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Cutaneous metastases of internal malignancies: an experience from a single institution

Background: Cutaneous metastases represent 2% of all skin tumours. Their recognition can be challenging, as they may present with different clinical features, with consequent frequent delay and failure in diagnosis. *Objectives*: To review our series of cutaneous metastatic lesions, analyse their frequency according to patient gender, histotype, localization of the primary tumour, and site of cutaneous metastasis, and correlate this data with clinicopathological parameters. *Materials & methods*: We conducted a retrospective review of all cases of cutaneous metastases from visceral neoplasms diagnosed in our dermatopathology department from July 2003 to February 2017. We registered clinical, histological, and immunohistochemical data. Additional immunohistochemical staining panels were elaborated to confirm or identify the origin of the primary tumour, or at least to specify the histological subtype. *Results*: We identified 45 histological diagnoses of cutaneous and mucocutaneous metastases. The primary tumour that was most likely to metastasize to the skin was breast cancer. Most cases of breast (89%) and lung cancer (86%) metastasized to the trunk. Of the lesions, 57.5% were nodules and 32.5% were plaques, more frequently multiple (64.4%). In 58% of cases, a metastasis was clinically suspected. Histological examination most frequently revealed an adenocarcinoma, sometimes suggestive of the site of origin. *Conclusions*: Cutaneous metastases should be primarily considered when discrete firm painless nodules emerge rapidly. Clinicians should carefully consider infiltrated lesions of the chest in women since scleroderma and erysipelas-like presentation can be a clue for undiagnosed breast cancer.

Key words: cutaneous metastasis, histopathology, immunohistochemistry, internal malignancy

Cutaneous metastases develop in about 0.6-10.4% of oncology patients, representing, in some cases, the first manifestation of an internal, misdiagnosed neoplasia [1-3]. The frequencies of the different histotypes of metastases are usually related to the frequency of the relative primary cancer according to age and gender [4, 5]. In men, malignancies that most often metastasize to the skin are located in the lung, large intestine, oral cavity, kidney, breast, oesophagus, pancreas, stomach, and liver. In contrast, in women, more often they are located in the breast, ovary, oral cavity, lung, and large intestine [1, 4, 6, 7]. The most involved sites are the head and neck, and trunk, but rarely the limbs [8]. Cutaneous metastases may present with different clinical features; typical features are painless nodules of firm or elastic consistency, which develop within a short time [9]. In other cases, they may mimic specific inflammatory or neoplastic dermatological conditions with consequent frequent delay and failure in their diagnosis [10, 11].
The prognosis of patients with cutaneous metastatic lesions is poor, with a median survival of approximately 7.5 months [12]. The diagnosis is based on histological examination, which most frequently reveals an adenocarcinoma, sometimes suggestive of the site of origin. Several immunohistochemical staining panels have been elaborated to specify the histological subtype, or at least to direct the oncologist towards which body area to investigate [13, 14]. The aim of this study was to review our series of cutaneous metastatic lesions, analyse their frequency according to type and localization of the primary tumour, as well as site of cutaneous metastasis, and further correlate this data with the clinicopathological parameters.

Materials and methods

Patients and tissues

We investigated all cases of muco-cutaneous and cutaneous metastases from visceral neoplasms diagnosed in our dermatopathology department from July 2003 to February 2017. All the biopsies were reviewed to confirm the diagnoses.

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Sections stained with hematoxylin and eosins were available in all cases. Of these, 38 had sufficient material for further histological and immunohistochemical studies, and a paraffin block of the lesion representative of each case was selected. Sections 3 μm thick were cut for standard hematoxylin-eosin and immunohistochemical staining. The immunohistochemical panels for each case were reviewed, and additional immunohistochemichal staining was performed if needed.
Clinical data regarding age, gender, clinical features, and diagnosis of lesions were obtained from the computerised medical records. Clinical images were retrieved for 29 patients. For statistical analysis, the skin surface was divided into four regions: head/neck, trunk, genital area, and extremities. If two or more regions were involved, metastases were considered to affect multiple sites. Clinical classification was based on the predominant primary or secondary skin lesion (patch, plaque, nodule, erosion, ulceration, and wheal). We only included metastases from internal malignancies, excluding all cases originating from haematological neoplasms and primary cutaneous malignant neoplasms.
The main goal of this retrospective analysis was to describe and illustrate the clinical, histopathological, and immunohistochemical features of our cutaneous metastases series.In particular, we analysed:

– (1) relative frequencies of skin metastases according to primary tumour and patient gender;
– (2) localisation of cutaneous metastases in relation to primary cancer and patient gender;
– (3) clinical features of cutaneous metastases in relation to primary cancer.

Data concerning the history of the internal malignancy, the relationship between the time of the histopathological examination of the primary tumour and that of the metastatic lesions, follow-up, and treatment were not considered because they were only partially available and this information was considered to be beyond the objectives of our study.

Immunohistochemical staining

When paraffin-embedded tissue was available, we used an imunohistochemical panel containing antibodies to the following: (1) either mammaglobin, GATA3, or gross cystic disease fluid protein-15 (GCDFP15) and oestrogen receptor for breast cancer; (2) thyroid transcription factor-1 (TTF-1), napsin A, and p40 protein for lung cancer; (3) CDX-2 and cytokeratin 20 (CK20) for colorectal cancer; (4) CDX2, CK7, and CK20 for pancreatic cancer; (5) prostate specific antigen (PSA) for prostatic cancer; (6) CK7, CK20, and p63 protein for transitional cancer; (7) calcitonin for medullary thyroid carcinoma; (8) anti-CD56 when neuroendocrine differentiation was suspected based on morphology using chromogranin and sinaptophysin staining; and (9) a panel with antibodies against p63, p40, podoplanin, and calretinin for cases with no morphological or immunohistochemical specific profiles in order to rule out an adnexal malignant tumour.
All antibodies were provided by DAKO and antigen-antibody detection was performed using the DAKO Omnis automated staining platform (DAKO A/S, Glostrup, Denmark) according to the manufacturer's instructions. Slides were finally prepared for light microscopy examination.

Table 1. Demographic summary based on the origin of skin metastases.

No. cases	Origin	Mean age	Sex
2	Bladder	63 (61-65)	2 M
18	Breast	74 (62-95)	17 F, 1 M
3	Colon	75 (71-83)	2 M, 1 F
7	Lung	73 (51-80)	7 M
1	Pancreas	71	1 M
2	Prostate	87 (85-90)	2 M
2	Stomach	66 (73-80)	1 M, 1 F
1	Thyroid	17	1 M
1	Uterus	77	1 F

Immunohistochemical evaluation

The extent of immunohistochemical reactivity to oestrogen receptors is specified as percentage; for other antibodies, reactivity is indicated as + (positivity) or - (negativity).

Statistical analysis

Group comparisons were performed using univariate two-sided Student's *t* test or the Mann-Whitney U test when appropriate (MedCalc Software, Mariakerke, Belgium).

Results

We reviewed 45 histological diagnoses from cutaneous and mucocutaneous tissues of 45 patients. The average age was 73, with the youngest patient 17 years and the oldest patient 95; most of the patients were between 60 and 80. Of the 45 patients, 25 (56%) were female and 20 (44%) were male.
The primary tumour most likely to metastasize to the skin was breast cancer. It was also the most common metastatic neoplasm in women ($p = 0.0004$), while lung cancer was the most common in men (*table 1*). In eight out of 45 cases (17.8%), the origin of the primary tumour was not found; in three cases, paraffin blocks were not available for further imunohistochemical analysis. Three cases showed an undifferentiated morphology, one showed neuroendocrine features but without medical history, and one showed adenocarcinoma morphology without significant immunohistochemical results or anamnestic data.
The distribution of cutaneous metastases was not completely random and occurred most frequently in proximity to the primary tumour. There was a statistically significant association between the site of cutaneous metastases and the origin of primary tumour ($p = 0.006$); most cases of breast (89%) and lung cancer (86%) metastasized to the trunk, even when more sites were involved. We related the site of cutaneous metastases to the primary tumour for male and female patients. In men, 45% of metastases were localised to the skin of the head and neck, and 60% to the trunk.

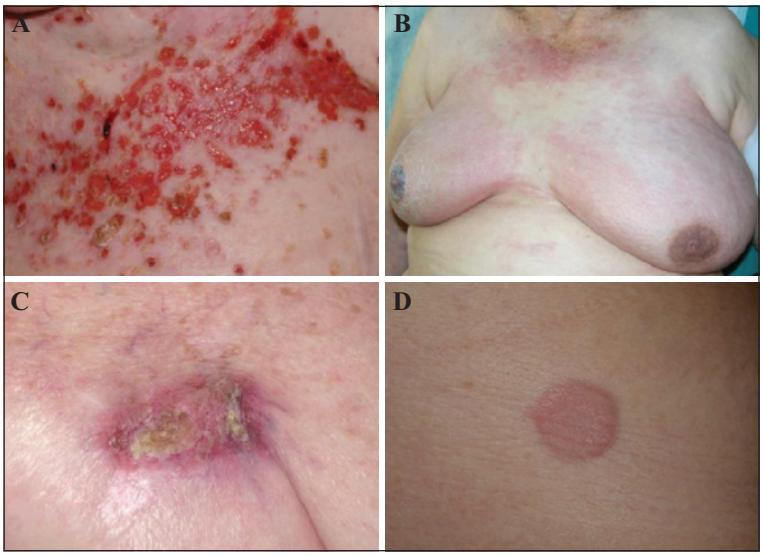

Figure 1. Different clinical subtypes of cutaneous metastases from breast carcinoma: an erosive-crusted form (**A**), carcinoma erysipelatodes (**B**), a radiodermatis-like form (**C**), and presentation of small plaques (**D**).

In women, 80% occurred on the trunk, with breast carcinoma metastasizing mainly to the chest (64.7%). There was a weak association between patient gender and the site of metastases ($p = 0.05$).

Clinical features of metastases were documented in 40 cases; 57.5% were nodules and 32.5% were plaques, more frequently multiple (64.4%) than single (*figure 1*). Only one case of patch, erosion, and ulceration was reported. In skin metastatic breast carcinoma, two plaques were erysipelas-like (carcinoma erysipelatoides) and two were scleroderma-like (carcinoma en Cuirasse). In 58% of cases, a metastasis was clinically suspected. In the other cases, metastasis was mistaken for squamous cell carcinoma, basal cell carcinoma, lymphomas, pyogenic granuloma, fibrohistiocytic tumour, scleroderma, radiodermatitis, folliculitis, or bullous disease. No statistically significant association was found when considering clinical features and origin of the primitive tumour.

Histologically, a metastatic pattern was infiltrative, sometimes with a vaguely nodular appearance but without forming a well-circumscribed nodule; the lesions tended to infiltrate the collagen bundles with no epidermotropism (*figure 2*). All cases showed a variable amount of necrosis, from punctate necrosis with cellular debris, to large areas with irregular contours. Of 18 cases of breast cancer metastases, nine cases (50%) showed an infiltrating ductal carcinoma morphology, and the other nine cases (50%) were diagnosed as infiltrating lobular carcinoma, confirmed by immunohistochemistry in all but one case. In addition, nine cases showed strong and diffuse positivity for oestrogen receptor in up to 90% of neoplastic cells. Of seven cases of lung metastases, four cases (57%) showed an adenocarcinoma morphology, confirmed in all but one case by immunohistochemistry; one out of seven cases (14%) showed a squamous morphology and one out of seven cases (14%) displayed neuroendocrine features and was classified as large cell neuroendocrine carcinoma. In one case (14%) there was no reactivity to any specific immunohistochemical marker and, according to WHO 2015, classification was categorized as large cell carcinoma.

Of the 45 cases, three (7%) showed an intestinal morphology with an immunohistochemical profile coherent with bowel origin; two (4%) originated from a gastric neoplasia (one case showed "signet ring" cells with a discohesive, infiltrative pattern) and one case (2%) was diagnosed with metastasis from an acinar pancreatic adenocarcinoma with diffuse perineural invasion. In two cases (4%), the origin was urothelial cell carcinoma and prostatic acinar adenocarcinoma in another two cases (4%), and one case (2%) showed squamous differentiation, coherent with origin from the uterine cervix. Only one case (2%) exhibited a poorly differentiated morphology; reactivity to calcitonin based on immunohistochemistry alone confirmed a thyroid origin of the neoplasia, which was a medullary carcinoma. The last eight cases (17.8%) showed a variable amount of cytokeratin AE1/AE3 positivity, but with no morphological or immunohistochemical specific profiles which would allow them to be classified; with no clinical information about these patients, we were unable to identify the origin of metastases. For the four cases with available paraffin blocks (with an undifferentiated or adenocarcinoma histotype), in order to rule out an adnexal malignant tumour, a panel comprising antibodies against p63, p40, podoplanin, and calretinin was tested; no immunoreactivity to these markers was observed, thus excluding this hypothesis.

Discussion

Cutaneous metastases are neoplastic lesions that arise from a primary malignancy that spreads to the skin. They occur rarely in patients with an underlying malignancy, representing 2% of all skin tumours [15]. They are usually associated with poor prognosis and often are a hallmark of a widely spread visceral cancer [16, 17]. They may represent failure of ongoing therapy or tumoural relapse, or, more rarely, may be the first sign of an asymptomatic, unsuspected occult malignancy [18, 19].

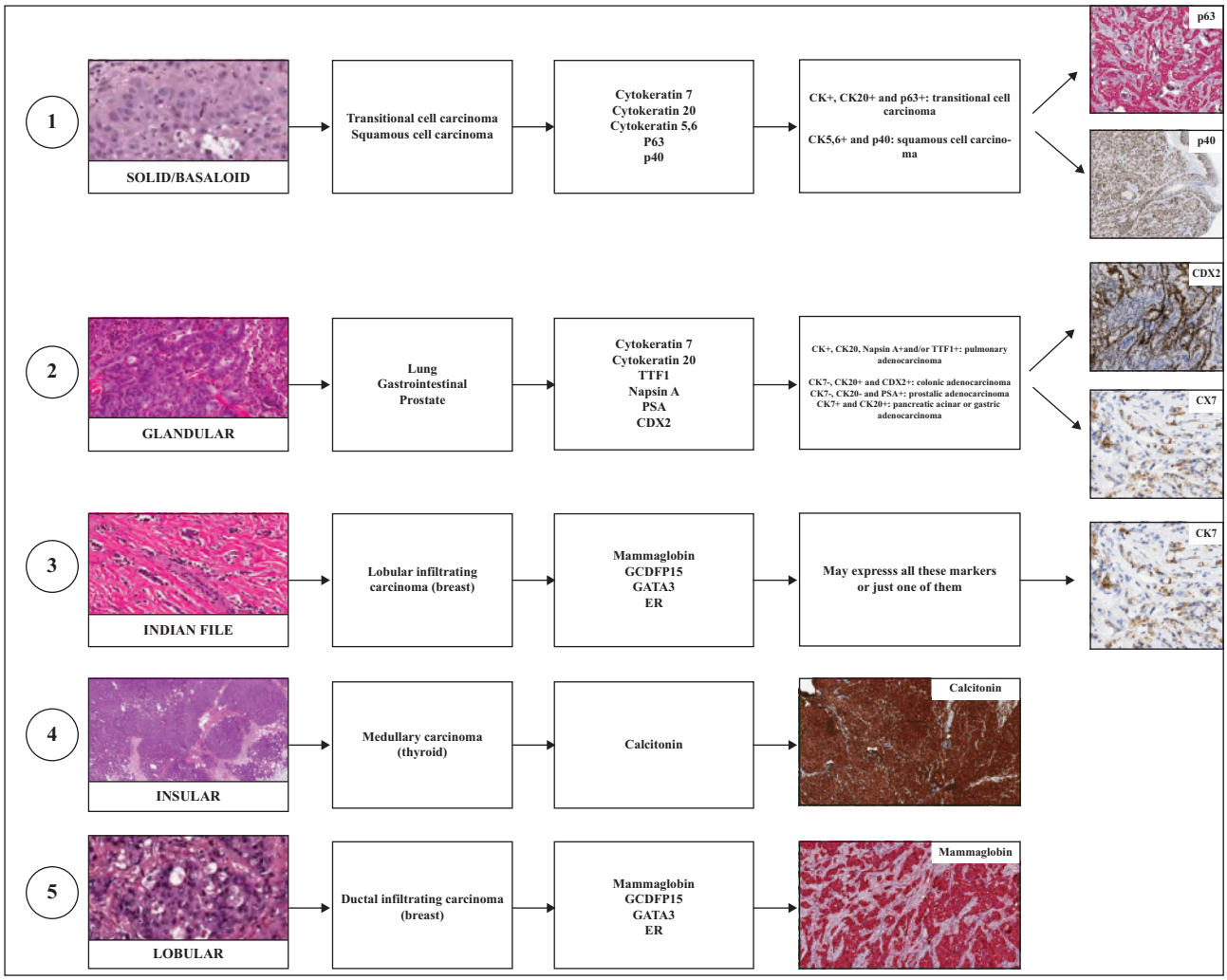

Figure 2. Morphological patterns with corresponding immunohistochemical analysis in order to identify or confirm the primary origin of metastases.

The interval between tumour diagnosis and the appearance of subsequent cutaneous metastases is variable, but in general, they occur within the first three years after diagnosis [20, 21], or, in the case of more aggressive tumours, within a few months [22].

Cutaneous and subcutaneous tissue infiltration can result from lymphatic embolization, haematogenous or contiguous dissemination, or also direct implantation during surgery [23]. In the latter case, a metastatic lesion is often closely associated with the site of local drainage, incision, surgery, needle puncture, or skin transplantation [24-27]. Although in most cases, there is no correlation between the mechanism of dissemination (*i.e.* lymphatic vs. haematogenous) and clinical presentation [23], some "inflammatory" carcinomas can mimic erysipelas or cellulitis, which almost always leads to extensive invasion of lymphatic vessels by neoplastic cells [28-30].

Some retrospective studies of cutaneous involvement by internal malignancies have been published in different countries [31-34]. However, such patterns may differ geographically (a study in Taiwan [35] found that internal malignancies metastasize with low rates compared with previous studies involving Caucasians) and the relative frequencies of metastatic skin disease tend to correlate with the frequencies of the different types of primary cancers for each sex [1, 4, 36, 37].

The neoplasms that most often metastasize to the skin are breast cancer in women and lung cancer in men. Other tumours with a greater propensity to metastasize to the skin include gastrointestinal tract carcinomas [4, 38].

Nodules are the most common clinical presentation. They usually range in size from 1 to 3 cm and appear as firm, solitary, or multiple lesions that are located in the dermis or subcutaneous tissue. Generally, their colour is similar to that of normal adjacent skin, although they may also appear pink to red-brown and are asymptomatic, and rarely pain or tenderness is reported. Occasionally, lesions may erode and ulcerate or develop a secondary infection [4, 39]. Other clinical presentations include inflammatory forms (carcinoma erysipelatoides) [40, 41], sclerodermiform lesions with induration and infiltration (carcinoma en cuirasse) [42], and telangiectatic carcinoma with prominent telangiectasias or lymphangioma circumscriptum-like pseudovesicular lesions [43]. Less

common are zosteriform, bullous [44], papulosquamous, plaque-like, ulcerated forms or those that may induce scarring alopecia on the scalp [45] or mimic erythema annulare centrifugum [46] or cutaneous vasculitis [47, 48].
Sometimes, metastases are difficult to distinguish from a primary cutaneous tumour, such as basal cell carcinoma, lymphoma, melanoma [49], keratoacanthoma, pyogenic granuloma [50, 51], dermatofibroma, pilomatricoma [52], leiomyosarcoma [53], granular cell tumour [54], Kaposi sarcoma, or angiosarcoma [55].
The upper trunk and abdomen are the most commonly involved sites reported in the literature, followed by the head and neck, whereas metastases in the extremities are uncommon. The head and neck region and the anterior chest are the areas of greatest predilection in men. The anterior chest wall and the abdomen are the most commonly involved sites in women [14, 56].
The histomorphological pattern of all the lesions was infiltrative; no lesion formed a well-circumscribed nodule. The neoplastic elements showed a tendency to infiltrate in single cells or aggregate in the collagen fibres of the dermis, with a variable amount of necrosis and, in some cases, with aspects of perineural infiltration. The infiltrative pattern was particularly predominant in breast lobular carcinoma metastases and gastric metastasis with "signet ring" features. No epidermotrophism was found.
A panel of antibodies specific to each suspected origin was set up, and this allowed us to confirm the primitivity of the lesion; only one case of breast cancer metastasis showed no immunoreactivity to antibodies normally expressed by tumours of the breast. This can be explained considering that metastases tend to de-differentiate, both in a morphological sense (acquiring a poorly-differentiated phenotype compared to the original tumour) and in an immunohistochemical sense (losing the expression of markers that are expressed in primitive locations of neoplasms).
The histopathological distinction between primary adnexal carcinomas and metastatic adenocarcinoma to the skin often presents a diagnostic challenge. The immunohistochemical markers, p63, p40, podoplanin, and calretinin, which are preferentially expressed in primary adnexal carcinomas are helpful in distinguishing these entities, with the exception of cutaneous metastases from salivary gland or bladder carcinomas [57, 58].
Our findings regarding histotype, clinical findings, and location of the primary tumour and skin metastases are in concordance with most of the reported findings in the literature. In 50-81.8% of the cases, a metastasis was suspected before performing a biopsy [59, 60], in agreement with our results (58%). In particular, we confirm that the clinical presentations of the skin metastases are often highly variable, non-specific, and subtle, and may be mistaken for certain dermatological conditions. Nevertheless, cutaneous metastases should be primarily considered when discrete firm painless nodules emerge rapidly without any explanation.
Interestingly, we found a statistically significant association between the origin of the tumour and the site of the cutaneous metastases. This should lead us to carefully consider the infiltrated lesions of the chest in women since scleroderma and erysipelas-like presentation can be a clue for undiagnosed breast cancer.
In conclusion, clinicians treating patients with internal carcinomas should look for skin involvement even after a long asymptomatic period, paying special attention to all skin nodules, non-healing ulcers, and persistent indurate erythema. A high level of suspicion is recommended when new skin lesions are found in cancer patients. ■

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