



SPECTRUM OF CUTANEOUS METASTASIS FROM INTERNAL MALIGNANCIES: A STUDY OF CLINICO-PATHOLOGICAL AND SURVIVAL EVALUATION OF 126 PATIENTS

Oncology

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ABSTRACT

Cutaneous metastasis (CM) from internal malignancy are relatively uncommon and accounts for 0.7% to 9%. CM may herald the diagnosis of internal malignancy, and early recognition can lead to accurate and prompt diagnosis and timely treatment. The most common cancer metastasizing to the skin are breast, lung, colorectal and melanoma.

Material and Methods: This retrospective study analyzed 126 patients of CM registered in the department between year 2007 to 2016. All the patients were histopathologically proven primary and cutaneous lesions. CM were analyzed on the basis of type and site of presentation, other distant visceral and skeletal metastasis, time interval between primary malignancy and development of cutaneous metastasis and survival.

Results: This study included 50 males (39.6%) and 76 females (60.3%) with a median age of 46.5 years (range 16-80 years). The presence of CM in different body sites were abdomen (49.2%), chest (44.4%), extremities (17.4%), face (15.8%), back (12.6%), surgical scar (12.6%), scalp (11%), inguinal region (8%), and breast (6.3%). Eighty two percent of the patients were presented with nodular lesions. CM was the first sign of internal malignancy in 14 patients from different malignancies. Thirty patients presented with CM on surgical scar from different primary malignancies. Four patients presented with metastasis in female breast. Scalp metastasis was exhibited in 21 patients. The survival of the patients after recognition of the cutaneous metastasis ranged from one to 46 months, depending on tumor type. Overall mean survival time was 13.54 (11.5-15.6) months. Overall survival comparison using log rank hypothesis was done with chi-square statistic value of 14.673 ($p < 0.023$) with 95% confidence limit.

Conclusion: CM are important to recognize early, they often dramatically alters treatment plan. The appearance of these cutaneous metastasis signals widespread distant and systemic metastatic internal malignancy, resulting in poor outcome and patient survival.

KEYWORDS

Cutaneous metastasis, internal malignancy, patterns, nodules

Introduction

Cutaneous metastases (CM) are the spread of a tumor from primary site of its origin to the skin. CM from internal malignancy are relatively uncommon and accounts for 0.7% to 9%. These are important to recognize early. The early recognition can lead to accurate and prompt diagnosis and suitable treatment. The identification of CM often astonishingly alters therapeutic strategy. They may be the first manifestation of unwarned occult malignancy or an indicator of recurrence of malignancy after treatment or failure of on going therapy.

[1] The biologic basis of CM is inadequately understood. The tumor cells need to detach from the primary site, invade a blood or lymphatic vessel, circulate in them, extravasate, reattach in a distant site, finally, survive and proliferate at the secondary site. [2] Some tumors have predilection for metastasize to distinct areas. Recognition of these patterns can be useful in directing the search for an underlying tumor. [3][4][5] The emergence of these lesions signals widespread metastatic disease, resulting in a poor prognosis and high mortality rate. Engrossing advances in chemotherapy have greatly increased survival in recent years. This study furthermore apprise the patterns and presentation of CM from internal malignancies.

Material and methods

This retrospective study analyzed 126 patients of CM registered in the department between year 2007 and 2016. The medical records were collected from the data files. All these patients had an underlying diagnosis of histopathologically proven primary malignancy. Skin biopsies and histopathological examinations were performed from suspected cutaneous lesions. The patients information on demographic characteristics, clinical and pathological variables like age and sex, primary malignancy, histopathology, CM presentation and site, other distant visceral and skeletal metastasis, period between the

appearance of the primary malignancy and CM and survival after CM were tabulated and analyzed.

Statistical Analysis

Statistical analysis was conducted by using IBM SPSS software 19 version, New York U.S. Kaplan-Meier survival analysis was done by using log rank hypothesis and chi-square test for the comparison of survival distribution among the groups since the appearance of CM. Statistical significance was determined at $p < 0.05$.

Results

This study included 50 males (39.6%) and 76 females (60.3%) with a median age of 46.5 years (range 16-80 years). Eighty four (67%) patients were belonged to > 40 years age group and 42 patients (33%) were < 40 years age group. The distribution of primary malignancies and their histopathology shown in diagram. [Graph-1 & 3]

The presence of CM in different body sites were abdomen (49.2%), chest (44.4%), extremities (17.4%), face (15.8%), back (12.6%), surgical scar (12.6%), scalp (11%), inguinal region (8%), and breast (6.3%). The type of clinical presentation of CM lesions were nodules, papules, inflammatory plaques, ulceration and zosteriform nodule. Eighty two percent of the patients were presented with nodular lesions. [Graph-2]

Cutaneous metastasis was the first sign of internal malignancy in 14 patients from renal cell carcinoma (1), small cell carcinoma lung (2), adenocarcinoma lung (1), infiltrating ductal carcinoma breast (2), uterine sarcoma (1), adenocarcinoma ovary (1), adenocarcinoma oesophagus (2), adenocarcinoma stomach (2) and adenocarcinoma rectum (2).

Scalp metastasis was exhibited in nine patients from breast

malignancies, lung (5), melanoma (3), cervix (2) and rectum (2).

Patients presented with CM on surgical scar from breast (12), squamous cell carcinoma head and neck (5), melanoma ano-rectum (4), adenocarcinoma rectum (3), gall bladder adenocarcinoma (3), uterine sarcoma (2) and seminoma testis (1).

Patients presented with metastasis in female breast was uterine sarcoma (2), synovial cell sarcoma (1) and lung adenocarcinoma (1).

The appearance of CM signals widespread disease, patients presented with other systemic metastasis sites also eg; liver (38%), lung (36.5%), lymph nodes (33.3%), bone (20.6%), brain (9.5%) and some other sites. (12.6%). [Graph-4]

The appearance of CM was the first sign of internal malignancy in some patients and others developed them later on follow-up. In this study the patients who have developed cutaneous lesions in follow-up period, that time ranged from minimum one month to maximum 42 months.

The survival of the patients after recognition of the cutaneous metastasis ranged from one to 46 months, depending on tumor type. Overall mean survival time was 13.54 (11.5-15.6) months. Overall survival comparison using log rank hypothesis was done with chi-square statistic value of 14.673 (p=0.023) with 95% confidence limit. [Figure]

Discussion

Cutaneous metastasis usually occur mainly in the age group between 50 and 70 years. In our study the median age of the patients was 46.5 years and 66.6% patients were belonged to more than 40 years age group. [1]

Spencer et al noticed that incidence of various tumors metastasizing to the skin correlate with the sex-wise frequency of occurrence of various primary malignancies. [6] Breast carcinoma is the commonest cause of CM in women followed by carcinoma of the large intestine, lungs and ovaries. The primary sites of carcinoma with CM among men in decreasing order are lungs, large intestine, oral cavity, kidney and stomach. CM as the first sign of internal malignancy are seen most frequently with carcinoma of the lung, kidney and ovary. [5] In our study the CM most commonly developed from breast in females and from lung and gastrointestinal carcinoma in males.

In a study of 164 breast carcinoma patients with CM Mordenti et al, noticed that the lesions were located at mastectomy site in 50 patients, and on other sites were anterior aspect of chest (75), axilla (8), back (8), scalp (5), periauricular area (5), supraclavicular area (4), face (2), neck (2), upper (3) and lower extremities (2). In all patients, appearance of cutaneous lesions followed the diagnosis of breast carcinoma (range 2 months-8 years; mean 4.1 years). The cutaneous lesions were presented in form of nodules, papules, telangiectatic, erysipeloid, en cuirasse, alopecia neoplastica and zosteriform pattern. The prognosis of patients with CM depends on the type and behavior of the underlying primary tumor and on its response to treatment. CM from breast carcinoma are usually associated with advanced stages of the disease as observed in this study and therefore in most cases, they represent a poor prognostic sign. [7] All the breast carcinoma patients presented with CM associated with at least one or multiple, distant or systemic metastasis in our study, considered a poor prognosis.

Malignant melanomas accounts for less than 2% of skin cancers but responsible for the vast majority of deaths from skin cancers. Majority of melanoma arises from skin but other sites are eyes, mucosa, gastrointestinal tract, genitourinary tract, and leptomeninges. The prognosis of a melanoma lesion based on the depth of invasion, the presence or absence of ulceration and the nodal status. Other factors affected melanoma specific survival include age, lymph node involvement, and extranodal extension. [8]

A multivariable analysis determined that anatomic primary site was an independent predictor of overall survival and disease specific survival in mucosal melanoma. Tumors in the nasal cavity and oral cavity were associated with better survival than tumors in the nasopharynx and paranasal sinuses. [9]

Conjunctival melanoma lesion is uncommon but potentially lethal. The most frequent site of metastasis is lung, followed by the liver, brain and bone. Regional lymph node metastasis and CM is frequent. The survival of five patients of conjunctival melanoma in our study ranged from one month to eight months only. [10]

Surgery is the definitive treatment for early stage melanoma, chemotherapy is generally reserved for adjuvant treatment of advanced melanoma. In operated patients of melanoma anal canal and rectum we have noticed CM at surgical scar site, which is indicative of disease aggressiveness and poor prognosis.

In a retrospective study, Song et al found that 2.8% of patients with advanced non small cell lung cancer initially presented with CM and that these metastases were indicative of a poor prognosis. In their study, 60 out of 2130 patients with advanced NSCLC had an initial diagnosis of CM. The overall length of survival for patients with CM was 3.9 months, compared with 10 months for patients who did not present with CM. [11] We have found two SCLC and three NSCLC cases with CM as a initial presentation of carcinoma lung.

Systemic metastasis from colonic adenocarcinoma usually spreads to the liver, peritoneum, pelvis, lung and bone in decreasing order of frequency. Besides systemic metastasis certain internal malignancies appear to metastasize to the specific cutaneous sites. Rectal malignancy metastasize to the middle or lower demis of the abdomen and the perianal skin, usually to the abdominal wall and around the umbilicus, the metastasis also often appear after surgery for rectal carcinoma. While rare cases have been reported with lesions of the scalp, face, neck, glans penis, surgical scars and distal upper and lower extremities. In our study we have noticed rare presentation of CM to scalp and incision scar from rectal carcinoma. [12] [13] (Figure)

In present study most common clinical presentation of the CM was nodules (82.5%) Lookingbill et al concludes that nodules were the most frequent clinical presentation followed with inflammatory, cicatricial and bullous lesions seen among 4020 patients. Incision scar metastases are common. Breast cancer and melanoma were the most common primary tumor. After recognition of metastasis mean patient survival ranged from one to 34 months, depending on tumor type. CM are not uncommon and frequently are the first sign of extranodal metastatic disease particularly in patients with melanoma, breast or mucosal cancers of head and neck. [14] (Figures)

Neuroendocrine cell [NEC] carcinomas of the colon and rectum are uncommon comprising less than 1% of colon and rectal cancer and CM of these tumors are rare presentation. NE carcinoma diagnosis was confirmed by IHC markers, synaptophysin, chromogranin and neuron specific enolase. NEC carcinoma of colon and rectum has very poor prognosis. [15]

In a study Schoenlaub et al, evaluate survival after CM development according to the type of cancer. In the study of 200 patients, the median survival after CM was 6.5 months (mean 22.8 +/- 43.8 months). Median survival was calculated according to the primary neoplasm, breast carcinoma: 13.8 months, melanoma: 13.5 months, lung carcinoma: 2.9 months. The outcome of patients with CM of lung carcinoma was worse than those with melanoma and breast cancer. [16]

The average time interval between the diagnosis of primary malignancy and CM is approximately around 18 months in our study, in comparison to 33 months in a study by Hussein et al. Overall mean survival time was 13.54 (11.5-15.6) months. CM indicates a widespread disease, around 50% of patients died within the first six months of its appearance. [17]

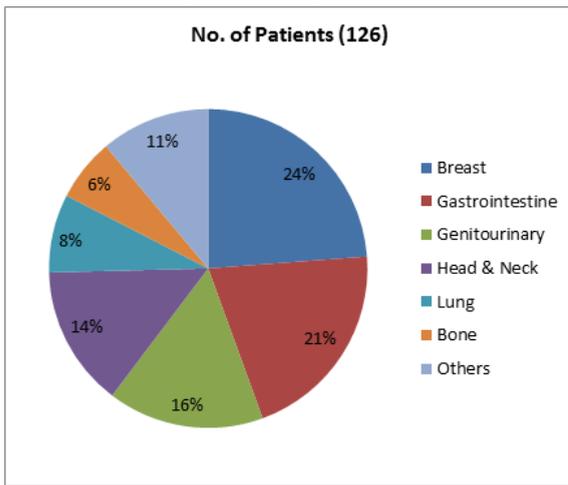
Conclusion

CM are important to recognize early, these usually occur late in the course of malignancy but sometimes it may present simultaneously or before the diagnosis of primary tumor. Once they appear a thorough clinical and diagnostic work up is necessary. The appearance of these CM signals widespread distant and systemic metastatic internal malignancies, often dramatically alters treatment plan, resulting in poor outcome and patient survival.

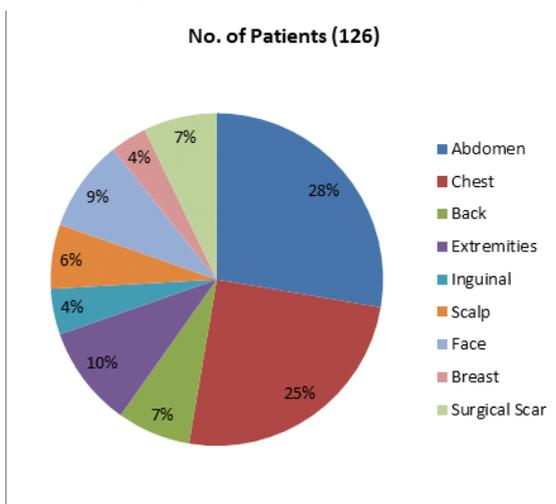
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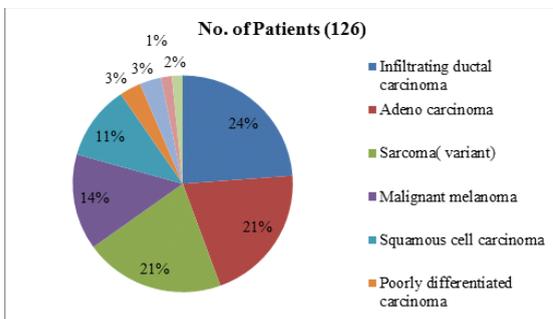
Graph -1 : Primary tumor site



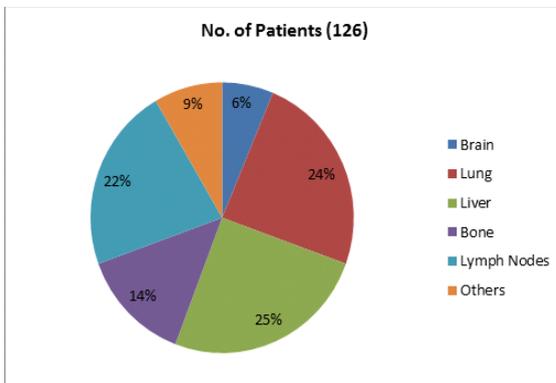
Graph -2 : Site of cutaneous metastasis



Graph -3 : Tumor Histopathology



Graph -4 : Systemic metastasis



Graph 5: Disease Free Survival

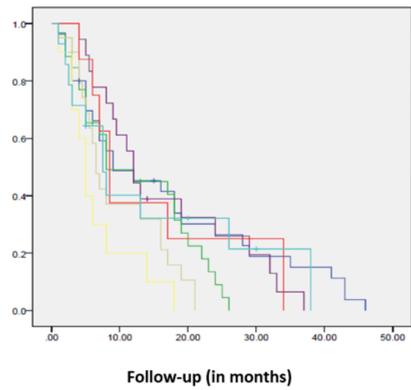


Figure -1:Scalp metastasis from carcinoma rectum
 Figure-2:Chest wall metastasis from carcinoma lung
 Figure-3:Abdominal wall metastasis from renal cell carcinoma
 Figure-4:Surgical scar metastasis from rectal melanoma

References

1. Sarid D,Wigler N,Gutkin Z,Merimsky O,Leider-Trejo L,Ron IG.Cutaneous and subcutaneous metastases of rectal cancer,Int J Clin Oncol 2004;9:202-5
2. Hussein MR.Skin metastasis : A pathologist's perspective. J Cutan Pathol 2010;37: 11-20
3. MH Brownstein,EB Helwig.Patterns of cutaneous metastasis.Arch of Dermatol. 1972;105(6):862-868.
4. Lookingbill DP,Spangler N,Sexton FM.Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients.J Am Acad Dermatol 1990;22:19-26
5. Shwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol,1995;33:161-182.
6. Spencer PS, Helm TN. Skin metastases in cancer patients . Cutis 1987; 39 : 119-121.
7. C Mordenti,K Peris,C Fagnoli,L Ceroni,S Chimenti.Cutaneous metastatic breast carcinoma: A study of 164 patients.Acta Dermatoven,2000;9(4):143-48.
8. Murali R, Desilva C,Thompson JF,Scolyer RA.Factors predicting recurrence and survival in sentinel lymph node –positive melanoma patients.Ann Surg.2011 Jun.253(6):1155-64.]
9. Jethanamest d, Vila PM, Sikora AG, Morris LG.Predictors of survival in mucosal melanoma of head and neck.Ann Surg Oncol.2011Oct.18(10):2748-56.
10. Gokman S H,Ardic F. Malignant conjunctival tumors invading the orbit.Ophthalmologica.2008.222(5):338-43.
11. Song Z,Lin B,Shao L,Zhang Y.Cutaneous metastasis as a initial presentation in advanced non small cell lung cancer and its poor survival prognosis.J Cancer Res Clin Oncol 2012;138(10):1613-17
12. Braveman LM.Skin sign of systemic diseases .2 nd ed.Philadelphia:sanders; 1981.p816.]
13. De Friend DJ,Kramer E,Prescon R,Corson J,Gallagher P.Cutaneous perianal occurrence of cancer after anterior resection using the EEA stapling device .Ann R Coll Surg Engl 1992;74:142-3]
14. Lookingbill DP,Spanler N,Helm KF.Cutaneous metastases in patients with metastatic carcinomas: A retrospective study of 4020 patients. J Am Acad Dermatol 1993;8:29,228-36
15. Grabowski p,schindler I,Foss HD,Riecken EO et al.Neuroendocrine differentiation is a relevant prognostic factor in stage III-IV colorectal cancer.Eur J Gastroenterol Hepatol 2001;13:404-11
16. Schoenlaub P,Sarraux A,Grosshans E,Heid E,Cribrier B.Survival after cutaneous metastasis :a study of 200 cases.2001;128(12):1310-1315
17. Hussein MR.Skin metastasis : A pathologist's perspective.J Cutan Pathol 2010;37: 11-20