Cutaneous manifestations of underlying malignancies presenting to a tertiary care teaching hospital

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ABSTRACT

Background: The skin is the largest organ in the human body. Many types of cancers can cause lesions to appear on the skin. An association between systemic malignancy and cutaneous manifestations has long been recognized. Recognition of these lesions is important for diagnosis at early stages and hence we analyzed the presentation of various skin manifestations in relation to various malignancies.

Methods: We did a prospective study from June 2016 to November 2017 on 50 confirmed cases of internal malignancy with skin manifestations attending the DVL and Oncology OPD of NRI Medical College and General Hospital and Cancer Institute. Detailed history, cutaneous examination, and investigations were done.

Results: Study population included 23 males and 27 females. The majority of cases (34%) were aged above 60 years. In females, reproductive tract malignancies were the highest (37%). In males, Non-Hodgkin's lymphoma (17.3%) and carcinoma rectum (17.3%) were commonly seen. Generalized pruritus was the major presenting cutaneous manifestation (16.4%). Paraneoplastic dermatoses were the most frequent cutaneous markers (67.2%).

Conclusions: Cutaneous manifestation from an internal malignancy is a relatively uncommon phenomenon. But at times, they may be the only presenting feature. Cutaneous paraneoplastic syndromes are important clinical markers that may precede or occur simultaneously or after the diagnosis of a given neoplasm and recognizing them may lead to a higher chance of cure and better prognosis for the patient.

Keywords: Cutaneous manifestations, Carcinoma, Internal malignancy, Neoplasm, Paraneoplastic dermatoses

INTRODUCTION

The skin is the largest organ in the human body.1 It has the ability to mirror the changes in the organism it envelopes. Many types of cancer can cause lesions to appear on the skin. An association between systemic malignancy and cutaneous manifestations has long been recognized. Cutaneous manifestations may be primary or secondary to an underlying malignancy.2 Cutaneous metastases may be the initial manifestation of some neoplasms.3 They may also be noticed concurrently with the diagnosis or following an established diagnosis.3 But cutaneous metastasis from an internal malignancy is a relatively uncommon phenomenon. The incidence reported varies from 0.7 to 10.4% among variously reported studies.2,5 The metastatic deposits indicate a higher stage of malignant disease and signify the lack of response of the malignant disease to treatment. The most frequent cancer that metastasizes to the skin, lung cancer in men and breast cancer in women.6 In comparison to metastasis in other organs, metastasis to the skin is easily visible and can be detected by the physician with relative ease which enhances and emphasizes the role of the clinician in appreciating various appearance of these
lesions. The cutaneous features that can occur are numerous and heterogeneous involving various etiologic agents and mechanisms. They may occur purely as direct tumor invasion of a skin or may be distant metastases as a part of paraneoplastic phenomena besides a number of inherited syndromes which are frequently associated with cutaneous as well as internal malignancies but are rare. These cutaneous manifestations can be specific or nonspecific. Cutaneous metastases, genodermatoses, paraneoplastic dermatoses and cutaneous markers on exposure to carcinogens are some of the specific lesions while infections and changes due to chemotherapy and radiotherapy are nonspecific. Generalized xerosis and pruritus are common cutaneous manifestations of advanced malignant disease. Recognition of these lesions is important as they help in diagnosing neoplasms at early stages, hence resulting in better outcomes. With increase in the incidence of cancer in India in the past few decades, because of changes in lifestyle-related behavior, it is essential to recognize neoplasms at early stages. But the literature in India is very limited with regards to prevalence of these cutaneous markers in neoplasms. Hence we carried out our study with the objective of determining the frequency of various cutaneous manifestations in cases with internal malignancies. We have also attempted to study the incidence of both specific and nonspecific skin lesions occurring in different malignancies. Prevalence of cutaneous markers in genetic syndromes predisposed to malignancies was also studied.

METHODS

Source of data

The study was conducted in NRI Medical College and General Hospital and Cancer Institute from June 2016 to November 2017. All cases confirmed with malignancy with skin changes attending the Dermatology, Venereology and Leprosy and Oncology Outpatient departments at NRI medical college and General hospital and cancer institute were recorded. 50 cases were included in the present study.

Study population

Patients of all age groups and both sexes with malignancy were eligible for the study.

Inclusion criteria

Inclusion criteria were cases confirmed to be malignant with skin manifestations were included; the course of malignancy and the course of skin disease should run a parallel course; the relation between the skin disease and the malignancy should be uniform.

Exclusion criteria

Exclusion criteria were cases confirmed with malignancy, without skin changes were excluded; cases with cutaneous complications of treatment were excluded; cases with HIV seropositivity were excluded; cases with any other disease altering or causing the cutaneous dermatosis were excluded.

Study methodology

The present study was a prospective and clinical study. Ethical clearance was obtained from the institution before the commencement of the study. Consent was taken from all the subjects after explaining the purpose of the study.

Between June 2016 to November 2017, all the cases confirmed with malignancy with skin manifestations, attending the DVL and Oncology OPD of NRI Medical College and General Hospital and Cancer Institute were asked to participate in the study. The patients fulfilling the inclusion and exclusion criteria were noted. Data regarding the skin manifestation and malignancy, age and sex were recorded for all patients. It includes duration and history of skin manifestation and internal malignancy, cutaneous and systemic examination. Investigations to confirm the malignancy like biopsy, bone marrow aspiration cytology, CT scan, CECT scan, ultrasound scan, peripheral smear, fine needle aspiration cytology, immunohistochemistry and tumor markers were done and findings were recorded. Detailed cutaneous examination and investigations to confirm the skin marker was done wherever necessary.

Statistical methods

Age, gender, carcinoma, cutaneous markers, cutaneous manifestations, carcinomas and cutaneous dermatoses were considered as the outcome variable.

Descriptive analysis was carried out by frequency and proportion for categorical variables. P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

A total of 50 subjects were included in the analysis. Among the study population, 3 (6%) participants were aged less than 20 years, 10 (20%) were 21 to 30 years, 5 (10%) were aged 31 to 40 years, 9 (18%) were aged 41 to 50 years, 6 (12%) were 51 to 60 years and 17 (34%) were aged 61 and above. Among the study population male participants were 23 (46%) remaining 27 (54%) were female participants (Table 1).

In male subjects, 5 (21.8%) had respiratory tract malignancies. The number of gastrointestinal tract malignancies, lymphomas, leukemias, CTCL, sinonasal carcinoma, astrocytoma and carcinoma urinary bladder was 5 (21.8), 5 (21.8%), 4 (17.4%), 1 (4.3%), 1 (4.3%) and 1 (4.3%) respectively in male population. In female subjects, 10 (37%) had respiratory tract malignancies. The number of carcinoma breast, carcinomas of oral
In our study, some of the subjects presented with multiple markers. Hence 50 study subjects had more than 50 cutaneous manifestations or markers (n=61). Among the study population, 41 (82%) people had paraneoplastic dermatoses. The number of nonspecific manifestations, genodermatoses, direct tumor spread and cutaneous metastasis was 9 (18%), 5 (10%), 3 (6%) and 3 (6%) respectively. Among the study population, 11(22%) had generalized pruritus. The number of infections, seborrheic keratosis, xeroderma pigmentosum, generalized xerosis, acquired ichthyosis, clubbing, acanthosis nigricans, cutaneous metastasis, paget’s disease, neurofibromatosis, macular amyloidosis, peau d’orange appearance, paraneoplastic pemphigus, lymphomatoid papulosis, lichenoid eruption, insect bite rash and astecotic eczema were 9 (18%), 8 (16%), 4 (8%), 4 (8%), 4 (8%), 4 (8%), 3 (6%), 2 (4%), 1 (2%), 1 (2%), 1 (2%), 1 (2%), 1 (2%), 1 (2%), and 1 (2%) respectively (Table 3).

**Table 3: Descriptive analysis of cutaneous markers in the study population (n=50).**

| Cutaneous markers | Frequency | Percentage (%) |
|-------------------|-----------|----------------|
| Paraneoplastic dermatoses | 41 | 82 |
| Nonspecific manifestations | 9 | 18 |
| Genodermatoses | 5 | 10 |
| Direct tumor spread | 3 | 6 |
| Cutaneous metastasis | 3 | 6 |
| **Cutaneous Manifestations** | | |
| Generalized pruritus | 11 | 22 |
| Infections | 9 | 18 |
| Seborrheic keratosis | 8 | 16 |
| Xeroderma pigmentosum | 4 | 8 |
| Generalized xerosis | 4 | 8 |
| Acquired ichthyosis | 4 | 8 |
| Clubbing | 4 | 8 |
| Acanthosis nigricans | 4 | 8 |
| Cutaneous metastasis | 3 | 6 |
| Paget’s disease | 2 | 4 |
| Neurofibromatosis | 1 | 2 |
| Macular amyloidosis | 1 | 2 |
| Peau d’orange appearance | 1 | 2 |
| Paraneoplastic pemphigus | 1 | 2 |
| Lymphomatoid papulosis | 1 | 2 |
| Lichenoid eruption | 1 | 2 |
| Insect bite rash | 1 | 2 |
| Asteototic eczema | 1 | 2 |

*Some of the subjects presented with multiple markers.*
In this study, carcinoma cervix was the most common malignancy associated with cutaneous markers such as generalized pruritus, xerosis, seborrheic keratosis, tinea unguium and manuum. A case of Neurofibromatosis presented with carcinoma cervix. The next highest number of malignancies associated with cutaneous dermatoses was carcinomas of breast, rectum and non-Hodgkin's lymphoma. Carcinoma of the breast was noted with peau d’orange appearance, Paget's disease, cutaneous metastasis and seborrheic keratosis. All cases of direct tumor spread to the skin were of carcinoma breast. Macular amyloidosis, acquired ichthyosis, acanthosis nigricans and seborrheic keratosis was observed in carcinoma rectum cases. Non-Hodgkin's lymphoma was seen along with paraneoplastic pemphigus and lymphomatoid papulosis which were confirmed by histopathology. Other manifestations associated were generalized pruritus and pyoderma. Hodgkin's lymphoma, chronic myeloid leukemia, and carcinomas of lung and ovary, ranked the third most common malignancies. Hodgkin's lymphoma was associated with extensive warts, seborrheic keratosis, generalized pruritus and atopic eczema. 2 out of 3 cases of bronchogenic carcinoma were seen with grade III clubbing. The other markers were acquired ichthyosis, generalized pruritus, and xerosis. Carcinoma ovary cases presented with generalized pruritus, herpes zoster, and acanthosis nigricans. Lichenoid eruption, acquired ichthyosis, and herpes zoster were observed with chronic myeloid leukemia. Acanthosis nigricans and seborrheic keratosis were seen in association with astrocytoma. Carcinoma urinary bladder cases had seborrheic keratosis, generalized pruritus, and xerosis. Secondary cutaneous metastasis to the skin near the right clavicular region was the presenting feature in a case of carcinoma oesophagus. Hepatocellular carcinoma, carcinoma of gallbladder and acute myeloid leukemia were associated with generalized pruritus. There were four cases of Xeroderma Pigmentosum which presented with different malignancies like carcinoma of the maxillary sinus, lower lip, parotid and acute lymphocytic leukemia. Acanthosis nigricans as a marker was found in a case of sinonasal carcinoma. CTCL was observed with generalized pruritus and xerosis. A case of papillary carcinoma of thyroid had cutaneous metastasis, tinea corporis, and cruris. Oral candidiasis was associated with carcinoma tongue and gestational trophoblastic tumor. Insect bite rash was seen in a case of chronic lymphocytic leukemia. Clubbing of grade III with parrot beak appearance was a manifestation in carcinomas of trachea and larynx. Carcinoma of trachea also had pityriasis versicolor.

DISCUSSION

Skin often mirrors changes in the internal milieu. The single most basic biologic process that characterizes a malignant tumor is the ability to produce secondary deposits (metastases) at distant sites. The skin is an infrequent site for metastasis. But malignancies which affect internal organs may display cutaneous manifestations and may also be the presenting symptom or sign of underlying malignancy. Cutaneous metastasis from an internal malignancy is usually rare and may be an indication of disease at the later stage. An association between systemic malignancy and cutaneous manifestations has long been recognized. The cutaneous features that can occur are numerous and heterogeneous and are a result of metastases to the skin or from chemicals or hormones that are secreted by the tumor, resulting in identifiable cutaneous syndromes or inflammatory dermatoses, benign or malignant proliferative lesions. In cases of internal malignancy, cutaneous lesions may represent only the tip of the iceberg. But increased clinician awareness regarding the associations between these lesions and internal malignancy or inherited syndromes can facilitate screening and early diagnosis. Hence we did a prospective study from June 2016 to November 2017 on 50 confirmed cases of internal malignancy with skin manifestations attending the DVL and Oncology OPD of NRI Medical College and General Hospital and Cancer Institute after getting clearance from the institutional ethics committee. In our study population, 23 were males and 27 were females accounting for 54% of total cases. Ayyamperumal et al did their study on 52 subjects with skin changes similar to our study. Our study population was comparable in terms of sex distribution with that of Rajagopal et al with 52% males and 48% females while Ayyamperumal et al in their study included 65% males and 35% females. In our study, there was no significant difference in the proportion of the sex of the subjects presenting with cutaneous manifestations. Cutaneous metastases can arise at any age. However, in keeping with the increased incidence of malignant disease in later life, most cutaneous metastases occur after the fifth decade as reported by Rajagopal et al and Ayyamperumal et al in their study included 65% males and 35% females. In our study, the most common malignancy encountered was carcinoma cervix which constituted up to 12% of total cases, followed by carcinoma breast, rectum, and non-Hodgkin's lymphoma each contributing to 8%. In contrast to the present study carcinoma cervix (5.6%) was the fourth common malignancy as stated by Ayyamperumal et al. In their study, the most common malignancies were leukemias and lymphomas (17.2%) followed by carcinoma breast (13.46%). The higher rate of reproductive tract malignancies in our study might be due to the early age at marriage and parity of the females in this part of the country. It also indicates an increased incidence of human papilloma virus infection. In our study, in females, reproductive tract malignancies were the highest with 37.1% cases, the next being carcinoma breast (14.8%) and carcinoma oral cavity (11.1%) while Rajagopal et al and Ayyamperumal et al in their study reported carcinoma of the breast to be the commonest. In males, non-Hodgkin's lymphoma (17.3%), carcinoma
rectum (17.3%) and carcinoma lung (13%) were commonly seen. Increased incidence of carcinoma lung in males in our study may be due to the widely prevailing smoking habits. Similar to our study, Rajagopal et al and Ayyamperumal et al also reported lymphoma to be the commonest in males. Internal malignancies lead to cutaneous manifestations through immunological, metabolic and metastatic consequences. These manifestations can be either specific malignant infiltrates or non-specific lesions. Specific infiltrates that show characteristic malignant cells on histopathological examination can occur due to contiguous or non-contiguous spread. Non-specific lesions can be due to infections, non-infective conditions and changes due to chemotherapy.

In our study, generalized pruritus was the major presenting cutaneous manifestation accounting for 22% of the subjects. Seborrheic keratosis ranked next with 16%. Generalized pruritus was observed in various neoplasms like acute myeloid leukemia, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, hepatocellular carcinoma, carcinoma of the gallbladder, cutaneous T cell lymphoma, lung carcinoma, carcinoma urinary bladder, carcinoma cervix and carcinoma ovary in our study. In concurrence with the present study, Kilic et al reported that generalized pruritus was associated with hematological malignancies and also reported generalized pruritus to be the most frequent manifestation. Similar to our study, Ayyamperumal et al reported pruritus associated with hepatocellular carcinoma, polycythemia vera, and carcinoma stomach while Rajagopal et al reported pruritus with Hodgkin’s lymphoma and Non-Hodgkin’s lymphoma. Pruritus was the second and the third common manifestation in the studies done by Ayyamperumal et al and Rajagopal et al respectively. Both of them reported cutaneous metastasis to be the commonest cutaneous marker which was seen only in about 4.9% of our study subjects while paraneoplastic dermatoses were the most frequent cutaneous marker in our study seen in about 82% of subjects. This difference could have been due to the increase in awareness among the people and early presentation to the hospital because of availability of better diagnostic and therapeutic modalities in our study setting. Hence the subjects presented with paraneoplastic dermatoses most often rather than secondary cutaneous metastasis to the skin.

Direct tumor spread to the skin or contiguous metastasis was seen in 3 cases of breast carcinoma, which showed peau ‘d’ orange appearance in 1 case and Paget’s disease in other 2 cases. These findings were in accordance with findings of the study by Brownstein et al, Rajagopal et al and Ayyamperumal et al who showed that breast carcinoma was the most common cause of contiguous metastasis to the skin. Cutaneous metastasis was also seen in a case of carcinoma of the oesophagus which presented as a nodule over the right clavicular region and papillary carcinoma of the thyroid with nodule to the back of the neck in our study. Rajagopal et al also reported a case of carcinoma oesophagus with secondary metastasis as a nodule over right arm and also a case of carcinoma of thyroid with nodules over the right cheek. The results of these and our study imply that when a patient presents with an eczematous lesion or an ulcer or any nonspecific lesion over the breast or skin, an underlying carcinoma should be suspected. In our study, Generalized xerosis was observed in cutaneous T cell lymphoma, carcinoma lung, carcinoma cervix and carcinoma urinary bladder which was in contrast to that observed by Kilic et al, who reported them in association with hematological malignancies. Non-Hodgkin’s lymphoma was the most frequent in subjects with Non-contiguous metastasis in the study by Ayyamperumal et al while in our study NHL presented with various manifestations in 4 cases with each subject presenting with pyoderma, paraneoplastic pemphigus, generalized pruritus, lymphomatoid papulosis. Xeroderma Pigmentosum was seen in 4 cases in the current study, associated with carcinoma parotid, carcinoma lower lip, carcinoma maxillary sinus and acute lymphocytic leukemia while Kraemer et al reported that there was an increase in predisposition to neoplasms of oral cavity, brain, and eye in xeroderma pigmentosum patients while Somaono et al reported that there was a 2000 fold increased risk of basal cell carcinomas and squamous cell carcinomas of head and neck in these subjects. In our study, nonspecific manifestations were seen in 18% of subjects. The nonspecific markers which include infections noted in the study were herpes zoster, extensive warts, pyoderma, dermatophytosis, onychomycosis, oral candidiasis and pityriasis versicolor. Herpes zoster was the most common nonspecific cutaneous manifestation noted in the study which was associated with chronic myeloid leukemia and carcinoma ovary. In contrast to this study, herpes zoster which was the most common nonspecific manifestation in the study by Rajagopal et al was associated with carcinoma tongue, Hodgkin’s and Non-Hodgkin's lymphoma and they also reported 7 cases of dermatophytosis in their study. In our study, Paraneoplastic dermatoses occurred in (41) cases, genodermatoses in 5 cases, secondary cutaneous metastasis and contiguous metastasis to skin occurred in 3 cases each. The paraneoplastic dermatoses can occur even without an underlying malignancy. Thus, the skin manifestations that are extensive and do not subside with conventional treatment measures should warrant intensive diagnostic modalities in suspicion of a silent neoplasm. So, there is a need for physicians to be well educated about usual as well as unusual presentations and associations of these dermatoses.

Skin is an infrequent site of metastasis and skin that is damaged allows for the malignant cells to lodge and proliferate locally. Sometimes, cutaneous metastasis may be the only presenting feature. The type of histological pattern seen can be a clue to the organ of origin giving rise to the cutaneous metastasis. Hence lesions that do not fit into any disease specifically should be biopsied for histological confirmation and the probability of an
underlying malignancy should be kept in mind. Whatever the association, inspection of the skin remains an essential part of the complete physical examination and may also be useful for monitoring the activity and response to treatment of malignant disease.

As most of the carcinomas run a chronic course, a study period of 18 months may be short for a full evaluation and follow up. Our study was a descriptive study and hence the causality or temporal association could not be proved. Skin involvement in cancer patients may be biologically unrelated to the tumor occasionally, and instead may only be a part of a well defined inherited syndrome featuring an increased incidence of internal cancer.

In the future, studies with larger sample size and longer follow up are needed with a specific focus on the duration of malignancies and the cutaneous markers associated, the time span between the appearance of dermatoses and carcinoma.

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