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Original Article

Characteristics of primary cutaneous metastasis in Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia, in ten years

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Abstract

Background: Cutaneous metastasis (CM) is a rare condition characterized by skin infiltration and cell proliferation from malignant tumor. Breast cancer is the most common primary malignancy causing CM. This retrospective study aimed to recognize the characteristics of CM from internal organ malignancies, based on the medical records from the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia during October 2008-September 2018.

Methods: The diagnosis of CM referred to clinical manifestations, histopathological, and immunohistochemical examinations. All medical records of patients contained gender and age, primary malignancy, clinical manifestations and location of skin disorders, time interval between diagnosis of primary malignancy and occurrence of CM, and mortality. Data were collected and evaluated descriptively.

Results: A total of five subjects consisted of 3 patients with breast cancer, 1 patient with lung cancer, and 1 patient with prostate cancer. The subjects' age ranged from 40 to 49 years old (40%) and above 60 years old (40%) with the male to female ratio of 2:3. Breast cancer is found to be the most common malignancy (60%). All of the subjects had a skin lesion on the chest wall, abdomen, and back, and 60% of subjects had a nodule as a clinical manifestation. As much as 60% of subjects have died within four months after CM diagnosis was established.

Conclusion: Breast cancer is the most common cause of CM. The CM's primary malignancies are affected by sex, age, clinical manifestations, predilection, and mortality characteristics.

Keywords: *breast cancer, cutaneous metastasis, lung cancer, primary malignancy, prostate cancer*

Abstrak

Pendahuluan: Metastasis kutan (MK) merupakan kondisi yang langka dengan ciri adanya infiltrasi kulit dan proliferasi sel dari tumor ganas. Kanker payudara adalah keganasan primer tersering yang menyebabkan MK. Studi retrospektif ini bertujuan untuk mengenali karakteristik MK dari keganasan organ internal, berdasarkan rekam medis dari Divisi Tumor dan Bedah Kulit, Departemen Dermatologi dan Venereologi, Rumah Sakit Umum Pusat Dr. Hasan Sadikin Bandung, Indonesia, selama bulan Oktober 2008-September 2018.

Metode: Diagnosis MK ditegakkan berdasarkan manifestasi klinis, pemeriksaan histopatologis, dan imunohistokimia. Seluruh rekam medis pasien mencantumkan jenis kelamin dan usia, keganasan primer, manifestasi klinis dan lokasi kelainan kulit, interval waktu antara diagnosis keganasan primer dan kejadian MK, dan mortalitas. Data dikumpulkan dan dievaluasi secara deskriptif.

Hasil: Total lima subjek dalam studi ini terdiri dari 3 pasien kanker payudara, 1 pasien kanker paru-paru, dan 1 pasien kanker prostat. Rentang usia subjek yaitu 40-49 tahun (40%) dan di atas 60 tahun (40%), dengan rasio laki-laki dan perempuan 2:3. Kanker payudara merupakan keganasan yang paling umum ditemukan (60%). Semua subjek memiliki lesi kulit di dinding dada, abdomen, dan punggung, dan 60% subjek memiliki nodul sebagai manifestasi klinisnya. Sebanyak 60% subjek meninggal dalam empat bulan setelah diagnosis MK ditegakkan.

Kesimpulan: Kanker payudara adalah penyebab tersering MK. Keganasan primer dari MK dipengaruhi oleh karakteristik jenis kelamin, usia, manifestasi klinis, predileksi, dan mortalitas.

Kata kunci: *kanker paru-paru, kanker payudara, kanker prostat, keganasan primer, metastasis kutan*

Background

Malignancy is one of the leading causes of death worldwide. The ten most common malignancies in Indonesia are breast, cervical, lung, colorectal, liver, nasopharyngeal, non-Hodgkin lymphoma, leukemia, ovarian and thyroid.[1] Cutaneous metastasis (CM) is the infiltration of tumor cells to the skin due to proliferation or spread originating from a primary malignant tumor.[2,3] Metastasis is one of the characteristics of a life-threatening malignant tumor, and is an indication of a systemic disease causing a decrease in life expectancy.[2,4] CM is considered a rare condition with a prevalence of around 0.7-10.4% of all patients with malignancy and only about 2% of all skin tumors.[2,4,5] In a meta-analysis by Krathen et al. in 2003, the incidence of CM is approximately 5.3 %, with breast carcinoma as the most primary malignancy.[6] CM can be diagnosed as an early manifestation of a yet undetected internal organ malignancy or an early marker of cancer spread or a recurrence of a diagnosed malignancy.[3-5,7,8] The skin is not the main target organ for metastasis, so in general, when metastases have occurred to the skin, other organs have been involved, indicating a poor prognosis.[4,5] The clinical manifestations of CM are very diverse, ranging from macules, papules, plaques, nodules, tumors, and ulcers, or can even resemble other benign skin lesions.[2,3,9] The diagnosis of CM can assist the determination of tumor stage, subsequent therapies, and the prognosis of a malignancy.[1,4,10] The life expectancy of 50% of CM patients is six months on average, while CM caused by breast carcinoma has a higher life expectancy than by other carcinomas.[2]

The most common primary malignancies of CM are breast carcinoma in women and lung carcinoma in men.[11] Some malignancies tend to metastasize to specific body parts, hence the undiagnosed primary malignancy determination obtained by recognizing these locations.[2] History and physical examination can establish the initial diagnosis of CM.[2] A study conducted by Sariya et al. in Philadelphia in 2007 explained that only 50% of CM cases were diagnosed based on history and physical examination alone.[13] Excision or punch biopsy followed by histopathological and immunohistochemical examinations are needed to establish a definite diagnosis of CM and determine its primary malignancy.[2,4,11,14] The incidence of CM originating from breast carcinoma was around 23.9% of all CM, generally in the form of nodules with predilection on the chest wall, upper abdomen, hairy scalp, contralateral breast, and above scar tissue.[4,5] Perou et al. in 2000 molecularly divided breast carcinoma into four subtypes: luminal A, luminal B, human epidermal growth factor receptor2 (HER2) overexpressing, and triple-negative.[15,16] Breast carcinoma with HER2 subtype and B HER2 luminal positive are more likely to have a distant metastasis compared to the other subtypes.[17]

Skin metastases originating from prostate carcinoma are approximately less than 1%, usually as nodules with predilection on the abdomen, suprapubic, and anterior upper limb area.[3,18,19] CM originating from prostate carcinoma should be suspected in elderly male patients whose serum prostate specific antigen (PSA) is elevated and has multiple papulonodular lesions in the lower abdomen, pelvis and pubic area.[18] PSA is a specific antigen for prostate epithelial cells.[19,20] The percentage of lung carcinomas that metastasize to the skin is approximately 1-12%, generally as nodules with predilection on the chest wall, abdomen, head, and neck.[21,22] This study was conducted to determine which primary malignancy is associated with CM, the time interval between diagnosis of primary malignancy and CM, the predilection of the skin disorders, clinical manifestations, and mortality of CM patients with skin tumors who were operated on at Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia from October 1st 2008 to September 30th 2018.

Methods

This study was conducted retrospectively in the period of October 1st 2008 to September 30th 2018 on patients diagnosed with CM at the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia. The diagnosis of patient with CM referred to clinical manifestations, histopathological, and immunohistochemical examinations. All medical records of patients containing gender and age, primary malignancy, clinical manifestations and location of skin disorders, time interval between diagnosis of primary malignancy and occurrence of CM, and mortality. There were no exclusion criteria for this study. Total of five medical records of CM patients could be analyzed. The data were collected and evaluated descriptively.

Results

Age and gender

Table 1. Age and gender distribution of CM patients at the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia, October 2008 - September 2018 period

Age	Gender		Total
	Male	Female	
30-39 years old	1	0	1
40-49 years old	0	2	2
50-59 years old	0	0	0
60 years old or older	1	1	2
Total	2	3	5

Characteristics of CM patients based on primary malignancy

Table 2. Immunohistochemical examination results from skin biopsy of CM patients at the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia, October 2008 - September 2018 period

Patient	Diagnosis	Immunohistochemical Results	Conclusions
1	Breast carcinoma	- ER : negative - PR : negative - HER2 : 3 positive - Ki67 : positive > 20% tumor cell	Tipe HER 2 type
2	Breast carcinoma	- ER : negative - PR : weak positive - HER2 : 3 positive - Ki67 : positive >20% tumour cell	Luminal B HER 2 positive
3	Breast carcinoma	No available data	No available data
4	Prostate carcinoma	- CK : positive - CK7 : negative - CK20 : negative - Vimentin : negative - Hepar1 : negative	Carcinoma originates from the prostate
5	Lung carcinoma	- CK : positive - CD34 : normal positive	A carcinoma

Characteristics of primary malignancy

Table 3. Characteristics of primary malignancy of CM patients at the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia, October 2008 - September 2018 period

Primary malignancy	Total
Breast carcinoma	3
Lung carcinoma	1
Prostate carcinoma	1

Characteristics of time intervals between diagnosis of primary malignancy and CM

Table 4. Characteristics of time of onset of skin lesions in CM

Time of occurrence of skin lesions in CM	Total
Before the primary malignancy is diagnosed	2
After the primary malignancy is diagnosed	3

Table 5. Characteristics of clinical manifestations of CM patients at the Tumor and Dermatology Surgery Division, Department of Dermatology and Venereology, Dr. Hasan Sadikin General Hospital Bandung, Indonesia, October 2008 - September 2018 period

Clinical Manifestation	Total
Papulonodular	3
Carcinoma en cuirasse	1
Carcinoma en cuirasse + telangiectatic carcinoma	1

Predilection characteristics of skin disorders

Of the five patients in this study, all patients had skin lesions on the chest, abdomen, and back. Other than these regions, patients with prostate carcinoma also had skin lesions on the neck area, whereas patients with lung carcinoma had skin lesions on almost all regions.

Mortality characteristics

Of the five patients in this study, two patients suffering from CM originating from lung carcinoma and prostate carcinoma died within two weeks after the CM was diagnosed. One CM patient from breast carcinoma died within four months, the other two patients were still alive until the 11 and 13 months of this study.

Discussion

In the currently existing literature, CM is more common in old age with the highest incidence between the ages of 50 and 70.5.[7] Another study conducted by Benmously et al. in eight male patients and four female patients, between 1993 and 2007, in Tunisia, showed that the age range of CM patients was between 53 to 96-year-old with a mean age of 63.5-year-old for men and 76.5-year-old for women.[8] In a previous case report, there were only 4 CM patients with Human Immunodeficiency Virus (HIV) aged 36, 37, 43, and 47 years, respectively. This case report has similar results to our study, in which there was one CM patient aged 36-year-old (younger than the normal population of CM patients). The patient was suffering from a combination of lung carcinoma and HIV. Lung carcinoma in HIV-positive patients usually occurs at a young age, under 45-year-old.[23]

Previous studies had reported all malignancies had the possibility to metastasize to the skin. In daily practice, the most common malignancy in each gender turns out to be the one that most often metastases to the skin.[2,3,10]

Immunohistochemical examinations was applied to determine the source of primary malignancy easily, especially in CM cases with undifferentiated lesions.[2] The initial step in determining the three main cell types including epithelial, mesenchymal, or hematopoietic. Cytokeratins (CK) as markers that could be used to determine malignancy.[24] CK7 and CK20 examinations as two basic tests were used to determine the location of primary malignancies. CK7 was found in ductal, glandular, and transitional epithelial cells. CK20 was found only in gastrointestinal epithelial cells, urothelial cells, and Merkel cells.[25] A negative CK7 and CK20 test indicated that the primary tumor might originate in the prostate, kidney, or liver. Further the specific immunohistochemical tests such as PSA is performed for prostate carcinoma identification, hepar1 for liver carcinoma, and vimentin for renal carcinoma.[2] CK7, CK 20, ER, PR, gross cystic disease fluid protein-15 (GCDFP-15), carcinoembryonic antigen (CEA), HER2, mammaglobin, E-cadherin, epithelial membrane antigen (EMA), CD31, podoplanin, and epithelial mucin-1 (MUC1) are several immunohistochemistry tests which can help diagnose CM due to breast carcinoma. CK5/6, CK7, thyroid transcription factor-1 (TTF-1), Ber-EP4, CEA, surfactant, apoprotein A, CAM5.2, CK8/18, calretinin, and vimentin are immunohistochemistry tests producing positive results in lung-carcinoma-related CM.[3]

The characteristics of the primary malignancy of CM patients in this study were in accordance with previous studies, in which the most common primary malignancies that could cause CM was breast carcinoma. This was due to the high incidence of breast carcinoma and the location of the breast tumor, which was located more superficial (closer to the outer skin) than other internal organ tumors.[3] In 1971, Brown-stein and Helwig conducted a study in New York to determine the prevalence of primary malignancy causing CM in 724 men and women patients. Lung carcinoma in men was the most prevalent cause of CM (24%), followed by colon carcinoma (19%), melanoma (13%), and squamous cell carcinoma (12%), whereas in women, breast carcinoma was the most common cause of CM (69%), followed by colon carcinoma (9%), melanoma (5%), and ovarian carcinoma (4%).[26]

Another related study reported similar results conducted by Sittart et al. (1963-2008) in Brazil, revealed that breast carcinoma in women and lung carcinoma in men were the most common causes of CM.[27] In 2003, Krathen et al. conducted a meta-analysis with a total sample of 20,380 patients suffering from carcinoma and 1,080 patients suffering from CM.[6] The meta-analysis results were similar to the two previous results showed breast carcinoma was the primary malignancy causing CM frequently (24%). Lung, colorectal, ovarian, and bladder carcinomas had a similar incidence of approximately 3.4 - 4%, while prostate carcinoma was only 0.7%.[6] Prostate carcinoma was often found in men.[27] CM originating from prostate carcinoma were considered to be very rare, with an incidence of less than 1% and only a total of less than 80 cases had been published.[10,20,22,27,28]

In most cases, CM is usually diagnosed after the primary malignancy identified. However, in approximately a third of the case, CM was diagnosed before or concurrently with the primary malignancy.[2] Schwartz et al. reported that CM was mainly confirmed before the diagnosis of primary malignancy were in lung (60%), in renal (53%), or ovarian (40%) carcinoma.[10] In 20-60% of lung carcinoma cases, CM developed before or concurrently with the diagnosis of lung carcinoma.[21]

The intervals between the diagnosis of malignancy and metastasis varied.[4,5] Patients suffering from CM originated from breast carcinoma in this study were diagnosed within 12, 14, and 15 months (within the first three years) after the diagnosis of primary malignancy was established. This was in accordance with a previous study, which concluded that metastasis generally occurs in the first three years after the diagnosis of primary malignancy was established,[4,5] although CM cases had also been reported 22 years after primary malignancy diagnosis.[2] Another study by Benmously et al. also showed similar results, in which the mean interval time for diagnosis of primary malignancy and CM was 8.2 months, ranging from less than one month to four years.[8]

Hu et al. reported that out of a total of 141 patients who had excision or other therapies for the primary malignancy, CM with the most prolonged duration of onset was found in patients with breast carcinoma (47.2 months), compared with carcinoma of other organs such as colorectal (16.5 months), gastric (19.8 months), and lungs (15.7 months).[2] Clinical manifestations of CM originating from breast carcinoma usually manifest at a later period than malignancies from other organs.[5]

Mollet et al. reported that lung carcinoma was the most rapidly metastasizing malignancy that target the skin, with a mean period of 5.75 months after the diagnosis was established.[22] Previous case reports indicated that CM caused by prostate carcinoma was diagnosed after its primary malignancy diagnosis.[20,28,29]

The clinical manifestations of CM originating from internal organ carcinoma are atypical.[6] The manifestations that could occur are very diverse, ranging from common lesions such as macules, papules, plaques, nodules, tumors, and ulcers, to specific forms such as erysipeloid carcinoma, carcinoma en cuirasse, telangiectatic carcinoma, peau d'orange, Paget's disease, metastatic herpetiformis/ zosteriformis, clown nose, neoplastic alopecia, subungual metastases, and *Sister Mary Joseph* nodules.[2] In a retrospective study conducted by Lenz et al. on 4,020 patients, the most prevalent clinical manifestation observed in CM is in the form of nodule lesion.[30]

The main forms of clinical manifestations that are almost always associated with breast carcinoma are erythematous carcinoma (inflammatory carcinoma), carcinoma en cuirasse, and telangiectatic carcinoma.[7,31] Erysipeloid carcinoma is characterized by the presence of a firmly demarcated erythema plaque lesion with tenderness and is warmer than the surrounding tissue resembling erysipelas.[6,7] This form is found in less than 2% of all patients suffering from breast carcinoma.[7] Telangiectatic carcinoma was first

introduced by Weber in 1933 in a patient with breast carcinoma, with lesions characterized by papules, nodules, or unilateral purpuric plaques on the chest, usually proximal to the postoperative scar tissue. [2] In addition, this telangiectatic carcinoma could also provide a picture of purplish papulovesicle lesions due to dilated blood vessels. Carcinoma en cuirasse is a lesion in the form of papules or lenticular nodules with an erythematous or bluish-red base, then confluences to form sclerodermoid plaques.[10] In another retrospective study conducted by Mordenti et al, from a total 164 CM cases originated from breast carcinoma, 80% of patients showed papules or nodules skin lesions, 11.2% were telangiectatic carcinomas, 3% were erysipeloid carcinomas, 3% were carcinomas en cuirasse, 2% were neoplastic alopecia and 0.8% were zosteriforms.[4,30]

CM originating from prostate carcinoma generally showed clinical manifestations in the form of asymptomatic papules or nodules, which are solitary or multiple.[14,28,29] However, CM from prostate carcinoma increased the lesions imitating angiosarcoma, cellulitis, Paget disease, sebaceous cyst, Sister Mary Joseph nodule, telangiectasia, basal cell carcinoma, pyoderma, morphea, and tricycepelioma.[21]

The majority of CM originating from lung carcinoma presented the form of solitary or multiple nodules, movable or immovable from the surrounding tissue, hard or soft, and asymptomatic.[21,22] Zoosteriform-shaped skin lesions could also be found but with a small incidence.[10]

A study conducted in Turkey revealed that the predilection area of CM was associated with the primary underlying malignancy.[30] Skin lesions in CM patients from prostate carcinoma were predominantly located in the abdominal, inguinal, penis, and thighs area.[10,14] In addition, skin lesions can also be located on the hairy scalp, nose, and neck, but with a lower incidence rate.[10] Abrol et al. reported one case of CM patients originating from prostate carcinoma with neck and upper chest skin lesions.[19] Skin lesions of CM patients caused by breast carcinoma are most often found on the chest wall, upper abdomen, hairy scalp, contralateral breast, and scar tissue. In addition, skin disorders could also occur on the back, neck, upper arms, and lower abdomen but less frequently.[4] Most of the skin disorders in CM patients caused by lung carcinoma are located on the chest wall, stomach, head, and neck.[21,30] However, a study conducted by Hidaka et al. in 1996 with sixteen patients diagnosed with lung carcinoma indicated that the back was the most common area for metastases.[32] The patient with lung carcinoma in this study was found to have skin lesions in almost all parts of the body. This was hypothesized to be related to stage IV HIV disease condition as a comorbid in this patient. To date, Hamdan et al. reported only two cases of HIV patients accompanied by CM originating from lung carcinoma. However, none of these two patients showed any manifestations of skin abnormalities in almost any part of their body.[23]

The average life expectancy of patients with CM was between three to six months.[7,33] Another study conducted by Benmously et al. between 1993 and 2007 in Tunis concluded that the average life expectancy of patients with CM was nineteen months after CM diagnosis, ranging between six months to five years. The life expectancy of CM patients originating from breast carcinoma was better than carcinoma originating from other organs.[8] The majority of CM patients with prostate carcinoma as the primary malignancy did not survive six months, while the CM patient who originated from lung carcinoma only survived for three months as the skin lesions progressed.[7,28]

Conclusion

The majority of patients in this study were in the 40–49-year-old age group, with a male to female ratio of 2:3. The most prevalent primary malignancy which causes CM are breast carcinoma. The predilection regions of skin lesions in patients suffering from CM were the chest wall, abdomen, and back.

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