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REVIEW

Cutaneous metastases of visceral tumours: a review

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Abstract
Background Up to 10% of all visceral malignancies develop cutaneous metastases. As cutaneous metastases are underestimated and underdiagnosed they can be a clinical challenge. The clinical appearance and patterns of distribution of cutaneous metastases, the characterisation of clinical outcomes and available therapeutic options are compiled.
Patients and methods Literature (over the last 6 years) MESH in terms of cutaneous metastases was comprehensively evaluated. Characteristics from 92 available cases are elaborated and adjusted with terms (time unlimited) of published epidemiological reviews to single organs.
Results The broad clinical spectrum with differential diagnoses is displayed. An allocation of cutaneous metastases and a particular organ is not reliable. In 22% of all cases cutaneous metastases can lead to the diagnosis of an internal malignoma. The majority of cases reveal cutaneous metastases to emerge in a tumour-free interval in about 36 months, after a successful treatment of the primary tumour, most commonly along with other organ metastases. Probable survival turned out to be less than 12 months. Consistently with this end-stage condition, treatment aligns with rules of palliation. Local treatment of choice is excision. Only a minority of investigators attempted to come up with tumour-specific treatment strategies, and almost no randomised therapy studies can be presented.
Conclusion A reference guide of cutaneous metastases is given; the clinical spectrum is adjusted to an actual status; state of the art of the treatment is accomplished. An epidemiological, improved registration and diagnostic work-up for targeted therapies in conjunction with dermatologists are favoured.

Keywords Dermatology · Neoplasm metastasis · Skin neoplasms · Review (publication type) · Therapeutics

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Introduction

The prevalence of cutaneous metastases of visceral tumours amounts to 2% of all skin tumours. Their incidence varies from formerly 0.2 to 8.5 and 10.4% (Saeed et al. 2004; Spencer and Helm 1987; Kleyn et al. 2006; Lookingbill et al. 1993; Krathen et al. 2003; Mueller et al. 2004; Luh et al. 2002). Analyses dealing with 20,380 and 7,316 patients, respectively, from two tumour registries and seven autopsy studies estimated 5.3% of patients with visceral tumours as bearing cutaneous metastases e.g. 7% of renal cell cancer and 4% of colon cancer (Lookingbill et al. 1990; Krathen et al. 2003). Some autopsy studies list fewer cases (1–4%)—perhaps due to successfully performed excisions decreasing the number of metastases detectable at the time of decease (Poole and Fenske 1993).

Cutaneous metastases are particularly seen in association with breast cancer, followed by lung and colo-rectal, ovarian,

head, neck and throat, renal cell and gastrointestinal carcinoma (Azoulay et al. 2005; Wollina et al. 2004; Mueller et al. 2004; Moll and Moll 2005; Krathen et al. 2003). The majority of affected patients exceed the age of 60 (Koga et al. 2000; Azoulay et al. 2005; Schoenlaub et al. 2001).

Ranking depends on gender and on the epidemiology of tumour entities. Statistics of visceral tumours for males report in descending order: lung, colo-rectal, renal cell, and (non-colo-rectal) gastrointestinal carcinoma. Visceral tumours for females comprise in descending order: breast, colo-rectal, lung, ovarian and cervix–uterus carcinoma. Due to the low incidence of their primaries, cutaneous metastases of thyroid gland, pancreas or adrenal carcinoma or sarcomas are infrequently described.

Methods

Literature search strategy

We performed a search in Pubmed (National Library of Medicine 2008) using respective MeSH-terms for neoplasm with skin metastases of visceral organs, excluding melanomatous and epithelial skin tumours. The resulting search term ["Neoplasm metastasis"(MeSH) and "Skin neoplasms"(MeSH) and ("Urogenital neoplasms"(MeSH) or "Thoracic neoplasms"(MeSH) or "Pelvic neoplasms" (MeSH) or "Breast neoplasms"(MeSH) or "Esophageal neoplasms"(MeSH) or "Endocrine gland neoplasms" (MeSH) or "Abdominal neoplasms"(MeSH) or "Digestive system neoplasms"(MeSH))] not ["Melanoma"(MeSH) or "Carcinoma, basal cell"(MeSH) or "Neoplasms, squamous cell"(MeSH)] has been limited to papers in English, French, German or Spanish language. This search revealed 835 articles, including 60 reviews, and has been completed by hand selected articles.

Identification of articles for inclusion

The abstracts of these articles have been manually reviewed by two of the authors. Papers dealing with primary cutaneous malignancies have been omitted as well as papers that obviously did not fit into this subject.

The total amount of papers had been cut down to 92 case reports being published from January 2001 until December 2006 (Table 1), including 8 cases from pharynx/larynx, 9 from oesophagus/stomach, 7 from breast, 9 from lung/pleura, 7 from liver/gallbladder, 2 from pancreas, 8 from colo-rectal cancer, 9 times kidney cancer, 5 from bladder, 4 from prostate and testes, 11 from the female genital tract, 13 from parotid and thyroid. Up to 2007, 16 review articles dealing with cutaneous metastases of internal malignancies of single organs were identified. A commensal illustration together with the case reports was gathered. But concerning most organs the clinical pattern had to be newly framed.

Results

Clinical picture

Tumour metastases were described as single or multiple lesions with a moderate to firm consistency; they could grow aggregated or disseminated (Fig. 1). Clinical pictures more often showed smooth, shiny, dome-shaped nodules. Additionally, cutaneous metastases are portrayed as maculae, infiltrated or indurated plaques, discoid lesions, and tumour nodes with teleangiectasia (Fig. 2). Ulcerated tumour nodes and plaques, sometimes with maceration of the surrounding tissue, appeared in association with gastrointestinal tumours, hepatocellular carcinomas and pleuramesothelioma (Bachmeyer et al. 2004) (Fig. 3). Herpetiform, zosteriform or erysipelas-like formations (likewise epitomized as "erysipeloid-like carcinoma" or "carcinoma erysipelatoides or erysipelatodes") were frequently mentioned as patterns of cutaneous dissemination (Han et al. 2000; Cox and Cruz 1994; Bottoni et al. 2001) (Fig. 4). This descriptive term might also be applied to the congestion of lymphatic vessels which results in oedema, often erythematous, sometimes vesicular. Lymphangiosis carcinomatosa impressed as an inflammatory process, first and foremost beheld with mamma-carcinoma ("cancer en cuirasse", Fig. 5), but occasionally also related to cancers of gastric, pulmonary, prostatic, ovarian, laryngeal, palatine-tonsillar, pancreatic, colo-rectal, parotid, thyroid or uteric origin (Cox and Cruz 1994; Bottoni et al. 2001; Lee et al. 2001; Braverman 2002). Sclerodermic metastases of mamma carcinoma, also named "carcine eburnée" were described as whitish violet plaques. The clinical spectrum of cutaneous metastases furthermore comprised bullous and papulo-squamous lesions, scarred plaques, and pigmented tumour nodes. Alopecia neoplastica was rarely attributed to mamma-, lung-, colon- and renal cell-carcinoma (Gul et al. 2007; Wagner 2007). The majority of skin metastases remained asymptomatic, but sometimes they cause itching and tension (Stein and Spencer 2002) and in advanced stages pain.

Brownstein and Helwig published in 1972 and 1973 (Brownstein and Helwig 1972a, b, 1973) a classification of cutaneous metastases of visceral tumours by grouping them into nodular, inflammatory, fibrotic and sclerodermoid types. Although this classification is still in use (Mueller et al. 2004), and cited in current literature, it is too narrow to cover the variety of clinically seen metastatic phenomena (Table 1).

Table 1 Published cases with cutaneous metastases of cancers

Organ, tumour type	Age, gender	Location	Clinical description	Diagnosis post primary (months)	Survival (months)	Reference
Thoracic origin						
Pharynx/larynx						
Nasopharyngeal carcinoma	47, f	Chest	Painful nodule	12	8	Luk et al. (2004)
	30, m	Back	Cutaneous mass	48	9	Luk et al. (2004)
	63, m	Axilla, chest, abdomen	Painful nodules	6	8	Luk et al. (2004)
Squamous cell carcinoma	55, f	Face, upper limbs, back	Hard, fixed nodules	3	<1	Durvasula et al. (2005)
	58, m	Shoulder	Red-violet nodules	12	n.g.	Shamsadini et al. (2003)
	64, m	Trunk	Hyperpigmented lesions	84	n.g.	Prabhudesai et al. (2004)
Epidermoid carcinoma	64, m	Clavicular	Erythematous plaques	60	n.g.	Bottoni et al. (2001)
Neuroendocrine carcinoma	61, m	Chest	Red-lilac nodule	60	6	Ottinetti et al. (2003)
Oesophagus						
Adeno carcinoma	72, m	Scalp	Painful nodules	n.g.	12	Stein and Spencer (2002)
Breast						
Ductal	45, f	Fingers, toes	Yellowish-red painful nodules	13	<1	Karamouzis et al. (2005)
Lobular	47, f	Back	Eyelid-swelling	12	n.g.	Douglas et al. (2002)
Medullary	43, f	Chest	Yellow crusting plaques	84	n.g.	Cox and Cruz (1994)
	56, f	Arm	Erythematous plaques, red spots	3	n.g.	Cox and Cruz (1994)
	63, f	Chest	Keloidal plaques	12	n.g.	Mullinax and Cohen (2004)
Not specified	54, f	Thorax	Zosteriform erysipeloid	3	48	Bassioukas et al. (2005)
	54, f	Abdomen, scalp	Zosteriform violaceous black papules and nodules	>120	8	Brasanac et al. (2003)
Lung						Molina Garrido et al. (2006)
Basaloid	48, m	Chin	Violaceous mass	FS	3	Ro et al. (2003)
Small-cell	71, m	Lower lip	Red–pink, firm, ulcerated nodule	FS	n.g.	De Argila et al. (1999)
Papillary adeno carcinoma	50, f	Scalp	Fixed, reddish nodules	24	n.g.	Chang et al. (2001)
Well-differentiated foetal adeno carcinoma	56, m	Neck, shoulder, knee	Dark-red tumour with teleangiectasia	FS	12	Chao and Lee (2004)
Pleura						
Malignant mesothelioma	53, m	Flank	Confluent, reddish hard plaques	FS	n.g.	Maiorana et al. (2006)
	64, m	Lip	Keratotic ulcerated nodule	9	n.g.	Cassarino et al. (2003)
	60, m	Thoracoscopy scar	Subcutaneous nodule	7	n.g.	Gaudy-Marqueste et al. (2003)
	62, m	Thoracotomy scar	Erythematous inflammatory plaque	n.g.	n.g.	Gaudy-Marqueste et al. (2003)
	77, m	Thoracoscopy scar	Violaceous hemorrhagic nodule	3	2	Bachmeyer et al. (2004)

Table 1 continued

Organ, tumour type	Age, gender	Location	Clinical description	Diagnosis post primary (months)	Survival (months)	Reference
Gastro-intestinal origin						
Stomach						
Adeno carcinoma	36, f	Chest, arm	Erysipeloid	<1		Han et al. (2000)
	60, m	Face, scalp, thigh	Firm non-tender nodules	24	n.g.	Fruh et al. (2005)
	72, m	Forearm	Erysipeloid	24	6	Navarro et al. (2002)
Signet ring adeno carcinoma	33, m	Scalp, limbs, trunk	Nodules	FS	4	Charfeddine et al. (2001)
	44, m	Face, neck	Erysipeloid	FS	<1	Acikalin et al. (2005)
	73, m	Scalp, forehead	Red plaques	38	7	Lifshitz et al. (2005)
	65, f	Neck, chest	Firm nodules	12	n.g.	Michiwa et al. (2001)
Gastrointestinal stromal tumour	49, m	Cheek, jaw, thigh, groin	Soft tissue masses	72	n.g.	Shabahang and Livingstone (2002)
Liver						
Hepatocellular carcinoma	52, m	Scapula	Ulcerated painful mass	FS	n.g.	Ackerman et al. (2001)
	68, m	Abdominal injection scar	Eroded reddish papule	24	n.g.	Lee et al. (2004)
	57, f	Arm	Violaceous module	48	n.g.	Kanitakis et al. (2003)
Gallbladder						
Adeno carcinoma	47, f	Laparoscopy site, abdomen, extremities	Tender lump, firm subcutaneous nodules	FS	2	Pasricha et al. (2004)
Cholangio carcinoma	63, m	Scalp, knee	Hard fixed nodules	6	2	Lu et al. (2004)
	73, m	Scalp	Firm nodule	FS	1	Lu et al. (2004)
	78, f	Catheter site	Inflammatory nodule	FS	n.g.	Thouvenin-Heysch De La Borde et al. (2000)
Pancreas						Takeuchi et al. (2003)
Adeno carcinoma	77, m	Axilla	Tender firm nodule	FS	n.g.	Takeuchi et al. (2003)
	48, m	Buttock	Ulcerated nodule	FS	n.g.	Florez et al. (2000)
Colo-rectal						Rendi and Dhar (2003)
Adeno carcinoma	42, m	Scalp, shoulder	Dome-like nodule	3	8	Luh et al. (2002)
	46, m	Abdominal resection scar	Nodule	36	n.g.	Alexandrescu et al. (2005)
	60, m	Neck, trunk	Erysipeloid	20	n.g.	Wong et al. (2004)
	69, m	Chin	Withish nodule	36	8	Fyrmpas et al. (2006)
	69, m	Scrotum	Soft red plaques	5	6	Reuter et al. (2006)
	78, m	Cheek	Ulcerated lesion	1	11	Stavrianos et al. (2000)
	60, f	Abdomen	Subcutaneous nodule	16	60	Sarid et al. (2004)
	62, f	Abdominal resection scar	Ulcerated mass	60	n.g.	Alexandrescu et al. (2005)

Table 1 continued

Organ, tumour type	Age, gender	Location	Clinical description	Diagnosis post primary (months)	Survival (months)	Reference
Uro-genital origin						
Kidney						Dorairajan et al. (1999), Mueller et al. (2004)
Clear-cell adeno carcinoma	35, f	Face, neck	Lobulated masses	12	<1	Peris et al. (2001)
	69, f	Scalp	Painless mass	72	n.g.	Snow et al. (2001)
	55, m	Nose	Bleeding mass	FS	<1	Preetha et al. (2004)
	72, m	Subungual toe	Painful violaceous nodule	FS	n.g.	Perdona et al. (2005)
	77, m	Scalp	Angiomatous nodule	FS	n.g.	Barry et al. (2004)
	86, m	Head, ears, lips, neck	Purplish haemorrhagic papules	48	n.g.	Lim et al. (2005)
	36, m	Chin	Erythematous, tender, tense nodule	36	>2.5	Porter et al. (2006)
Granular-clear cell adeno carcinoma	65, m	Buttock	Fungated mass	96	n.g.	Lee et al. (2006)
Not specified	82, m	Scalp	Violaceous fragile nodule	24	n.g.	Katta (2000)
Bladder						Mueller et al. (2004)
Transitional cell carcinoma	51, m	Iliac fossa	Nodule	3	>276	Gowardhan et al. (2004)
	76, m	Glans	Ulcerated swelling	96	n.g.	Pomara et al. (2004)
	78, m	Trunk	Subcutaneous nodules	6	10	Akman et al. (2003)
	67, f	Abdomen, perigenital	Violaceous papules, ulcerated plaques	9	3	Rosati et al. (2003)
Micropapillary carcinoma	68, m	Resection scar trunk	Nodule	<2	<1	Dominici et al. (2001)
Prostate						(Mueller et al. 2004)
Adeno carcinoma	80, m	Umbilical	Nodules	108	2	Fukuda and Saito (2006)
	88, m	Suprapubic	Pink firm nodule	24	n.g.	Arita et al. (2002)
	92, m	Breast	Angiomatous nodule	60	n.g.	Drappier et al. (2003)
Testicle						Mueller et al. (2004)
Adeno carcinoma	67, m	Suprapubic	Red mass	FS	n.g.	Rubegni et al. (2006)
Ovary						
Serous adeno carcinoma	48, f	Abdomen, gluteal, lower extremities	Zosteriform erysipeloid	42	3	Schonmann et al. (2003)
Papillary adeno carcinoma of fallopian tube	55, f	Thigh, vulva, perineum	Nodules	24	<1	Wuntkal et al. (2004)
Tubular adeno carcinoma	66, f	Umbilical	Nodules	FS	n.g.	Touraud et al. (2000)
Adeno carcinoma	69, f	Breast	Erysipeloid	36	8	Martel et al. (2003)
Uterus						
Papillary serous carcinoma	54, f	Pubic area	Pruritic nodules	13	5	Kim et al. (2005)
	65, f	Lower abdomen	Pruritic erysipeloid	3	9	Elit et al. (2001)
Endometroid adeno carcinoma	58, f	Resection scar lower abdomen	Hemorrhagic nodules	14	2	Baydar et al. (2005)

Table 1 continued

Organ, tumour type	Age, gender	Location	Clinical description	Diagnosis post primary (months)	Survival (months)	Reference
Cervix						
Squamous cell carcinoma	45, f	Scalp	Painful swelling	8	n.g.	Maheshwari et al. (2001)
	47, f	Scalp	Firm nodule	60	n.g.	Park et al. (2003)
Vulva						
Squamous cell carcinoma	38, f	Abdomen, flank, buttock, groin	Violaceous nodules	>6	7	Ghaemmaghami et al. (2004)
	73, f	Thigh, calf	Itchy painful ulcerated red nodules	20	4	Tjalma and Watty (2003)
Other origin						
Parotid gland						
Adenoid cystic	63, f	Abdomen	Subcutaneous nodules	FS	2	Chang et al. (2003)
Thyroid						Dahl et al. (1997)
Papilllary	71, f	Scalp	Flesh coloured nodule	72	n.g.	Alwaheeb et al. (2004)
	82, f	Neck	Dark nodule	132	n.g.	Alwaheeb et al. (2004)
Follicular	52, f	Neck	Mass	4	9	Quinn et al. (2005)
	57, f	Sternoclavicular	Vascularized mass	96	13	Cariou et al. (2000)
	82, f	Abdomen, back, thigh	Ulcerated, violaceous nodules	24	2	Ghfir et al. (2005)
	75, m	Neck	Dermal mass	120	n.g.	Quinn et al. (2005)
	57, m	Scalp, neck	Nodule, mass	96	28	Quinn et al. (2005)
	73, m	Abdomen, sacrum	Destructive nodules	66	6	Quinn et al. (2005)
Medullary	29, m	Neck, chest	Red brownish papules	72	n.g.	Jee et al. (2003)
	34, m	Scalp, chest	Tender nodule	FS	n.g.	Alwaheeb et al. (2004)
	46, m	Scalp	Tender lesion	FS	n.g.	Alwaheeb et al. (2004)
Papillary anaplastic	72, f	Neck, chest	Erysipeloid	144	n.g.	Lee et al. (2001)

FS cutaneous metastases as first sign of the tumour, *n.g.* data are not given

Together with the subheadings organ specific reviews as far as available are cited. Summarizing overviews are given in Braverman (2002), Brenner et al. (2001), Brownstein and Helwig (1972a, 1972b, 1973), Lookingbill et al. (1990, 1993), Schoenlaub et al. (2001). For each case report type of tumour, age of patient, clinical appearance and localisation, time of diagnosis of cutaneous metastases, time of survival and author are listed

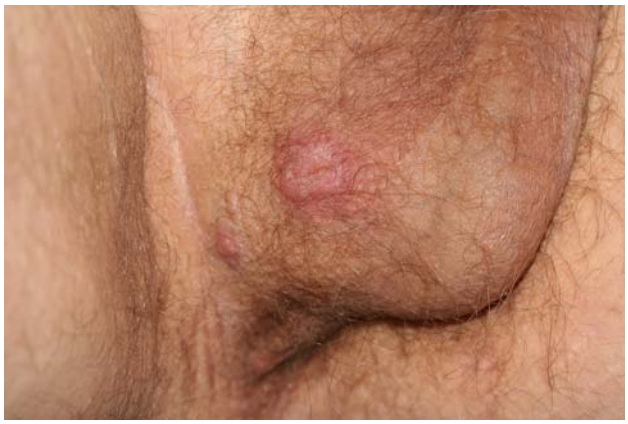

Fig. 1 Cutaneous metastasis of a colo-rectal cancer

Localisation

Although a reliable allocation of the localisation of a skin metastasis to the original tumour is not possible, some preferential associations are obvious. Mamma carcinomas prefer the thoracic region as site of their cutaneous metastases not only meant as a direct extension of the underlying tumour but by lymphatic spread. Face metastases of mamma carcinoma privilege eyelid and nose (Wagner 2007). Prostatic cancers have a certain affinity to the suprapubic region for placing their cutaneous metastases. Whilst gastrointestinal, colo-rectal, and urogenital tumours for the main part develop distant skin metastases on the abdomen, renal cell carcinomas disseminate predominantly on the upper trunk (Rendi and Dhar 2003). Skin metastases of 75 cases with renal cell carcinoma were on the torso (40%), the scalp (25.3%), and the limbs (10.7%) (Fig. 6) (Koga et al. 2000).

Umbilical skin metastases, also referred to as "Sister Mary Joseph's nodules", were associated with ovarian cancer, but may also be affiliated with gastrointestinal malignancies or prostatic cancer (Fukuda and Saito 2006; Stanko et al. 2007). Oesophageal, gastric and colonic cancers, cancers of biliary tract, pulmonary carcinomas and malignancies derived from renal cells preferred hairy scalp, neck, and face for a distant cutaneous spreading (Fruh et al. 2005;

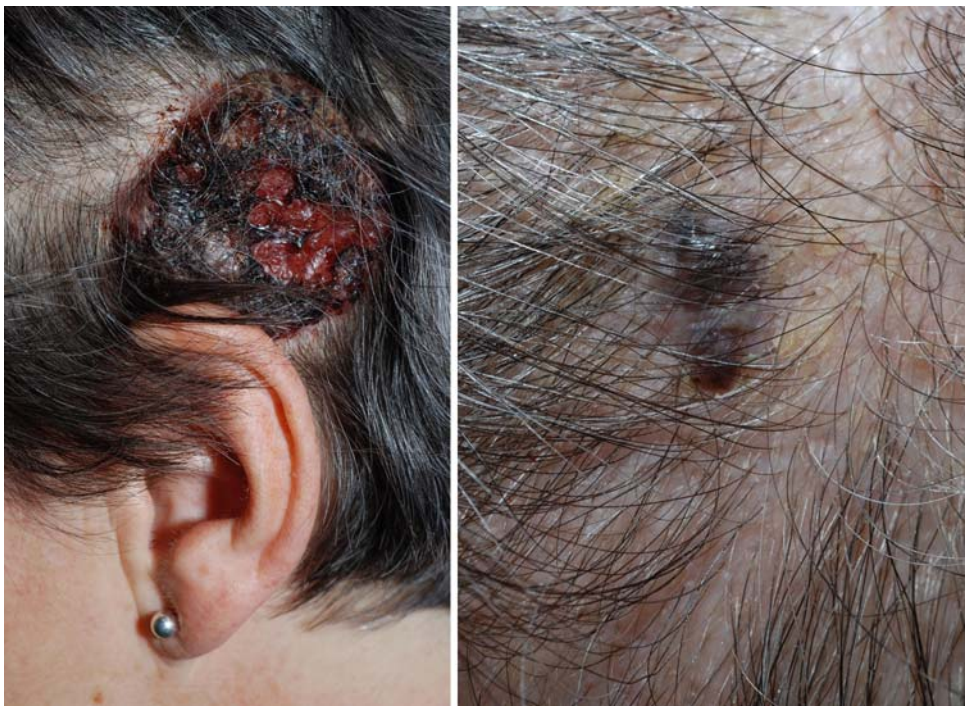

Fig. 2 On the scalp ulcerated metastasis and new developing tumour nodules from a colon cancer

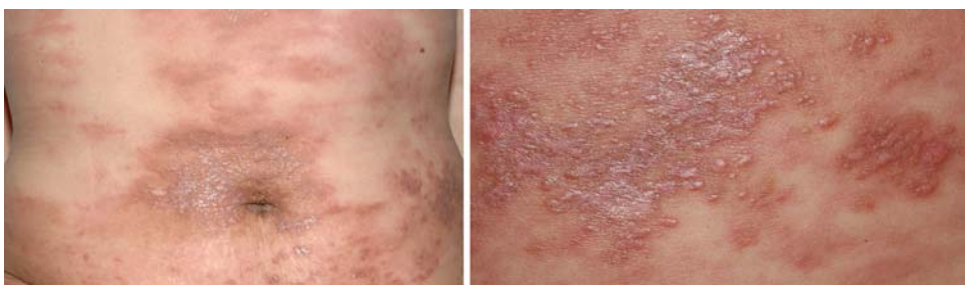

Fig. 3 Disseminated spreading of cutaneous metastases of a breast cancer aggregating in tumour plaques with a lichenoid aspect of papules

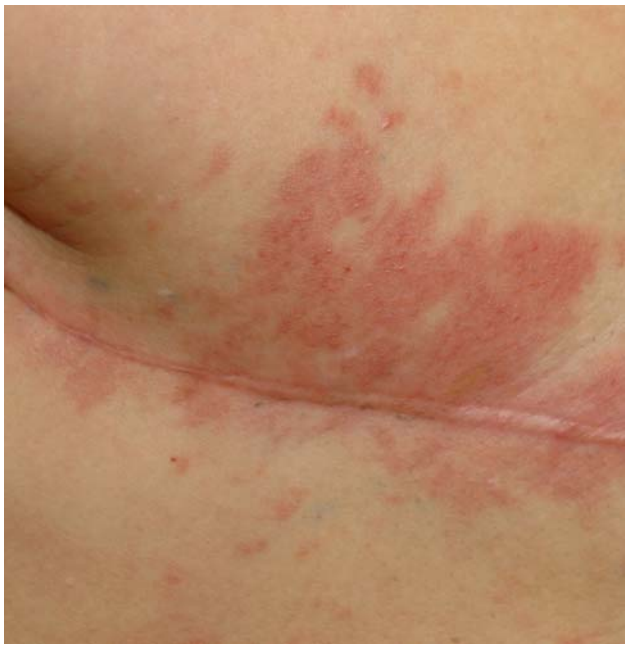

Fig. 4 An initial status of an erysipelas-like formation

Fyrmpas et al. 2006; Acikalin et al. 2005; Luh et al. 2002; Saeed et al. 2004; Snow et al. 2001) in terms of a common final path.

Cutaneous metastases can be classified as loco-regional-, in-transit- or distant metastases. Besides lymphatic spread the genesis of loco-regional cutaneous metastases can be caused by a tumour growth per continuitatem which may render a known or concealed malignancy to present on the dermal surface; sometimes induced by surgical procedures or by performing punctures, taps, biopsies, infiltrations, or other percutaneous measures for diagnostic or therapeutic reasons (Coman et al. 2007). Cancers of colo-rectal, laryngeal or hepatic origin, as well as pleuramesothelioma, seem to be highly apt to take advantage of artificial gaps or channels to propagate (Gaudy-Marqueste et al. 2003). Solitary cases are also described for thyroid cancers with stomal and peristomal metastases. After emergency tracheostomies, local metastases developed in the considerable frequency of 3–10% (Bottoni et al. 2001). The possible inoculation of metastases supports the attitude to reconsider invasive approaches for diagnostic evidence in cases with no meaningful therapeutic consequences.

Histology

The diagnosis of cutaneous metastatic malignancy depends almost entirely on the histopathology, and often proves to be an utmost challenge to the expert (Wollina et al. 2004), especially if no clinical history or symptoms deliver further hints. Usually immunohistochemistry is required for a correct assignment (Azoulay et al. 2005; Brasanac et al. 2003; Kanitakis et al. 2003; Moll and Moll 2005; Saeed et al. 2004). The vast majority of cutaneous metastases are confined to the dermis and/or subcutaneous fatty tissue. There, tumour cells can grow either in a nodular or star-like pattern, within or around dilated lymphatics or blood vessels, or in small groups in a linear arrangement dissecting collagen bundles referred to as "Indian filing". The connective tissue involved may appear relatively normal, fibrotic or may contain large amounts of mucin. Only occasionally the cutaneous spread reaches the epidermis and invades it (Aguilar et al. 1991). Such epidermotropic metastases mostly originated from mamma carcinoma, although single cases of hypopharyngeal carcinoma, alveolar rhabdomyosarcoma, intestinal and laryngeal carcinoma amongst others have been described (Brasanac et al. 2003).

Differential diagnoses

Phenotype of cutaneous tumours encompasses distinct concepts such as primary skin-borne malignancies, primary and secondary cutaneous lymphoma, besides metastases of visceral tumours. Depending on the clinical picture, the localisation and distribution of the lesions, heterogeneous clinical entities were taken into consideration as differential diagnoses of skin metastases of a visceral tumour. Metasta-

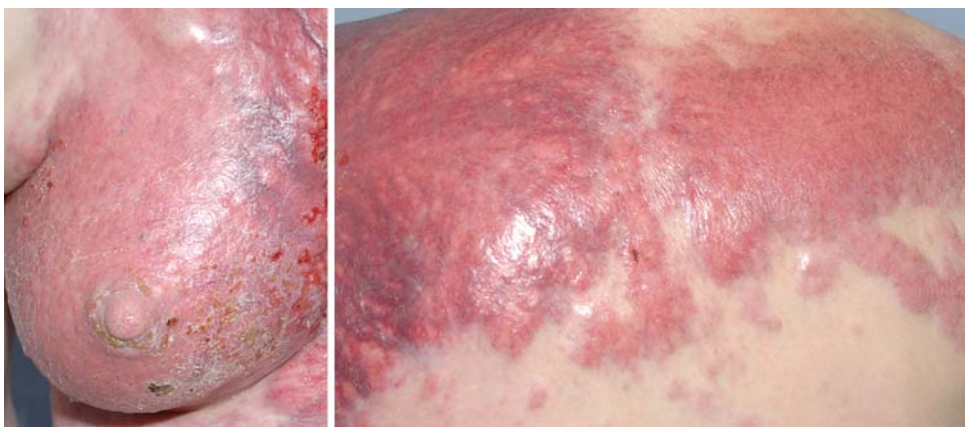

Fig. 5 "Cancer en cuirasse" of a breast cancer, with extension over the upper back

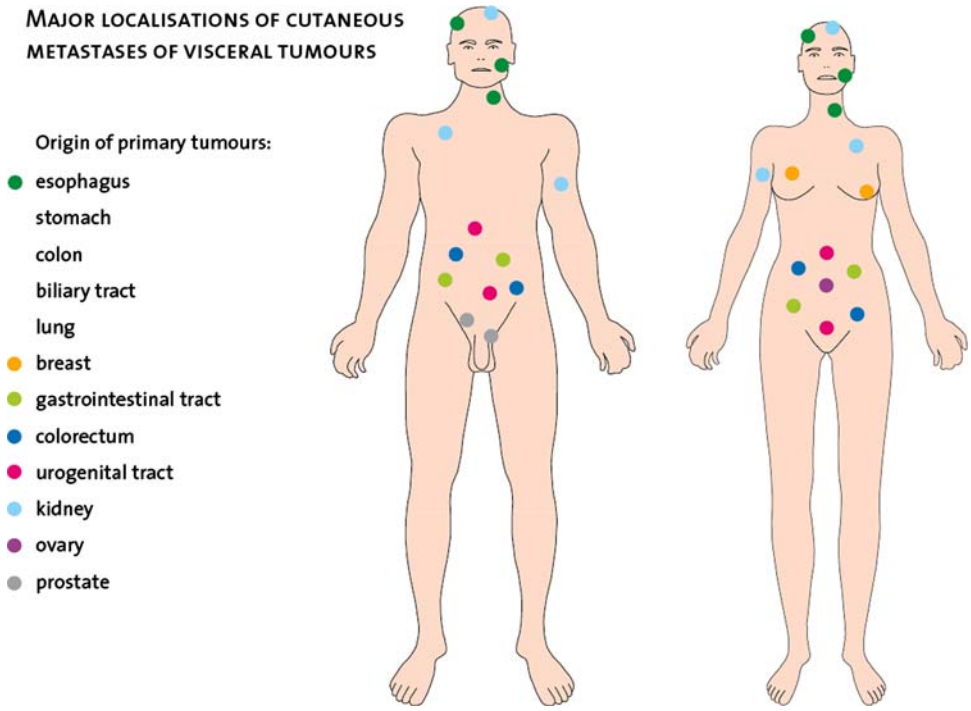

Fig. 6 Major localisations of cutaneous metastases of frequent visceral tumours

ses of the scalp lead to the assumption of basal cell carcinoma, epidermal cyst, adnexal tumour or alopecia not specified as neoplastica (Chang et al. 2001; Snow et al. 2001). A solitary cutaneous metastasis of a bronchial carcinoma described as painful, dome-shaped on sun-exposed skin was compared with a Merkel cell carcinoma (De Argila et al. 1999). Differential diagnoses of a lip tumour caused by a pleuromesothelioma were keratoacanthoma and squamous cell carcinoma (Cassarino et al. 2003). The appearance of a metastasis from renal cell carcinoma on the chin was compared with an abscess (Porter et al. 2006). Similar infectious diseases like folliculitis, perifolliculitis and furuncle were taken into consideration for mamma carcinoma metastases (Wagner 2007).

Stein and colleagues (Stein and Spencer 2002) described red, bluish to skin coloured, dome-shaped cutaneous scalp metastases of colon- and pancreas carcinoma as a primary cutaneous adenoid cystic carcinoma or pilar cyst. The differential diagnoses of red to bluish vascular tumours included hemangioma, pyogenic granuloma, Kaposi's sarcoma or hemangiosarcoma (Peris et al. 2001; Ackerman et al. 2001; Lee et al. 2004). Nodular grouped metastases were misconceived as erythema annulare centrifugum; yellowish red firm teleangiectatic plaques at the breast were described as keloids, circumscribed sleroderma and a purple-red discoloration of a foot in conjunction with an aortic angiosarcoma was misdiagnosed as vasculitis (Reichel and Wheeland 1993; Mullinax and Cohen 2004; Rudd et al. 2000).

Descriptive terms like inflammatory, zosteriform, erysipelas-like and ulcerated implicated diagnoses such as cutaneous infection, erysipelas, herpes zoster, cellulitis and ulcer (Acikalin et al. 2005). A laminar collocation of mamma carcinoma metastases growing on a lymphedema afforded the exclusion of a lymphangiosarcoma in terms of a Stewart–Treves syndrome. A current publication reveals, that 45% (21 of 47) of cutaneous lesions were not suspected of being metastases due to unusual clinical presentation (Sariya et al. 2007). Conclusively even probable clinical diagnoses should be examined in the context of a visceral carcinoma in anamnesis.

Disease course

Cutaneous metastases indicate an advanced stage of malignant disease and often flare up simultaneously with distant metastases after a tumour-free interval. In 6.4–7.8% cutaneous metastases are in the vanguard of other distant metastases (Lookingbill et al. 1993; Saeed et al. 2004). Hence solely diagnosed cutaneous metastases indicate re-staging and a close meshed follow-up to clarify extension and disease progress.

In some cases, cutaneous metastases may act as first signals of yet unknown malignancies (Lookingbill et al. 1990; Carroll et al. 2002) (Table 1). From our summary of case reports they are a primary hint for diagnosis of cancer in 20 of 92 elaborated cases (22%). From published overviews the lungs and the pancreas predominate as sites of unknown primary cancers, whereas tumours of the kidneys or the ovaries were also found (Seeber and Strumberg 2006; Schwartz 1995). In the adjacent case series four

cases with lung/pleura cancer, two with stomach cancer, four with liver/gallblader cancer, two with pancreas, three with kidney cancer, one with either testis- or ovary-cancer, one parotid- and two thyroid-cancer were found (Table 1). The interval between the initial diagnosis of a primary tumour and associated cutaneous metastases averages 3 years; but metastases having arisen as late as 22 years after its primary tumour have been described. Late appearance does not distinguish any specific neoplasia, as case reports exist for colon carcinoma, larynx, renal cell, urinary bladder, and mamma carcinoma (Dorairajan et al. 1999; Gowardhan et al. 2004; Lim et al. 2005; Braverman 2002). The probability of survival after the diagnosis of skin metastases drops below 1 year and deteriorates with multiple cutaneous metastases (Schoenlaub et al. 2001; Braverman 2002).

Treatment options

Treatment of skin metastases of visceral tumours almost exclusively pursues palliative goals, with primary choice of excision or radiation. Pulsed brachytherapy resulted in local control of dermatologically metastasized breast cancer in 41 of 46 patients (89%) (Fritz et al. 2000). Some investigators performed trials with systemic chemotherapy and intralesional chemo- or immunotherapy, e.g. interferon-alpha, with ambiguous results (Tjalma and Watty 2003). Intralesional IL-2 applications in cutaneous metastases of a gastric adenocarcinoma proved unsuccessful (Lifshitz et al. 2005), whereas cutaneous metastases of pancreatic cancers showed encouraging signs of regression under chemotherapy (Florez et al. 2000). It has to be emphasized that size and number of cutaneous lesions provide an easily accessible scale for assessing the responsiveness of the malignancy to the chosen therapeutic approach. In a randomised study on cutaneous metastases of mamma carcinoma, topical application of miltefosine clearly showed evidence of tumour control compared to placebo (Leonard et al. 2001). Ten patients with cutaneous metastases of colon- or mamma carcinoma were treated with a recombinant single-chain antibody-toxin targeted to ErbB2/HER2. The investigators achieved a complete remission in four of ten cases (Azemar et al. 2003). Further therapeutic options include electrocoagulation and electrovaporisation (Gothelf et al. 2003). In analogy the multiple therapeutic options for cutaneous melanoma metastases are namable as they are successfully applied (Radny 2006) and further drugs directed against stroma function and angiogenesis might be reconsidered (Hafner et al. 2006). The armamentarium of skin directed therapies might disclose a benefit for quality of life which is necessary because cutaneous metastases hold psychological and physiological strain for the patient.

Follow-up

The majority of tumour recurrences are brought to light by studiously and pointedly asked questions, and by an efficient physical examination. But is it recommended to palpate skin for the major tumours breast, lung, and colorectal cancer? Practice guidelines from the American Society of Clinical Oncology (ASCO) recommend physical examination for colo-rectal cancer patients in decreasing order over time (Desch et al. 2005). Laboratory tests and imaging procedures are recommended in surveillance programs for breast and lung cancer (Bast et al. 2001). The benefit of dermatological assessments in the follow-up and recognition of cutaneous metastases are not mentioned. And besides that the value of cutaneous metastases as marker lesions under chemotherapy in stage IV disease was never tested.

Routine examinations of cutaneous, subcutaneous, and visible mucous surfaces seem to be cost-effective and may facilitate early detection of metastases. Patients could be familiarized with self-examinations. Especially as in many case reports, patients reported that cutaneous lesions had existed for months, initially not bothering them, but lately annoying and disturbing. There is no evidence whether prognosis quo ad vitam can be improved by an early detection of skin metastases, although the hypothesis is maintained by single case reports (Porter et al. 2006). But at least some cases found to be intractable at the time of diagnosis might have been offered a better treatment result by an early detection. Therefore, medical surveillance programs might include dermatological examinations at least for high risk patients, and patients themselves should be encouraged to self-observation of the skin in order to attain an early diagnosis.

Conclusion

Over time a slight shift of the underlying primary tumours is observed, from mamma, stomach and lung cancer in the late sixties to mamma, colo-rectal and lung cancer at present (Mueller et al. 2004; Abrams et al. 1950). In the meantime the incidence of cutaneous metastases increased drastically from 2.7% in 1969, to 4.5% in 1993, and to 10% nowadays, due in part to a growing awareness of this condition, in part to a rise in cancer rates, and in part to longer survival times granting skin metastases an opportunity to develop (Poole and Fenske 1993).

In 45% of cases suspicion by first view did not point to a visceral tumour as also many differential diagnoses are possible (Sariya et al. 2007). As most cutaneous metastases developed metachronously an exact anamnesis is helpful.

In about 20% of cases cutaneous metastases arise as the primary clinical manifestation. Especially in these cases the clinical multifariousness of clinical appearance does not deliver a clue with regard to an assignment of the primary tumour. The localisations might give a hint towards the preferential target organ.

As a rule and owing to actual approaches cutaneous metastases of visceral tumours indicate a negative prognosis. Multiple cutaneous metastases often come along with disseminated tumour progression revealing end-stage disease.

The optimal surveillance strategy at least during 3 years after excision of high risk tumours should be a matter of debate. Trials for cost-effectiveness of follow-up with or without inexpensive skin examinations might clarify a possible benefit with incremental emphasis on improving quality of life.

Visible, function impairing, unresectable cutaneous metastases always impose a burden upon the patient, associated with physical pain and psychological strain. Besides curative indications they urgently claim a palliative intention. Interdisciplinary work is requested to bring ahead diagnostic endeavours. Improved therapeutic results might be conceivable with dermatologically available anticancer approaches.

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