocytic skin lesions is mandatory.

Also called basosquamous cell carcinoma and considered by some authors as a clinical form of basal cell carcinoma, metatypical carcinoma represents a controversial clinical entity. Reuniting clinical characteristics of both basal and squamous cell carcinoma, the approach of these cases represents a clinical challenge.

Case presentation:

We report the case of a 42-year-old female patient from the rural area, with no significant personal or family medical history, who presented to the doctor's office for the appearance of a painful cutaneous tumor located in the left submandibular region. The patient stated that the cutaneous mass appeared 1 month prior to presentation and increased rapidly in size.

Local examination revealed a polilobulated translucent tumor located in the left submandibular region, measuring 29x17 mm, raised above skin surface with 5 mm and characterized by irregular rolled pearly edges, ulcerated central surface and purplish-red color. The lesion presented an infiltrated base, cardboard consistency and purplish-red halo. No other suspicious cutaneous lesions were noticed when examining the entire body surface. General examination revealed no submandibular, cervical or pre and retraouricular lymphadenopathies or other abnormalities. Excisional biopsy was performed (Figure 1).

Histopathological hematoxylin-eosin examination revealed solid islands of polygonal cells with eosinophillic cytoplasm, big vesicular nuclei and keratin pearls. At 40x magnification, 10 mitotic figures were observed per

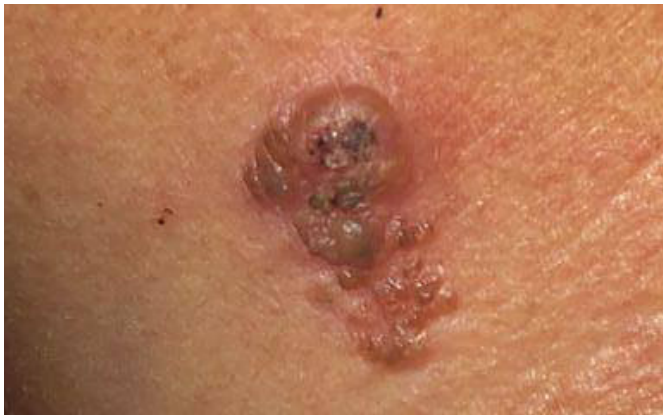

Fig. 1. Macroscopic image of the cutaneous tumor

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10 high power fields. Ki67 index was 45%. Peripheral palisading with basal cells presenting with basophilic cytoplasm and hyperchromatic nuclei was also observed. Tumor cells were positive for CTKAE1/AE3. The microscopic features were therefore consistent with the diagnosis of mixed metatypical carcinoma with the predominance of the squamous type. Regarding tumor margins, gross examination revealed that the lesion was located at 10 mm, 6 mm, 4 mm, respectively at 4 mm from the resection margin. This was consistent with the microscopical examination, which established that the surgical margins were negative (Figures 2 - 5).

Afterwards, the patient was referred to the Oncology Department, where she began three dimensional conformal radiation therapy of the tumor mass and superior and middle cervical lymph nodes. The full dose (50 Gy) was divided in 25 fractions, given 5 times a week with a rest over the weekend. There were no complications reported following radiotherapy, with good clinical outcome. The patient was clinically followed-up for one year, with dermatology visits performed at 3, 6 and 12 months. There were no clinical signs of recurrence or dermatoscopical suspicious lesions identified at these visits.

Discussions

Metatypical carcinoma represents approximately 2% of all cutaneous carcinomas [3]. First brought into attention by MacCormac in 1910, this type of tumor reunites characteristics of both basal and squamous cell carcinoma.

With regard to histopathology, two types of metatypical carcinoma have been described: mixed and intermediate. The intermediate type is characterized by two types of cells, grouped in nests or tumoral lobules, with an outer layer of basal cells and an inner layer of larger, paler and better defined cells, which resemble both basal and squamous cells. The mixed type is defined by the coexistence of basal cells and squamous cells aggregates, which present focal keratinization or pearls with a colloidal or parakeratotic center. Both subtypes have an increased mitotic activity. The intermediate type has a greater risk of metastases and recurrence [4]. In the reported case, the mixed type was identified.

Metatypical carcinoma represents a controversial clinical subject. Its very own existence as an independent clinical entity has been questioned. It is considered by some authors as an evolutive, transitional form between basal and squamous cell carcinoma [5], while other sources consider metatypical carcinoma as being a distinctive tumor.

It was initially suggested that metatypical carcinoma represents a collision tumor, with the basal and squamous cells components with different origins in the epidermis, without any transitional areas and which develop independently one from another [6]. Subsequently, taking into account the histopathological characteristics of metatypical carcinoma, it was postulated the squamatisation theory, according to which metatypical carcinoma originates in a basal cell carcinoma which suffers a process of squamous

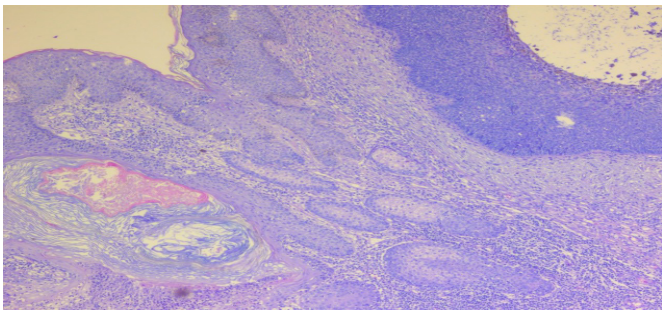

Fig. 2. Histological Hematoxylin-Eosin examination of the tumor shows a nodular architecture. 5X magnification reveals basophilic tumoral cells with peripheral palisading of the nuclei, along with a proliferation of tumoral cells with squamous features and large areas of lamellar keratin

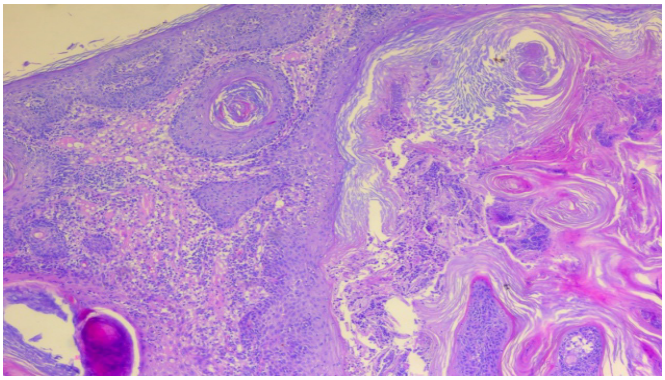

Fig. 3. Lamellar keratin along with the keratin pearls are colored in deep pink with Hematoxylin-Eosin staining method. The nodules with palisading nuclei also show keratinization.

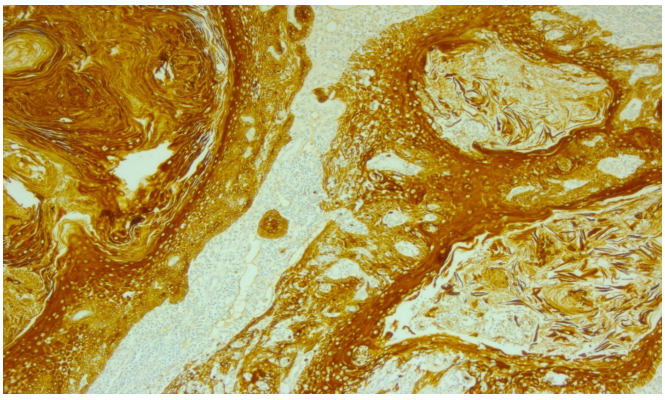

Fig. 4. Tumoral cells are positive for Cytokeratin AE1/AE3 (5X magnification)

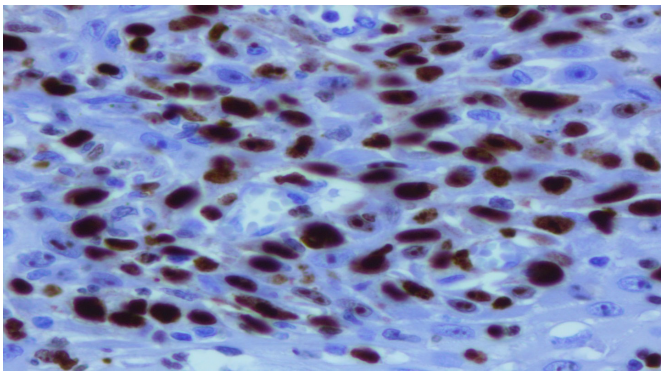

Fig. 5. Ki-67 imunostaining (40X magnification)

transformation [7]. This theory is being supported by the World Health Organisation definition, acording to which metatypical carcinomas result from a squamous differentiation of basal cell carcinomas [8]. Chiang et al. [9] defined in 2019 the genetics of this type of tumor, detailing how metatypical carcinoma originates in a basal cell carcinoma which suffers a process of squamous differentiation through ARID1A and RAS/MPK pathway mutations. Jones et al. [10] argued theoretically that it is very unlikely that an aggressive squamous cell carcinoma might evolve in the direction of a basal cell carcinoma. Even so, the possibility for a metatypical carcinoma to derive from a squamous cell carcinoma must still be taken into consideration, because a similar case has been reported [11]. The histopathogenesis of this condition remains incompletely known and it is debatable if metatypical carcinoma should be classified as basal cell carcinoma, as squamous cell carcinoma or as an independent clinical entity.

Clinical and epidemiological characteristics of this type of tumor were described in multiple clinical studies. The etiopathogenesis of this tumor is multifactorial, UV radiations, skin aging and smoking being important risk factors. Metatypical carcinoma is more frequently encountered in the cervico-facial region and it affects twice more men than women. The mean age at diagnosis is in the 7th decade [12]. Wermker et al. [13] reported that among cases with cervico-facial localization, the majority was located in the nasal region (31.5% of all cases) , followed by the preauricular region (20.2% of all cases) and 7.9% of all cases were located in the cervical region. In our case, this type of tumor was identified in a female patient, in the 5th decade of life and was located in the cervical region.

Clinical distinction of metatypical carcinoma from basal cell carcinoma is practically impossible. This diagnosis must be taken into consideration when a cutaneous lesion, with inconclusive clinical and dermatoscopical aspect, presents with an unpredictable evolution [14]. Additional investigations of these cases are important given the different clinical evolution. Although relatively rare, metatypical carcinoma presents with an aggressive growth and an increased risk for recurrence and metastases. This clinically aggressive behavior differentiates metatypical carcinoma from basal cell carcinoma. Certain studies consider metatypical carcinoma as being even more aggressive than squamous cell carcinoma [12]. Significant predictive factors for recurrence are: male sex, the immune status of the patient, positive resection margins, size of the tumor, perineural and lymphatic invasion. In our case, the resection margins were negative. Regarding the recurrence, one study pointed out that the most common was local recurrence, followed by local recurrence with regional lymph node metastases [15]. Distant metastases were described 4-7 years after the initial tumor and were located in the lymph nodes, lungs and bones [16,17].

Metatypical carcinoma represents both a diagnostic and therapeutic challenge. It must also be differentiated from the following: adenoid cystic carcinoma, undifferentiated small cell carcinomas, neuroendocrine tumors, basal cell carcinomas and squamous cell carcinomas.

Regarding the therapeutic approach of metatypical carcinoma, currently it does not exist an international consensus for these tumors [18]. Complete excision, with clear surgical margins, followed by local radiotherapy depending on the stage of the tumor, is essential for these cases. Due to its metastatic potential, periodic dermatological and oncological follow-up , as well as repeated imagistic investigations are mandatory for a good management of such cases. Our patient was monitored for 12 months, without any clinical signs of recurrence.

Conclusions

The particularity of this case consists in the diagnosis of a rare cutaneous tumor, a mixed metatypical carcinoma with the predominance of the squamous type, in a 42-year-old female patient.

For complete evaluation of patients with metatypical carcinoma, the elaboration of international therapeutic protocols is required. Careful follow-up of patients diagnosed with this rare and aggressive type of cutaneous tumor is mandatory for precocious identification of possible metastases and improvement of long and short-term prognosis.

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Conflict of interests

None to declare.

Authors' contribution

OMT - conceptualization, investigation, acquisition of data, writing - original draft, revision and editing; ACT - acquistion of data, interpretation of data; ST - acquisition of data, interpretation of data; OSC - acquisition of data, interpretation of data, writing – revision; SHM- conceptualization, investigation, supervision, writing – revision, final approval.

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