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RESEARCH

Skin Metastasis of Internal Cancers: A Single Institution Experience

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Abstract Skin metastatization of internal cancers are rare and a few studies are available analyzing its clinicopathological features. The reported incidence of skin metastasis is influenced by two factors: the relative proportion of cancers covered by skin in the various cohorts and the large differences in the prevalences of various cancer types. Futhermore, the anatomical distribution of skin metastases of various cancer types is aslo not well known. Therefore we have collected a skin metastasis cohort of biopsy and authopsy cases (n=80) from the archive of our department and analysed its clinicopathologic features. The adjusted skin metastasis prevalence data of various inner cancers indicated that kidney-, lung- and colorectal cancers have a strong positive preference for skin metastatisation while pancreatic cancer has a negative one. We have provided evidences that lower gastrointestinal- and genitourinary cancers preferred infradiaphragmatic skin regions unlike upper gastrointestinal cancers while lung- and kidney cancers preferred supradiaphragmatic regions. We have also detected that ventral skin regional metastasis is slightly more prevalent irrespective of the cancer type. Our study provide the first statistical data for the variations in skin preference of metastatisation among various cancer types as well as for the significant variations in their regional distributions.

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Introduction

Skin is a rare location for distant metastases of malignant tumors especially from internal organs, its prevalence however has grown, linked to the longer survival of patients by reason of more efficient oncological therapies. Compared to the sixties [1], skin metastasis prevalence has changed from 1 % to 5–10 % according to newer studies [2], while the more objective autopsy studies show a lower prevalence (1–4 %). Skin metastases generally develop in the late, disseminated stage, but may also be the first clinical manifestation of an asymptomatically progressing cancer [3–5]. The clinical picture of skin metastasis is highly variable, therefore presenting a serious differential diagnostic problem for dermatologists and oncologists. The most common cancers giving skin metastasis are melanoma in men followed by lung-, colorectal-, oral- and kidney cancers. In woman the most frequent primary of skin metastasis is breast cancer followed by colorectal-, lung-, kidney-, ovarian cancers and malignant melanoma [3–5].

There are two problems with these statistics. Concerning "real" skin metastasis as distant organ metastasis, the tumors which may involve the skin either as part of the local invasion process (melanoma, breast cancer) or during the locoregional lymphatic dissemination have to be discriminated from those tumors in which no such mechanisms are known i.e. inner organ cancers such as lung-, colorectal-, kidney cancer etc. The other problem is the fact that incidence of skin metastases of inner organ cancers is influenced by the relative prevalence of these cancers. Another catch is that one of the most common locations of skin metastasis is the surgical scar, where local iatrogenic cancer cell contamination or preferential wound-homing are both possible alternative mechanisms [6–8].

The present study summarizes the clinicopathological features of skin metastases diagnosed at our department. We have

attempted to select only those cases in which local confounding processes can be excluded for skin-involvement and analysed distant metastasis exclusively. Further, we focused on the question whether there is any relationship between the location of the primary tumor and its skin metastasis pattern.

Material and Methods

Biopsy samples and data were collected retrospectively from the archives of the 2nd Department of Pathology, Semmelweis University between 1993 and 2010. Specimens included surgical biopsy, fine needle aspiration cytology and autopsy samples. In case of the former two sampling methods, clinical data were collected (if available) such as location of skin metastasis, interval between diagnosis of the primary tumor and skin metastasis (less than 1 month interval was defined as a synchronous occurrence), and surgical treatment of the primary tumor. Furthermore, among the autopsy cases the location of all metastases was determined. Diagnosis of the primary tumor was based on either histological or cytological examination in every case. The origin of skin metastases was proved by obvious histo- or cytomorphological features, immunohisto- or cytochemistry was performed only in ambiguous cases. The absolute prevalence of skin metastases was determined by using only the autopsy group data, while the organ-specific relative prevalence of skin metastases was also calculated based on overall cancer mortality statistics in our autopsy database. The protocol was approved by the local ethical comittee (TUKEB114/2012).

The study includes only skin metastasis from solid malignancies of those internal organs which have neither direct anatomical nor lymphatic or vascular connection with the skin. Therefore, hematologic tumors, primary skin tumors, breast and head-neck (pharynx, larynx and thyroid) cancers were excluded. Surgical wound metastases were also excluded.

Differential diagnostic immunohistochemical reactions were performed on paraffin embedded tissue samples using primary antibodies including pan cytokeratin (AE1-AE3, DAKO), cytokeratin 7 (DAKO), cytokeratin 20 (DAKO), vimentin (DAKO), thyroid transcription factor-1 (Bio-Genex), chromogranin (DAKO), synaptophysin (Bio-Genex) and prostate specific antigene (DAKO). Immunocytochemical reactions were performed on unstained smears using the primary antibodies listed above. Reactions were carried out in Ventana ES automatic immunostainer (Ventana Medical Systems, Inc.; Tucson, AZ) using avidin-biotin peroxidase technique and diaminobenzidine as chromogen according to the manufacturer's protocol (iView DAB Detection Kit; Ventana Medical Systems).

Further immunohistochemical reactions were performed on the available paraffin blocks to demonstrate lymphatic or hematogenic invasion in order to conclude the possible pathomechanism of the skin metastasis. Endothelial cells were detected by CD 31, CD 34 , and D-240 (DAKO) antibodies.

Comparisons between the distribution of skin metastases of different primary tumors were assessed by chi-square test. Differences were considered to be significant at $p<0.05$.

Results

Our cohort comprised 80 patients (43 men and 37 women) diagnosed with skin metastases either with biopsy or at authopsy were aged from 33 to 88 years (mean 62.2 years). We have calculated the prevalence of skin metastases from internal cancers 0.9 % based on our authopsy records (13 cases/1449). In 34 cases (43 %) the skin metastasis was diagnosed simultaneously with the primary tumor or as the first lesion of the patient's neoplastic disease. Among patients with known malignancy the skin metastasis developed 2 to 154 months after the initial diagnosis (mean 23.6 months). The primary tumor was surgically resected in 42 cases (53 %) synchronously with the skin metastasis or before the development of the skin metastasis. The most common biopsy method was fine needle aspiration in 40 cases, surgical local resection was performed in 29 cases, autopsy sampling was done in 13 cases. Clinicopathological features of our cohort is summarized in Table 1.

The most common location of primary tumors giving skin metastasis was the large bowel, followed by lung, upper gastrointestinal tract, kidney, liver, ovary, uterus, prostate and urinary vesicle. Since incidence of various primary tumors is very different we made an attempt to correct skin metastasis prevalence data for the relative incidence of the primary tumors based on incidence data of our authopsies. This analysis indicated that kidney cancer was the most and pancreatic cancer the less frequent visceral malignancy metastasizing to the skin (Fig. 1.). It is of note that it seems based on these data that lung- and colorectal cancer also has a moderate positive while liver cancer has a moderate negative prefrence for skin metastasis.

The exact locations (based on available clinical data in 74 cases) of skin metastases are shown on Fig. 2. The most commonly affected area was the abdominal skin region (34 cases), followed by the anterior chest and head and neck with 15 cases each, the back in 7 cases, the extremities in 5 cases and the genitals in 1 case. Our data showed striking differences between various cancer types in relation to the localization of their skin metastases. Almost half of the lung cancer skin metastases were in chest skin and a third located in the head and neck region (Fig. 2b). Contrary to this

Table 1 Clinicopathological characteristics of the skin metastasis cohort

Localisation of primary tumor	All	Lower gastro-intestinal tract	Lung	Upper gastro-intestinal tract	Kidney	Liver	Gynecologic	Pancreas	Lower urinary tract
Patients									
Number of cases	80	27	21	9	7	6	5	3	2
Age	62,2 (33–89)	61 (36–80)	61,2 (41–89)	62,9 (33–88)	64,1 (59–76)	54,7 (33–71)	60,4 (34–77)	75 (68–80)	77,5 (74–81)
Sex(male;female)	43:37	13:14	11:10	6:3	5:2	5:1		2:1	1:1
Biopsy method									
Surgical excision	27	12	2	3	4	3	3	1	1
Fine needle cytology	40	12	11	5	2	3	2	1	1
Autopsy	13	3	8	1	1	0	0	1	0
Diagnosis of primary tumor									
Unknown primary tumor or synchron primary tumor and skin metastasis	35	5	17	3	4	2	2	1	0
Known primary tumor	45	22	4	6	3	4	3	2	2
Interval between the diagnosis of primary tumor and skin metastasis (months)	23,6(2–154)	23(2–108)	13,7(10–17)	15,4(6–26)	53(2–154)	9,3(4–14)	24	10	48
Surgical therapy of primary tumor									
Resection	42	24	0	5	6	3	4	0	1
Inoperable	38	3	21	4	1	3	1	3	1

pattern, two thirds of the colorectal cancer skin metastases were localized to the abdominal skin and the rest equally distributed in the skin of the head and neck, chest and upper extremity (Fig. 2a). When colon and rectal cancers were separated it became evident that although colon cancer follows the abdominal predominance (13/18, 72.2 %), rectal cancer did not (2/4,50 %) in our series (Fig. 2a). In our cohort

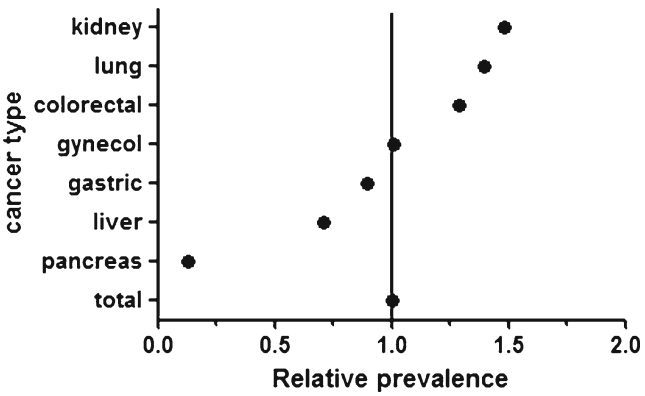

Fig. 1 Relative frequences of skin metastases (n=80, this study) of various cancer types. Relative frequency calculated according to local cancer prevalences (n=1443), <1=negative preference, >1=positive preference for skin metastasis formation

the skin metastasis distribution of both liver and kidney cancers followed the lung cancer pattern (Fig. 2b, d).

Ipsilateral and controlateral skin metastases were equal in number among the malignancies of paired organs and the large bowel. We were looking for cancer type-specific differences in anatomical distribution of skin metastases and statistically analyzed two issues: the variation in supra- versus infradiaphragmatic localization and the ventral versus dorsal distributions in our cohort. This analysis provided statistical evidence for the cancer type differences in the location of skin metastases relative to the diaphragm. Similarly to some previous reports [3–5], lower gastrointestinal and genitourinary cancers preferred the infradiaphragmatic skin regions unlike upper gastrointestinal cancers, while lung and kidney cancers preferred the supradiaphragmatic skin regions. Our data also indicated that in harmony with some previous reports, ventral skin region metastases are the most common, irrespective of cancer type (Table 2).

To explore the possible pathomechanism leading to skin metastatization, we have tested lymphovascular invasion rate in available metastatic samples [9] using immunohistochemistry to differentiate between blood (CD31+/CD34+) and lymphatic (D-240+) vessels. Definitive vascular invasion was proved only in 4 cases (28.6 %). Immunohistochemical

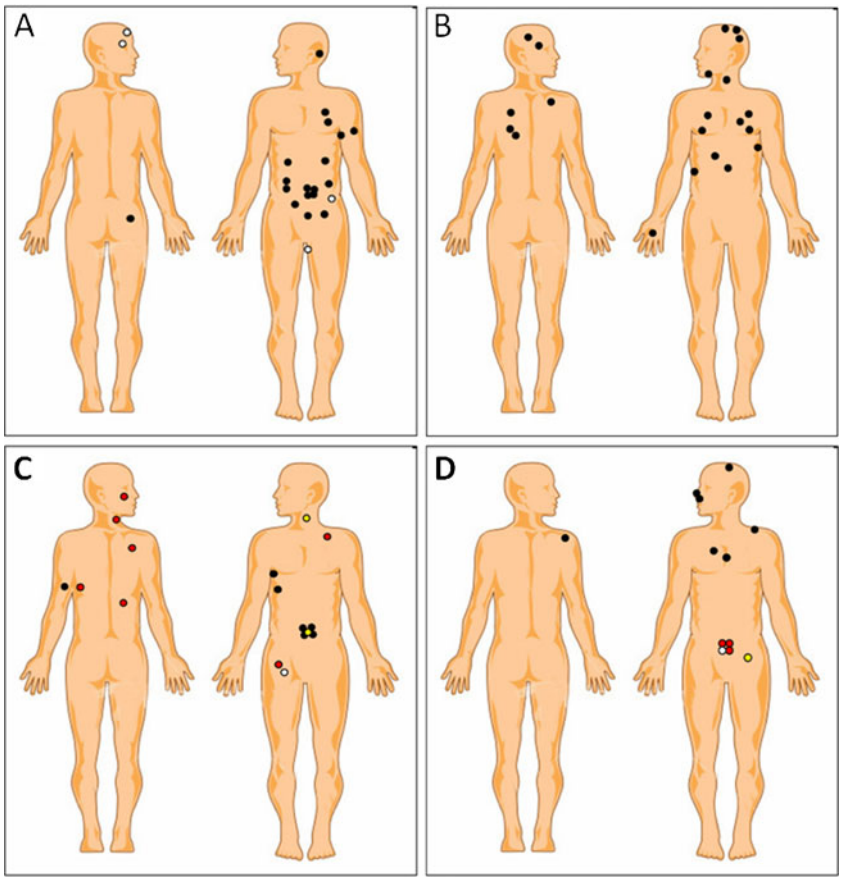

Fig. 2 Anatomical distribution of skin metastases (n=74, this study). **a** Lower gastrointestinal cancers. Colon=*black*, rectal=*white*, **b** Lung cancer, **c** Upper gastrointestinal cancers. *Black*=gastric cancer, *red*=liver cancer, *white*=esophageal, *yellow*=pancreatic, **d** Urogenital cancers. *Black*=kidney, *red*=ovarian, vaginal=*yellow*, prostatic=*white*

detection of different types of endothelium showed 3 lymphatic (21.5 %) and 1 blood vessel invasions (7.1 %), the former in lung and colon adenocarcinoma, the latter in a colon adenocarcinoma case (Fig. 3a–d). As another possible mechanism leading to skin metastasis, we have tested peripheral nerve involvement in our cohort where histological samples

Table 2 Regional distribution of skin metastases

	Lokalization	of skin metastasis	
	Supradiaphramatic (n/%)	Infradiaphragmatic (n/%)	
Localisation of the primary tumor			p
Lower gastrointestinal	7 (25,9 %)	20 (74,1 %)	
Lung	19 (90,5 %)	2 (9,5 %)	
Upper gastrointestinal	3 (33,3 %)	6 (66,7 %)	
Kidney	6 (85,8 %)	1 (14,2 %)	
Liver	3 (60 %)	2 (40 %)	
Gynecologic	0	5 (100 %)	
All	38 (56,7 %)	29 (43,3 %)	p=0.005
	Ventral	Dorsal	
Lower gastrointestinal	26 (96,3 %)	1 (3,7 %)	
Lung	17 (81 %)	4 (19 %)	
Upper gastrointestinal	6 (85,8 %)	1 (14,2 %)	
Kidney	6 (75 %)	2 (25 %)	
Liver	4 (57,1 %)	3 (42,9 %)	
All	61 (84.7 %)	11(15.3 %)	p=0.228
	Ipsilateral	Controlateral	
All[a]	9 (45 %)	11 (55 %)	p=0,968

Significance was tested on paired data using chi2 test

[a]Overall distribution of ipsi/controlaterally located cutaneous metastases of 10 large bowel, 7 lung, 3 kidney carcinoma cases

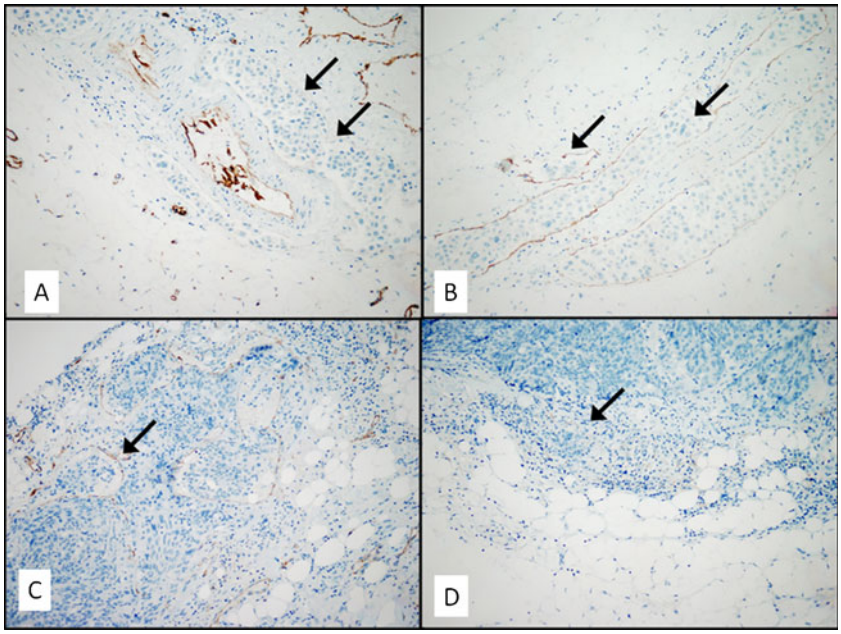

Fig. 3 Detection of lymphovascular invasion in skin metastases. **a** negative CD 31 and **b** positive D-240 reaction in lymphovascular invasion of a lung cancer skin metastasis (200x). **c** positive CD-31 and **d** negative D-240 reaction in hematogenic invasion of a colon cancer skin metastasis (200x)

were obtained but none of them contained nerve tissue excluding the possibility of perineural spreading (data not shown).

Discussion

Many physicians consider skin alterations a frequent manifestation of internal disease, at the same time, neoplastic diseases rarely spread to the skin particularly from internal organs [6, 10–12]. In our study autopsies revealed only less than 1 % prevalence of skin metastasis among gastrointestinal, lung, hepatobiliary and urogentital tract cancers. This finding corresponds with the lower margin of the literaturary data, however exclusion of cancer types commonly giving skin metastases, such as breast and head & neck tumors, must be taken into account in this setting. Lung and breast cancers are considered to have the greatest tendency to give skin metastasis [7]. Our results showed the largest number of skin metastases among colorectal cancers, but it should be noted that this overrepresentation could be a result of our principally gastrointestinal profiled clinical departments. The skin metastases of breast cancer cases were not included in this study, however the number of these cases exceeded one hundred at our institute. We also assessed the relative prevalence of skin metastases of visceral organs providing a scale which shows the affinity of different cancers for metastasizing to the skin. Interestingly, kidney cancer was found to have the biggest potential to form skin metastasis, followed by lung and colon cancers. On the other hand, gastric, liver and pancreas cancers have less probality to spread into the skin. These differences between the cutaneous metastatic potential presume a specific homing mechanism in the skin rather than a difference either in vascular anatomy or in the ability of vascular invasion of the given cancer types.

Skin metastases generally develop in the end stage of neoplastic disease, after the primary tumor has been clinically detected, but some tumor types—most frequently lung cancer—could remain occult until presentation of the skin manifestation [8, 13]. Our data revealed that 43 % of patients presented with skin metastasis as the first or synchronous clinical presentation of the neoplastic disease which is much higher compared to the proportion of 22-23 % reported in former studies. The interval between diagnosis of primary tumor and development of skin metastasis varied in wide range from some weeks to more than a decade with the longest being 13 years in one case. This patient underwent nephrectomy and died of multiple brain and lung metastases which developed parallel with the skin metastasis. In our study the mean latency was 23.6 months, in concordance with the literature. Correct survival data were unavailable for most of our patients, prognosis after skin metastasis is very poor with only 7.5 months life expectancy, according to the literature [10]. Long term survival after surgical excision of skin metastasis was described only in a case of solitary skin metastasis of renal cell carcinoma [14].

With regard to metastasis pattern to other distant locations we did not find any definable correlation in the autopsy cases. All kinds of distant metastasis patterns could be revealed from brain to bones. Interestingly, only one case of pancreatic cancer with regional lymph node metastasis did not progress to any distant organ, but the skin.

Skin metastasis of visceral organs could be logically assumed as a result of hematogenic rather than lymphotic spread of tumor cells. Blood circulation dependent tumor

spreading would indicate a randomly distributed skin metastasis pattern, but there is clear evidence that most visceral tumors have preferred skin regions for metastasization. We also concluded that on one hand, some visceral cancer types give metastases into the vicinity of the organ, such as lung cancer with mainly supradiaphragmatic, colorectal cancer with mainly subdiaphragmatic and genitourinary cancers with lower abdominal site skin metastases. Strong significant relationship was found between the supra- and subdiaphragmatic distributions of skin metastases of different origin. These group of cancers may represent the lymphatic way of metastasise to the skin. At the same time, it is more difficult to understand why these kinds of skin metastases do not respect the laterality of the primary tumor in contrast to the regional lymph node metastases of the same organs. On the other hand, the second group of visceral cancers metastasizes to more distant skin regions may be due to hematogenous way of metastasization. We found such tumors with totally random skin metastasis distribution, e.g. liver cancer, while there is still a particular skin region preference in this group, e.g. the head&neck location in kidney cancer cases. This phenomenon could be another argument favouring the role of some "homing" mechanism which determines the terminal point of circulating tumor cells in the skin tissue.

Definitive vascular invasion was proved only in four cases. Immunohistochemical detection of different types of endothelium showed three lymphatic and one hematogenic vessel invasion, the former in lung and colon adenocarcinoma, the latter in a colon adenocarcinoma case. Lymphatic invasion, however, could be a secondary infiltration pattern after the development of the skin colony of the tumor cells.

The blood supply of the skin is derived from the subclavian and external carotid branches on the head&neck, from the spinal arteries on the trunk region and from the arteries of extremities. We could not find any data on a direct connection between blood or lymphatic vessels of the skin and the viscerals, therefore the simple migration of tumor cells into the skin, via the regional lymphatic or blood vessels seems unlikely. One well known exception exists, namely the periumbilical region which remains to be linked with the abdominal viscera via the umbilical artery. This phenomenon could explain the development of the so called Sister Mary Joseph's nodule, which is the metastatic tumor of the umbilicus deriving commonly from the abdominal organs, frequently associated with peritoneal carcinosis [7, 9].

In summary, skin metastases from visceral malignancies are rare with an autopsy-based prevalence less than 1 % in our study, compared to the much higher proportion with cancers developing in organs with rich lymphatic connections with the skin e.g. breast or head&neck tumors. We also concluded that visceral cancer types have largely different cutaneous metastatic ability. As regards clinical significance, on the one hand skin metastasis can develop as a first sign of an asymptomatic neoplastic disease, raising a challenging differential diagnostic problem for dermatologists, whereas on the other hand, from an oncologist's point of view, skin metastasis indicates a very poor prognosis for the patient's managed cancer. The distribution of skin metastases is not random, our results fortified that most of the visceral tumors have favoured skin regions to metastasize, however the exact explanation of this phenomenon is still obscure. In a clinical setting, this characteristic pattern could help to plan further diagnostic procedures in case of unknown primary tumors.

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