

SPECTRUM OF CUTANEOUS MANIFESTATIONS IN PATIENTS WITH INTERNAL MALIGNANCIES: A CLINICO-EPIDEMIOLOGICAL STUDY

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Abstract

Background: The skin can provide important clues to systemic disease and internal malignancies; recognition of these clues facilitates both early diagnosis and prompt treatment of internal malignancy. This study was undertaken with objectives of knowing the spectrum of cutaneous manifestation in patients suffering from various internal malignancies.

Methods: A total of 1000 patients with internal malignancies were screened in this study. Relevant investigations for diagnosis of internal malignancy and dermatological disorders were carried out.

Result: Skin changes were present in 644 cases (64.4%). Majority of the patients were in the age group of 40-60 years. In seven patients dermatological changes were the presenting sign of internal malignancy. Specific skin lesions were found in 16 cases (1.6%) out of which cutaneous metastases was present in 11 patients (1.1%), lymphoma cutis in 3 (0.3%), carcinoma en cuirasse and inflammatory carcinoma of breast in one patient each. Four hundred and eighty six patients had dermatological conditions under nonspecific category and 222 patients had therapy related cutaneous adversities. Few patients had more than one skin changes. Most common nonspecific skin lesions were paraneoplastic dermatoses (21.8%), fungal infection (9.0%), xerosis (6.6%) and viral infections (6.9%). Radiation dermatitis was the most common therapy related changes seen in 12.8% patients.

Conclusion: A patient of internal malignancy can present with specific or nonspecific skin changes and can be a presenting sign of internal malignancy. Elderly patients with unusual dermatological presentation and unresponsive to conventional therapy must be thoroughly investigated for internal malignancy.

Key words: cutaneous manifestation of malignancies, cutaneous metastasis

Introduction

Skin being the largest and most visible organ of the body, may provide a useful indicator for systemic diseases including malignancies. Internal malignancies may affect the skin both directly and indirectly. Direct involvement implies the presence of tumor cells within the skin which may occur either by local extension or by tumor metastasis through hematogenous and lymphatic routes.¹ Indirect involvement by internal malignancies includes, genodermatoses, paraneoplastic disorders, certain indirect cutaneous markers and adverse effects of either chemotherapy or radiotherapy.² These cutaneous markers of malignancy may occur before, at the same time as or after the diagnosis of the tumor.^{3,4} The timely diagnosis of these conditions is important as paraneoplastic dermatoses often cause considerable morbidity and in some instances may lead to detection of an otherwise clinically occult tumor at an early and treatable stage. To best of our knowledge, previous reports regarding incidence of cutaneous manifestations of internal malignancies are limited and include mainly case series, reviews and retrospective studies. To know the overall frequency and clinical profile of skin diseases associated with internal malignancies we conducted a study among the patients attending outpatient department of dermatology and regional cancer research and treatment center in Bikaner, North India.

Materials and Methods

One thousand patients of internal malignancies of various duration involving different organs, with or without treatment, were included in present study. Only those cases confirmed to be having internal malignancy were included. A detailed epidemiological data was collected; also history regarding malignancy and dermatological complaints, details about cutaneous changes, systemic examination, relevant investigations and treatment details of internal malignancy were recorded in a printed proforma. Skin biopsies for histopathology, scrapings for fungal infections and Gram staining, culture and sensitivity of purulent material were done whenever required. Diagnosis of malignancies was done by oncologist on the basis of clinical examination and relevant investigations including cytological, histopathological, biochemical, hormonal and radiological examination for respective malignancies. Clinical photographs of skin manifestations were also taken in patients having specific skin lesion.

Results

Out of 1000 patients studied, 477 (47.7%) were males and 523 (52.3%) were females. Majority of the patients were in the age group of 41-50 years (322; 32.2% patients) followed by 259 (25.9%) patients in 51-60 years age group. Only 4 patients were below 10 years (Fig. 1).

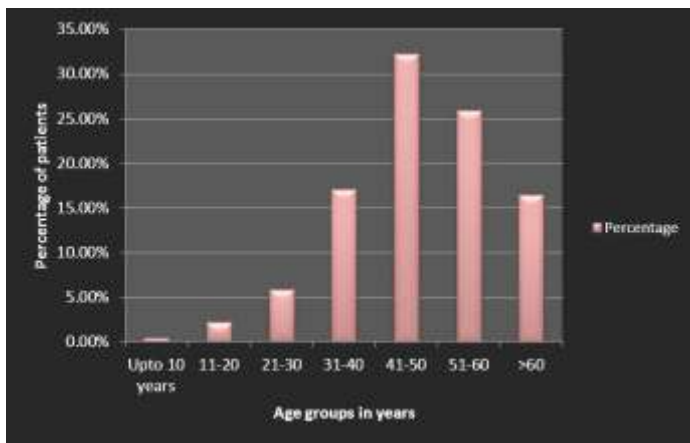


Figure 1: Distribution of cutaneous metastases



Figure 2: Cutaneous metastases in a breast carcinoma patient

Overall, most common malignancy was carcinoma breast (20.4%) followed by carcinoma cervix (19.6%), lymphoma (12.8%), leukaemia (6.7%), carcinoma oral cavity (6.6%), broncho-pulmonary carcinoma (6.4%) and carcinoma ovary (4.5%). The other malignancies encountered were carcinoma oesophagus, laryngeal carcinoma, gastro-intestinal malignancies, pharyngeal carcinomas, hepato-biliary carcinoma, carcinoma prostate, secondary metastasis with unknown primary, multiple myeloma, carcinoma of testes, urinary bladder, vagina, endometrium, brain and thyroid in decreasing order of frequency.

The malignancies observed in males were lymphomas in 125 (12.5%), broncho-pulmonary carcinomas in 62 (6.2%) and oral cavity malignancies in 56 (5.6%) cases, while in females there was carcinoma breast in 204 (20.4%), carcinoma cervix in 196 (19.6%) and carcinoma ovary in 45 (4.5%) cases.

Skin lesions were found in 644 (64.4%) patients out of 1000 cases studied. Out of 644 patients, in only seven (1.08%) patients cutaneous diseases were diagnosed before diagnosis of internal malignancy.

A total of 51 different types of dermatological manifestations were seen. We observed three categories of cutaneous changes in patients of internal malignancies; 486 patients had nonspecific changes whereas 222 cases were found to have treatment related skin changes and only 16 patients had specific dermatological lesions pertaining to malignancies. Thirty four patients suffered from more than one cutaneous finding.

Cutaneous metastases was the commonest specific lesion in 11(1.1%) patients followed by lymphoma cutis in 03 (0.3%), carcinoma en-cuirasse and inflammatory carcinoma of breast in one patient each (Fig. 2-5).

Out of 11 patients of cutaneous metastases, 8 patients showed contiguous metastases from underlying carcinoma while 3 patients had non-contiguous metastases occurring at a distant site. Most common site of cutaneous metastases was anterior chest wall in 4 cases and most common type of lesion was nodules in 7 cases. There were 3 cases of metastases, manifesting as presenting sign of internal malignancy (Table 1).

Most common non specific cutaneous lesions were paraneoplastic disorders affecting 218 (21.8%) patients followed by infections and infestations in 207 (20.7%) patients (Table 2).

Among them most common skin changes were fungal infections in 90 (9.0%), viral infections in 69 (6.9%), xerosis in 66 (6.6%) and pruritus in 39 (3.9%) cases. Other non-specific skin lesions included intertrigo, seborrheic dermatitis, lichenoid eruptions, perianal dermatitis, photodermatitis, eczematous eruption around nipple areola complex, pityriasis rosea, aphthous ulcers, icterus, koilonychia, lymphangiectasis, psoriasiform dermatitis and hidradenitis suppurativa.

Therapy related skin changes were encountered in a total of 222 (22.2%) cases. Radiation dermatitis was the most common in 12.8% patient (Fig. 6), alopecia in 74 (7.4%), flagellate pigmentation was found in 4 cases (Fig. 7).



Figure 3a: Lymphoma cutis in a patient with non-Hodgkin's lymphoma



Figure 3b: Lymphoma cutis in a patient with non-Hodgkin's lymphoma



Figure 4: Carcinoma en-cuirasse in a breast carcinoma patient.



Figure-5: Inflammatory-carcinoma-of-breast

S.No.	Type of the skin lesion	Number of skin lesions	Site of lesions	Time of diagnosis	Associated internal malignancy
(a) Contiguous metastases 8 cases					
01	Non tender, firm to hard nodules	Multiple	Anterior chest wall (inferior quadrant)	Before	Carcinoma breast
02	Fungated ulcerated plaque	Single	Anterior chest wall	Before	Carcinoma breast
03	Erythematous, nontender, firm, papulonodules and fungating ulcers	Multiple	Anterior chest wall	After	Carcinoma breast
04	Ulcerated nodule	Single	Anterior chest wall	After	Carcinoma breast
05	Nontender, skin colored nodule	Single	Axilla	After	Carcinoma breast
06	Hard pigmented plaque	Single	Pubic region	After	Carcinoma cervix
07	Nontender, hard grouped nodules	Multiple	Mental area	After	Carcinoma gingivo-buccal sulcus
08	Hard nodulo-ulcerative plaque	Single	Anterior neck, submandibular area	After	Laryngeal carcinoma
(b) Noncontiguous metastases 3 cases					
01	Nontender, hard skin colored nodules	Multiple	All over body	After	Nasopharyngeal carcinoma, NHL
02	Hard, subcutaneous nodule	Single	Neck	Before	Ca testis
03	Ulcerated plaque	Single	Penis	After	NHL

Table 1: Distribution of cutaneous metastases

Discussion

Skin is the window to systemic diseases and malignancies, as it is readily visible. Our study revealed a high prevalence (64.4%) of dermatological manifestations in patients suffering from internal malignancies which was greater than the observations of previous studies by Rajagopal et al⁵ (27.3%), Kilic et al⁶ (45.14%) and Ayyamperumal et al⁷ (6.93%). In present study females were more commonly affected than males in contrast to previous studies.^{5,6,7,8}

Skin is an infrequent site for metastases and the rates of metastases from internal malignant diseases to the skin varies between 0.7% and 9%.^{9,10} In present study incidence of cutaneous metastasis was 1.1% which is consistent with findings of Kilic et al.⁶ Cutaneous metastases commonly present as single or multiple nodules, which are always firm and rubbery to stony hard in consistency, often fixed to underlying tissue.¹⁰ In present study, 3 out of 8 cases with contiguous metastases and 1 out of 3 cases of noncontiguous metastases had multiple lesions. Beside the nodules, we also encountered plaques, papules and ulcers. Anterior chest wall was the most common site for metastases as reported in earlier studies conducted by Rajagopal et al,⁵ Ayyamperumal et al,⁷ Benmously et al,¹¹ Gul et al¹² and Kanitakis.¹³ The common primary malignancies reported with cutaneous metastases are lung cancers in males, and breast cancer in females.^{11,14,15} In our

Non-specific skin lesions	Number of patients (n)	Total of patients (%)
Paraneoplastic dermatoses	Papulovesicular disorders (12) <ul style="list-style-type: none"> • PPK (06) • Ichthyosis (05) • Bazex syndrome (01) Vascular disorders (27) <ul style="list-style-type: none"> • Erythema multiforme (08) • Vasculitis (06) • Purpura (04) • Necrotizing ulcers (04) • Flushing (02) • Thrombocytopenia (02) • Acral gangrene (01) Nail changes (56) <ul style="list-style-type: none"> • Hyperpigmentation (54) • Onychodystrophy (12) • Subungular hyperkeratosis (08) • Clubbing (02) Bullous disease (01) <ul style="list-style-type: none"> • Paraneoplastic pemphigus Miscellaneous (122) <ul style="list-style-type: none"> • Xerosis (66) • Generalized pruritus (22) • Localized pruritus (17) • Pruritic nodules (14) • Hyperpigmentation (03) 	218 (21.8%)
Infectious and infestations	<ul style="list-style-type: none"> • Pioderma (23) • Herpes zoster (57) • Herpes simplex (9) • Verruca vulgaris (3) • Tinea (65) • Candida (08) • Paronychia (11) • Pityriasis versicolor (06) • Scabies (15) 	197 (19.7%)
Other non-specific diseases	<ul style="list-style-type: none"> • Intertrigo (15) • Seborrheic dermatitis (11) • Lichenoid eruptions (11) • Perianal dermatitis (06) • Photodermatitis (06) • Eczematous eruptions around nipple areola complex (05) • Pityriasis rosea (03) • Aphthous ulcers (05) • Icterus (03) • Koilonychia (02) • Lymphangiectasis (01) • Psoriasisiform dermatitis (02) • Hidradenitis suppurativa (01) 	71 (7.1%)

Table2: Distribution-of-nonspecific-skin-changes

study carcinoma breast was found to be the commonest malignancy in females and Non-Hodgkin lymphoma in males. Risk of infections is generally increased in internal malignancies due to an immunocompromised status which is caused either by chemotherapy or disease process itself.¹⁶ Most frequent non-specific skin lesions encountered in our study were fungal infections in 90 (9.0%) patients which is similar to study conducted by Kilic et al.⁶ Herpes zoster was present in 5.7% cases and found to be disseminated, nondermatomal and ulcerated in most of the cases. It has been reported to be most often seen in hematological malignancies like chronic lymphocytic leukemia and lymphomas,^{5,6,17} while present study revealed carcinoma breast to be the most common malignancy

associated with herpes zoster.

Xerosis and nonspecific pruritus were found in 6.6% and 3.9% out of 1000 cases in our study. Among the malignant diseases, it was most often observed in leukemia and lymphomas. Goldman and Koh found pruritus in 35% of patients suffering from Hodgkin's disease.¹⁸ In our study xerosis was most commonly associated with carcinoma breast (1.8%) and carcinoma cervix (1.6%) while pruritus was associated with carcinoma cervix (0.7%) and carcinoma breast (0.6%). Lymphoma was the third most common malignancy with four cases. This difference may be due to more prevalence of the carcinoma of breast and cervix cases in our study. Up to 50% of the patients with pruritus without any obvious dermatological cause also have an underlying systemic disease process including malignancies.¹⁹ Persistent pruritus not otherwise explained by an obvious dermatologic condition should prompt an investigation for underlying systemic cause.

Palmoplantar keratoderma (PPK) both acquired and familial forms are also related with malignancies.^{20,21} We found acquired palmoplantar keratoderma in 6 patients, most commonly associated with hematological malignancy (0.4%) which was similar to study by Kilic et al.⁶ In one case palmoplantar keratoderma was presenting sign of carcinoma brain (astrocytoma). Kilic et al⁶ also reported diffuse hyperpigmentation in 0.28% patients with gastrointestinal carcinomas. In our study it was seen in hepato-cellular carcinoma, carcinoma lung and multiple myeloma with a prevalence of 0.3%.

In our study we encountered 27 (2.7%) cases of vascular disorders. These included erythema multiformae (0.8%), vasculitis (0.6%), purpura (0.4%), necrotizing ulcers (0.4%), flushing (0.2%), thrombophlebitis (0.2%) and acral gangrene (0.1%). In one case of vasculitis, Raynaud's phenomenon was also positive and it was associated with non-Hodgkin's Lymphoma (NHL). Cutaneous vasculitis is more likely to be associated with hematologic cancers.²² Flushing is most commonly associated with carcinoid syndrome of gastrointestinal and bronchial origin²³ but in our study one case was associated with carcinoma of testis and other was the case of acute lymphocytic leukemia (ALL).

Radiation dermatitis was the most common treatment related change in 12.8% patients followed by alopecia in 7.4% patients. Drug induced urticaria were found in 16 (1.6%) patients which was higher than the findings of Kilic et al⁶ study (0.42%) and Rajagopal et al⁵ study (0.66%). The antigens originating from various foci from the tumor may be urticariogenic. Flagellate pigmentation was found in 4 (0.4%) patients due to bleomycin which was almost similar with Rajagopal et al study (0.3%).

In addition, our study showed some cutaneous manifestations which had very low incidence such as scabies, intertrigo, seborrheic dermatitis, lichenoid eruptions, perianal dermatitis, photodermatitis, eczematous eruption around nipple areola complex, pityriasis rosea, aphthous ulcers, icterus, koilonychia, paraneoplastic pemphigus, Bazex' syndrome, lymphangiectasis and psoriasiform dermatitis.

Conclusion

We conclude that skin is an indicator of milieu interior. Skin manifestations might occur before, simultaneously or after the diagnosis of internal malignant disease. A patient presenting with dermatological manifestation with unusual presentation, long duration and resistant to treatment should be thoroughly investigated for internal malignancies.

Limitations

In the study all types of malignancies could not be covered so some cutaneous findings could have been missed and also genodermatoses were not covered.

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