Metatypical carcinoma.
A review of 327 cases

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INTRODUCTION: *Metatypical cell carcinoma is a quite rare malignancy (5% of all non melanoma skin cancers), with features of basal cell carcinoma and squamous cell carcinoma. It is described as coexistence of basal cell carcinoma and squamous cell carcinoma with no transition zone between them.*
MATERIALS AND METHODS: *We performed a retrospective study of 327 consecutive patients, diagnosed for metatypical carcinoma. Statistical analysis was made to determinate most affected areas, gender prevalence, average age, presence of ulceration and infiltration, peripheral clearance rate.*
RESULTS: *A relevant difference came out between two genders. X2 test emphasized a relation between females and the presence of carcinoma on the scalp. In addition a strong correlation between mixed subtype and ulceration was evident. A strong relation between intermediate subtype and positive surgical margin was found; this data could identify a more aggressive behavior of intermediate type.*
DISCUSSION: *Differently from melanoma that usually arises on sun exposed areas, no relation was found between sun exposion and this tumor. This characteristic stresses on the importance of other risks factor apart from sun exposition.*
CONCLUSIONS: *We identify some correlation between our data that cannot be explained with previous interpretation of sun exposition.*

KEY WORDS: Metatypical carcinoma, Metatypical carcinoma epidemiology, Metatypical carcinoma risk factors.

Introduction

Nonmelanoma skin cancer (NMSC) is the most common cancer in the world with an incidence 18-20 times greater than that of malignant melanoma [1]. The lifetime risks of developing NMSC were estimated to be 29 percent to 55 percent for basal cell carcinoma (BCC) and 7-11 percent for squamous cell carcinoma (SCC) [2]. 80 percent of NMSC are BCC and 20 percent are SCC.
Basal cell carcinoma, which probably arises from immature pluripotential cells, is the most common malignant tumor of the skin in Caucasian [3]. It occurs mostly on sun-exposed areas such as neck and face. Altought it is a cancer, it's a slow-growing locally invasive tumor that rarely, if ever metastatize [4].
Primary cutaneous squamous cell carcinoma (SCC) is a malignant tumor that may arise from the keratinising cells of the epidermis or its appendages. It is more rare than BCC but is known to be more aggressive, destroying underlying structures in the face or the hands and thus requiring extensive and sometimes destructive surgery. On rare instances, cutaneous SCC may metastasize to regional lymph nodes or distant sites, just like SCC from other organs such as the lungs.

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Metatypical cell carcinoma (MTC) is a quite rare malignancy (5% of all non melanoma skin cancers), with features of basal cell carcinoma and squamous cell carcinoma [5]. It was first reported as a distinct histologic variant in 1910 by MacCormac in a series of rodent ulcers [6]. It was described as coexistence of basal cell carcinoma and squamous cell carcinoma with no transition zone between them. Some authors believe that MTC is a variant of BCC, whereas others have suggested that BSC may behave more aggressively, with a propensity for local recurrence and a potential risk for distant metastatic spread. This behaviour, anyway, differs substantially from that of BCC. An evidence of MTC aggressiveness is proliferative index. It is 4 times greater than in BCC and 8 times greater than in normal skin epidermidis [7].
According to Ferrand M. MTC presents two subtypes: intermediate and mixed.

Materials and methods

We performed a retrospective study of 327 consecutive patients, diagnosed for metatypical carcinoma from 1993 to 2003 and from March 2007 to November 2009. Patients were admitted to the department of Plastic Surgery of the University of Rome "la Sapienza" and treated at the same site. Only people diagnosed for MTC according to histological analysis were accepted to the study. The study included 114 females and 213 males. Tumors were analyzed and measured from the surgeon, excision margins were marked on the basis of palpable or visual alteration of the burden. The minimum surgical margin was equal to the short axis of the ellipse. Therapy was made according to guidelines. Generally peripheral margin of 3 mm beyond apparent clinical margin was taken on the facial and neck areas, of 5 mm was taken in other sites, but if lesions had a rapid and aggressive growth a wider excision was performed. In these cases 5 mm of peripheral margin was taken for neck and face a margin of 10 mm for other areas in order to increase the peripheral clearance rate. We performed a full-depth dermal incision to avoid possible relapses, due to a marked peculiarity of metatypical carcinoma to be aggressive and to metastasize.
After excision a histological analysis was carry out to have a diagnosis. Features analyzed were size, typology, presence of ulceration, infiltration of contiguous structures and clearance of excision margins. If margins were not free from tumor other excisions were made until clear margins were obtained.
Additional therapies were performed after intervention such as radiotherapy and chemotherapy.
At the end a statistical analysis was made to determinate most affected areas, prevalence between gender, average age, presence of ulceration and infiltration, peripheral clearance rate. A possible correlation between two variables was valuated with X^2 method.

Results

The study considered a group of 327 patients affected by MTC. Average age was 69,5 years old. A relevant difference came out between two genders. 213 Males (65%) were affected in comparison with only 114 females (35%). Concerning areas affected, first is cervico-facial area with a prevalence of 220 cases (67,3%), second trunk 33 cases (10,1%), third other areas 29 cases (8,86%), fourth limbs 32 cases (9,80%), fifth scalp with 13 cases (4%). (Tab. I)
We applied statistical analysis with X^2 in order to identify a relation between gender and affected area and it emphasized a relation between females and the presence of carcinoma on the scalp. X^2 is 4.242, with a p= 0.039. No other significant correlations were individuated between variables.
Considering histological subtypes there is a strong prevalence of intermediate 239 (72.8%) in comparison with mixed 88 (27.2%).
Then we stressed on the presence of ulceration (29%) and the relation of this with both histological subtypes. A strong correlation between mixed subtype and ulceration was evident (X^2=8.212, p=0.00416). (Tab. II)
Average diameter of lesions is 1.22 mm, the biggest lesion measured 5.3 cm, the smallest 0.2 cm. Margins taken were 3 mm on cervico-facial area and 5 mm on other areas. In addition a bigger margin was taken in aggressive lesion, and after recurrences.
Relapses occurred in 32 cases (10%), all in cervico-facial area. A relation between relapses and histological subtype was evident. Only 3 (10%) relapses occurred on mixed MTC, despite of 29 (90%) occurred on intermediate type (X^2=5.7 p=0.016). No metastases were documented.

TABLE I - *Relation between affected areas and gender.*

Areas affected	Males (100%)	Females (100%)	Significance (X^2)
Cervico-facial	144 (67.6%)	77 (67.4%)	No
Trunk	24 (11.2%)	11 (9.6%)	No
Limbs	22 (10.2%)	12 (10.5%)	No
Scalp	5 (2.3%)	8 (7.0%)	X^2=4.242 p=0.039
Other	22 (10,2%)	13 (8,7%)	No

TABLE II - *Relation between histological subtype and presence of ulceration.*

Subtype Ulceration	Mixed	Intermediate	Tot
Present	36 (41.1%)	59 (24.6%)	94
Absent	52 (58.9%)	180 (75.4%)	232

Discussion

Nonmelanoma skin cancers (NMSC) are by far the most common form of human malignancy[8]. The major environmental cause of NMSC is exposition to solar ultraviolet radiation. In addition habit of smoking and a blistering sunburn skin are related to the development of NMSC. Although their frequency, metastases are not so common and they are rarely mortal. Despite this comforting data there's a strong evidence of increased risk of melanoma among people who have a previous NMSC. [9] Apart from melanoma a relation with the rise of other tumors was individuated [10]. Anyway there is an apparent absence of any single environmental agent that could explain the multiple cancer risks and this indicates that intrinsic risk factors may be responsible for this phenomenon.

An important distinction has to be made between BCC and SCC. BCC is the most common skin cancer and there are few cases in literature of its metastases. In the other hand SCC is more rare than BCC but is more prone to metastasize. In addition to these two types there is a third, intermediate entity, metatypical carcinoma, defined as basosquamous carcinoma, too.

Metatypical carcinoma was first reported as a distinct histologic variant in 1910 by MacCormac. It was considered as an intermediate form with BCC and SCC at each end of the spectrum. In 1928 Montgomery defined it as a fully distinct neoplasm [11]. In 1974 WHO confirmed the demarcation of MTC from BCC and SCC [12]. Macroscopically MTC is very similar to BCC and this characteristic easily misleads [13]. Despite their aspect distinction between these two NMSC is crucial because of their different behaviors [14]. BCC almost never metastasize, in the other hand MTC is more similar to SCC and has a worse prognosis [15]. Significant indicators for prognosis of MTC seem to be gender (male), positive margins and lymphatic and perineural invasions [16-17].

Diagnosis is based on histological analysis. Histologically MTC is divided into two subtypes: intermediated and mixed. In the intermediate form transitional zones and tumor islets are found together, thus combining features of BCC and SCC (Fig. 1a) [18]. In mixed subtype typical basal cells coexist with areas of conglomerated squamous cells, squamous pearls could be present. (Fig. 1b) According to Katzanseva, both subtypes present a higher percentage of proliferating cells and large number of mitotic figures. These findings support hypothesis that MTC may be responsible for some cases of biologically aggressive cutaneous carcinomas. An important help to diagnosis can be expression of keratin. BCC express keratin 8 and 17, MTC on the contrary always express a very low level of these keratin [19-20].

In our study we found a major prevalence of MTC in men 65% (213) than in women 35% (114). Cervicofacial and trunk are the most affected areas, this location individuates the importance of sun exposition in the rise of MTC [21]. But differently from melanoma that usually arises on facial and limbs areas in women and on trunk in men, no relation was found between sun exposited areas and gender in this tumor. This characteristic stresses on the importance of other risks factor apart from sun exposition. To reinforce this theory a bigger prevalence of scalp lesion was found in women in comparison with men (p=0.039). Obviously women's scalp is less exposed to sun than men's, so development of MTC necessarily depends on other factors.

According to 2008 guidelines a peripheral surgical margin of 3 mm will clear the tumor in 85% of cases, a 5 mm margin up to 95% of cases [22-26]. In our report we individuated a tumor clearance of 83% with a 5 mm margin excision. An even worse clearance was found in cervico-facial area, due to a smaller peripheral margin taken in this zone (3mm). In addition any NMSC on

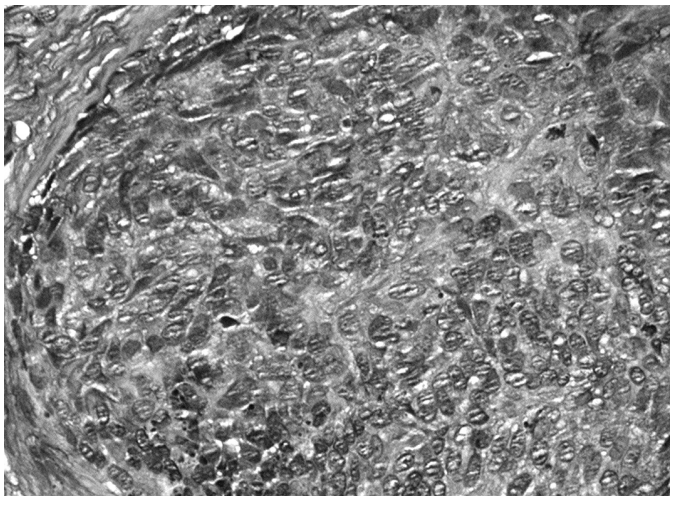

Fig. 1A: Histological features of intermediate subtype: transitional zones and tumor islets are found together (20x).

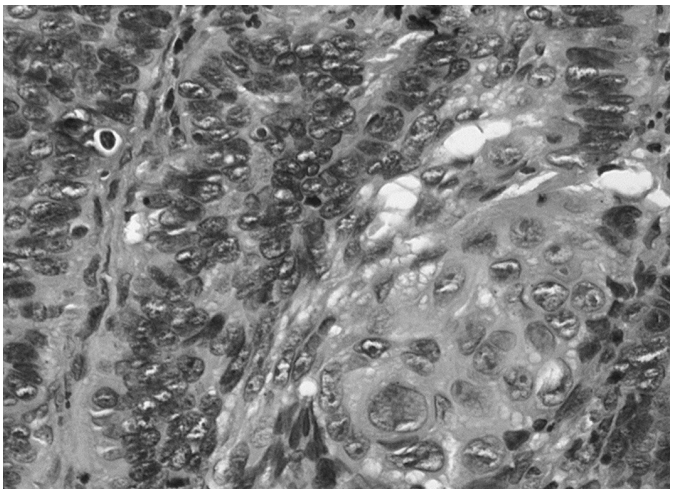

Fig. 1B: Histological features of mixed subtype typical basal cells coexist with areas of conglomerated squamous cells (20x).

the forhead and temporal area are characterized by a propensity to relapse.
No studies on the adequate peripheral surgical margin in MTC were made, but probably in MTC a wider excision, due to an aggressive behavior of the malignancy [27].
In addition a strong relation between intermediate subtype and positive surgical margin was found; this data could identify a more aggressive behavior of intermediate type (p=0,016) and necessity of a more radical intervention.

Conclusions

Our report stressed on the importance of more studies on the MTC. We identify some correlation between our data that cannot be explained with previous interpretation of sun exposition. So additional investigation on causes of MTC rise should be done.
Furthermore some authors evidenced a different cytological behavior of this tumor that can clinically useful. Identification of keratins can be used to early identify this kind of NMSC. A more depth knowledge of MTC mechanisms of transformation could clear up its capacity to metastasize in concordance with its higher aggressiveness. These data can bring to the awareness of necessity of a stronger intervention on this tumor in order to avoid local recurrences and spread metastases.

Riassunto

Lo studio qui descritto è stato effettuato su 327 pazienti con diagnosi di carcinoma metatipico ricoverati presso il Dipartimento di Chirurgia Plastica e Ricostruttiva del Policlinico Umberto I. Lo studio prende in analisi, in primo luogo, le relazioni intercorrenti tra la localizzazione delle lesioni e il sesso dei pazienti, giungendo a concludere che l'esposizione solare non può essere considerato come unico fattore causa dell'insorgenza del carcinoma. Successivamente viene considerata la relazione tra istotipo e presenza di ulcerazione e aggressività della neoplasia, questa analisi evidenzia che il sottotipo intermedio sviluppa un maggior numero di recidive e necessità di maggior radicalità chirurgica. Infine si evince la necessità di linee guida più specifiche per il management di questo carcinoma che non può essere assimilato nè ad un basalioma nè ad uno spinalioma.

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