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ORIGINAL ARTICLE

A single-centre experience of secondary cutaneous tumours with special reference to precocious metastases

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Abstract

Background Secondary involvement of skin by tumour comprises 2% of cutaneous neoplasia, in a small proportion of cases serving as the primary manifestation of occult disease.

Methods Cases of cutaneous metastases (CM) were retrieved from our pathology files between 2013 and 2018 and clinical and histopathological data reviewed.

Results There were 159 cases (median age 70). A majority of clinical presentations comprised isolated, papulonodular lesions. While the anatomic distribution of lesions often bore a proximate relationship to the primary tumour, distant sites of involvement were frequently encountered. Melanoma gave rise to the greatest number of metastases, followed by tumours of the breast, colorectum, and squamous cell carcinoma. In six cases (3.8%), CM served as the presenting feature of occult malignancy. These patients presented at a more advanced age and with distant sites of involvement. The microscopic features of CM include nodules, nests, and cords or single cell infiltrates typically in deeper compartments in the absence of overlying epidermal or adnexal precursor lesions.

Conclusions CMs are a frequent development in the natural history of melanoma and breast tumours. In practice, a wide spectrum of tumours may give rise to CM and a small proportion more importantly, signal the existence of previously unknown neoplasia.

Keyword Cutaneous metastasis

Introduction

Metastases comprise 2% of cutaneous neoplasia and typically represent a late manifestation of widely disseminated malignancy [1]. Frequently cutaneous involvement develops in the setting of a previously diagnosed tumour however metastases may serve as the presenting feature of clinically occult disease, referred to as 'precocious metastasis' (PCM) [2, 3]. The clinical manifestations are protean and have been described in detail. The incidence of cutaneous metastasis (CM) is similar amongst men and women; however the tumour profiles differ. In men, melanoma, squamous cell carcinoma (SCC) of the head and neck and tumours of the lung and gastrointestinal tract are most frequently encountered, whereas in women breast cancer and melanoma predominate [1]. CM is extremely uncommon in paediatric malignancy [4]. While CM generally confers a poor prognosis, survival is dependent on a number of variables including primary tumour type, systemic burden and patient characteristics.

Key Learning Points
- CMs develop in approximately 1% of cancer patients and may present singular diagnostic challenges particularly in the setting of unsuspected malignancy.
- Occasionally CMs simulate benign dermatoses.
- CMs develop with greater frequency in women owing to the dermatotrophic nature of invasive ductal carcinoma of the breast.
- Melanoma and tumours of the gastrointestinal tract are the most common source of CMs in men.
- Since CM precedes the diagnosis of internal malignancy in almost 4% of cases, tissue biopsy may provide a crucial opportunity for intervention.

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Histopathological diagnosis is achieved in most cases on the basis of tumour morphology including comparison with prior morphology and supportive immunohistochemistry. Poorly cellular deposits, extensive tumour or inflammatory-related tissue destruction and undifferentiated tumours are frequent challenges particularly when a site of origin is not established. We set out to examine the clinical features, patterns of presentation and histologic findings of cutaneous metastases in a large cohort of patients with particular emphasis on the precocious metastases.

Materials and methods

The cases in this study were retrospectively identified over 6 years from the pathology archive of a tertiary referral centre. Cutaneous tumours coded as metastatic tumour were retrieved from the files. The submitted material included all available formalin-fixed paraffin embedded (FFPE) tissue blocks, hematoxylin and eosin sections and corresponding immunohistochemical stains. Demographic data, clinical features including patterns of presentation and histologic features, were recorded. Follow-up pathology data was also documented where available. Satellite/in transit metastases and tumour arising in excision scars were excluded from the study. Cutaneous involvement by secondary haematological malignancy was not included in this study. Patient data generated in this review was used in compliance with EU General Data Protection Regulation (GDPR).

Results

A total of 159 cases were retrieved for inclusion in this study, 98 were female and 61 were male. The median age of onset was 70 years (range 23–95 years).

Clinical presentation

The majority of CMs irrespective of tumour subtype presented as solid lesions ($n = 36$), typically papulonodular in appearance (Table 1). Multiple sites of involvement were observed in five cases, three from a primary melanoma. Metastatic melanoma frequently incorporated pigmentary change. Metastatic tumours of breast displayed a broad spectrum of clinical morphology including chest wall papules, 'en cuirasse' skin thickening and erythematous eruptions (Fig. 1). Anterior margin status of previous surgical excision specimens was not available in all cases. Biopsy of a non-resolving rash that developed on the neck of one patient confirmed metastatic salivary ductal adenocarcinoma. Biopsy material from an ulcerated lesion of the abdominal wall in an elderly woman confirmed the presence of endometrioid endometrial carcinoma. Dermatological findings in a small number of cases belied the underlying disease process. Of note, multiple lesions on the abdominal wall thought to represent benign keratoses were sampled to reveal deposits of metastatic colorectal carcinoma. A nodular deposit of metastatic melanoma on the scalp of an elderly man bore the clinical features of an epidermoid cyst.

Table 1 Summary of clinical features of cutaneous metastases obtained from clinical requisition form where available

Clinical presentation	Number (%)
Papulonodules	33 (21%)
Pigment change	5 (3%)
Keratosis	2 (1%)
Rash	2 (1%)
Ulcer	2 (1%)
Skin thickening	1 (0.6%)
Cyst	1 (0.6%)

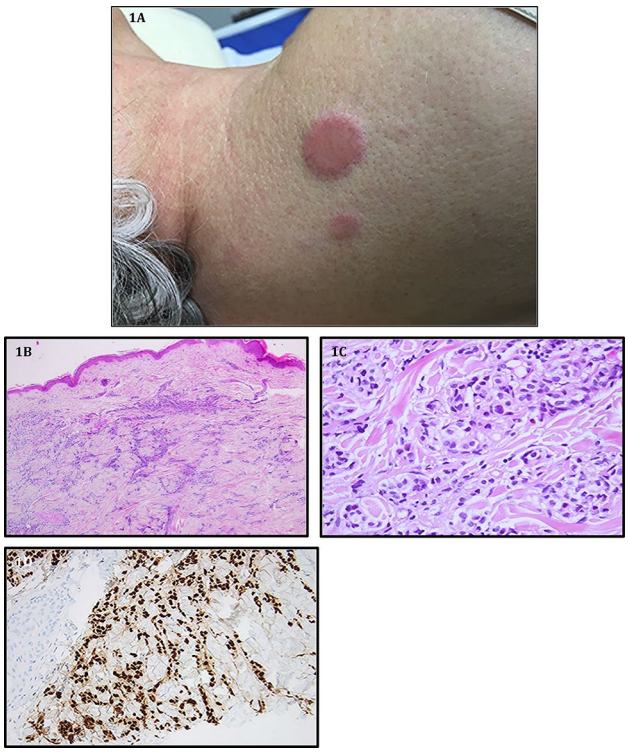

Fig. 1 Metastatic lobular carcinoma. (A) Papulonodular lesions on the neck. (B) Cellular, poorly circumscribed dermal based lesion (hematoxylin–eosin, original magnifications X 20). (C) Poorly cohesive tumour cells dissect through dermal collagen in a characteristic linear arrangement. (D) Strong tumour cell positivity for ER

Table 2 Sites of cutaneous metastases by tumour type

	Head and neck	Breast and axilla	Chest	Abdomen	Back	Upper extremity	Lower extremity
Melanoma	17	-	2	2	4	8	48
SCC	11	-	-	-	1	-	4
Breast	1	18	-	1	1	-	1
Ductal carcinoma	1	4	-	-	-	1	
Lobular carcinoma							
Colorectum	1	-	1	4	-	-	2
Lung	1	-	1	-	1	-	-
Renal	1	-	-	-	1	1	-
Salivary	5	-	-	-	-	-	-
Thyroid	4	-	-	-	-	-	-
Oesophagus	-	-	2	-	-	-	-
Gallbladder	-	-	-	1	-	-	-
Pancreas	-	-	-	2	-	-	-
Gastric	-	-	1	-	-	-	-
Ovary	-	2	-	1	-	-	-
Endometrial	-	-	-	2	-	-	-
Vulva	-	-	-	1	-	-	-

Site of metastases

In general, metastatic sites of solid organ tumours bore a proximate relationship to the origin of primary disease (Table 2). Our results support the previously noted tendency of renal cell carcinoma to widely infiltrate remote sites. We report three cases of distant metastatic clear cell renal cell carcinoma with infiltration of periorbital tissue and lower extremity.

Timing of metastases

As part of this study, the electronic patient record was examined to determine patterns of presentation in order to provide an overview of the natural history of CM. We adapted the categories elaborated by Weedon et al. to stratify the temporal relationships between diagnosis of the primary lesion and development of secondary cutaneous disease (Table 3). [5]

The interval between initial presentation and the onset of cutaneous metastasis varied between tumour subtypes with the shortest interval noted in the upper gastrointestinal series (range 1–27 months, median 13 months). The greatest interval between initial diagnosis and disease activity onset in the skin was noted to be seven years, occurring in an elderly patient with late resurgence of metastatic ductal carcinoma of the breast. In all, metachronous tumours accounted for 79% ($n=125$). While all secondary cutaneous tumours were more likely to develop many months to years after the primary diagnosis had been made, synchronous diagnoses were more likely to be rendered in the non-melanocytic group of tumours (Table 3).

Tumour subtypes

Melanoma gave rise to the greatest number of cutaneous metastases (51%, $n=81$) and was more prevalent in women (1.6:1).

Secondary cutaneous involvement as the presenting feature of malignancy

Our series encompasses six precocious metastases (PCM) distributed amongst five females and one male (Table 4). Patients in this group presented at a more advanced age when compared to those with synchronous or metachronous cutaneous disease (median 74 years, range 46–86 years). There were two melanomas, two breast carcinomas, one lung carcinoma and one squamous cell carcinoma of unknown

Table 3 Temporal relationship between diagnosis of primary lesion and cutaneous metastasis in melanoma and non-melanocytic tumours

		Melanocytic	Non-melanocytic	Total
Synchronous	Cutaneous metastases represent first indication of underlying malignancy	5	12	17
Metachronous	Cutaneous metastases develop > 1 month after primary cancer has been diagnosed	70	55	125
Precocious	Simultaneous diagnoses (< 1 month) of primary tumour and cutaneous metastasis	2	4	6

Table 4 Clinical and histopathologic features of tumours presenting initially with cutaneous metastasis

	Clinical presentation	Tumour	Histologic compartment	Immunoexpression profile	Location of primary tumour
1.	Nodule, axilla	Ductal carcinoma	Superficial/deep dermis	AE1/AE3, ER, CK7	Breast
2.	Papules, neck	Lobular carcinoma	Dermis	AE1/AE3, ER, CK7	Breast
3.	Pigmented lesion, gluteus	Melanoma	Subcutis/deep dermis	HMB45, SOX10, MelA	Unknown
4.	Pigmented lesion, forearm	Melanoma	Subcutis	S100	Unknown
5.	Soft tissue swelling, neck	Adenocarcinoma, micopapillary	Subcutis	AE1/AE3, CK7, TTF-1	Lung
6.	Nodule, axilla	Pleomorphic sarcomatoid squamous cell carcinoma	Dermis	AE1/AE3, MNF116, p63, CK5/6, CD10	Unknown

primary. We report three cases of CM of unknown primary site (2%) following thorough clinical review. These include two melanomas and a pleomorphic sarcomatoid squamous cell carcinoma.

Histopathology and immunohistochemistry

CMs typically spanned the subcutis and deep dermis (38%, $n=60$) or were confined to the dermis alone (34%, $n=54$). Restriction of disease to subcutis was not an unusual finding (22%, $n=35$). Evolution of the lesion by extension of a dermal based tumour into the epidermis was present in 5% ($n=8$) of cases. In one case of metastatic endometrioid, endometrial carcinoma this resulted in overlying ulceration. The tumour retained a highly conserved architecture and cellular morphology including squamoid morule formation. Two cases demonstrated diffuse involvement of all compartments with ulceration and suppuration. In the author's experience, restriction of tumour cells to the epidermis alone is an unusual finding in CMs.

Microscopic findings consisted predominantly of nodules, nests and cords or single cell infiltrate of atypical cells in the absence of overlying epidermal dysplasia (Fig. 2). On scanning power, most deposits were asymmetric, characterised by an irregular and in some cases moth-eaten interface with the surrounding tissue and generally had a broad base providing an overall pyramidal or oblong silhouette.

While substantial variation in the preservation of glandular architecture was noted in adenocarcinoma, the morphologic features were typically sufficient to indicate the primary site. The use of a combination cytokeratin stain such as AE1/AE3 and CAM5.2 in addition to EMA readily demonstrated malignant glandular tissue.

For the most part CM melanoma posed little in the way of diagnostic challenge. A tendency toward moderate to severe cytologic atypia, macronucleation, nucleolar prominence as well as melanin pigment deposition permitted early consideration of a diagnosis of melanoma. In 71 cases of CM melanoma (88%), a diagnosis was made on the basis of tumour morphology alone. In the remaining 10 cases (12%), immunohistochemistry was supportive and no observed heterogeneity existed in immunostaining profiles between primary and CM tumours. In both cases of PCM melanoma, highly pleomorphic atypical melanocytes were confined to subcutis in the absence of any significant epidermal pathology. Immunohistochemistry showed diffuse, strong positivity for SOX10, MelA and HMB45 in one case, and S100 immunopositivity in the second confirming the diagnosis. Both cases were worked up for primary melanoma following multi-disciplinary team discussion which failed to reveal the primary focus of disease.

We observed a range of reactive change in the surrounding tissue including desmoplasia, dermal mucin and erythrocyte extravasation. The presence of infiltrating neoplastic cells in paucicellular metastases was frequently masked by the degree of inflammation. Angiolymphatic invasion was occasionally identified, particularly at the periphery or base of the lesion. Secondary epidermal change included acantholysis, basal degeneration and lymphocyte exocytosis.

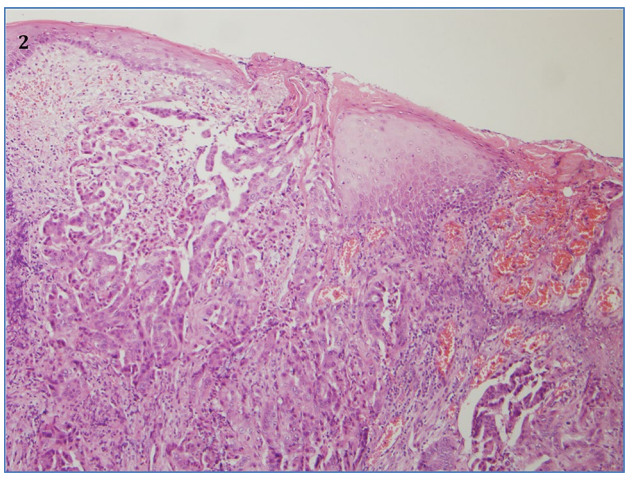

Fig. 2 Metastatic gallbladder adenocarcinoma. Histology shows a moderately differentiated adenocarcinoma in a man with a remote history of gallbladder carcinoma

Discussion

The incidence of CM, while varying amongst authors, is thought to be 0.7–0.9% of patients with cancer rising to 5.8% when data obtained from autopsy registries are included [6, 7]. The demography reflects that seen in the underlying malignancy, being principally a phenomenon of later life and occurring only rarely in the paediatric setting. In our series, 87% of patients were over the age of 50 at diagnosis. The distribution of tumours known to metastasise to skin has been well characterised [8, 9]. Melanoma is the most common primary source. Tumours of the colorectum, lung and oral cavity are commonly implicated in men, whereas breast and genital tract tumours are seen more frequently in women [1]. Interestingly, for reasons that have yet to be determined, certain tumours only rarely colonize skin including prostatic adenocarcinoma and testicular germ cell tumours. The wide morphologic spectrum may complicate diagnosis particularly amongst the 'precocious metastases'. Disease extent informs treatment options, surgical excision and palliative therapy often form the mainstay of care [10].

We set out to examine the clinical and histopathologic characteristics of secondary skin tumours emphasising the precocious metastases. Our results are consistent with previous findings that distinct patterns of metastatic disease exist amongst men and women [6, 9, 13]. In our series, melanoma, squamous cell carcinoma and colorectal tumours contributed the greatest number of metastases in men. This contrasts with the findings of several authors in which lung cancer was found to be the most common primary tumour to metastasise to skin in male patients [11–13]. Brownstein et al. found that primary lung tumours gave rise to 24% of CMs in men as compared to 4.9% in our study. The frequency of CM parallels primary tumour incidence. A sustained decline in the incidence and mortality rate of lung cancer in men in Ireland since 1998 may explain the comparatively few cases seen in this cohort as compared with previous international studies [14].

While the mechanisms underpinning cutaneous involvement in breast cancer remain incompletely understood, possible factors include a wealth of regional dermal lymphatics and the intimate relationship between the ductolobular unit and skin. Breast carcinoma accounted for 16% of all cases of CM indicating that it is the commonest non-melanocytic tumour to infiltrate skin, findings that are supported by several studies [15–17]. In a large retrospective series using tumour registry data, Lookingbill et al. found that 30% of patients with metastatic breast cancer developed secondary cutaneous disease, accounting for 50.4% of all CMs in their cohort [6]. Consistent with several previous studies, we found that ductal carcinoma colonizes skin more frequently than lobular carcinoma and note particular avidity to the chest ipsilateral to the primary tumour [16]. Approximately 6% of patients present initially with CM [6]. We describe two CMs from undiagnosed primary breast tumours incorporating both ductal and lobular subtypes. Lobular carcinoma has a greater tendency to metastasize to distant sites and may display a variety of clinical appearances [18]. Consequently, suspicious skin lesions in women in whom there is no previous history of malignancy warrant careful exclusion of metastatic disease.

CM is a frequent development in melanoma, and involvement of distant cutaneous sites may exceed 10% [19, 20]. Differences in the anatomical distribution of secondary disease have been observed between men and women, the chest and back are commonly involved in men and the lower extremities in women. In addition, sex remains a significant predictor of survival with men typically experiencing a more aggressive clinical course [21]. Even in advanced disease, women have superior five-year survival outcomes compared to men. A more protracted clinical course in women may thus favour the development of secondary cutaneous disease and account for the greater number of female presentations. Sample characteristics including increased susceptibility to developing melanoma in urbanized settings and in the South of Ireland have likely enriched our case numbers. Supportive immunohistochemistry was performed in 12% of cases demonstrating comparable expression profiles of melanocytic markers amongst primary and metastatic tumours.

In our series, 3.8% of biopsies signalled the presence of clinically occult disease largely consistent with previous studies [6, 22, 23]. We noted that the anatomical distribution of these lesions may not bear a proximate relationship to the primary disease focus. Melanoma, biphasic epithelial neoplasms and solid organ metastases are represented in our series of PCMs reinforcing the concept that no restriction applies to the tumours that can manifest initially with cutaneous involvement. Discrimination between primary and secondary phenomena may be fraught with difficulty particularly in the absence of a history of malignancy and given the considerable morphologic overlap that exists between certain solid organ metastases and primary adnexal tumours. Careful examination of overlying epidermis and adnexal epithelia may disclose precursor lesions that can be helpful in excluding involvement by secondary disease. Sampling error and processing artifact may conceal contiguity with the epidermis and the tissue may have to be examined in multiple planes. A paucity of adnexal specific immunoantibodies and overlapping staining profiles particularly in tumours showing enteric differentiation further complicate accurate diagnosis [24–26].

Microscopic features of CM include a broad base and poor circumscription, usually within the subcutis and mid to deep dermis. Associated intravascular and lymphatic disease

is not uncommon. Neoplastic cells may infiltrate in a nodular arrangement or as nests, cords or single cells. Established gland formation can be useful in providing a differential site of origin in well to moderately differentiated adenocarcinoma, but in high-grade tumours where adenocarcinoma is suspected, secondary features should be sought including signet ring cells and extracellular mucin. Cytonuclear atypia is generally pronounced in metastatic tumours. Comparison of morphology with material from the suspected primary tumour should always be sought where possible.

Our rate of CMs of unknown primary site (2%) is consistent with previous published series [2, 3, 7]. Factors precluding definitive diagnosis include sampling inadequacy, paucicellular tumour, extensive tumour or inflammatory-related tissue destruction and poorly differentiated tumours with unrevealing or aberrant immunostain profiles. While allowing for these limiting factors, tumour cell lineage can be assigned in most cases on the basis of histomorphology and immunohistochemistry.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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