

A CLINICAL STUDY OF PARANEOPLASTIC DERMATOSES IN INTERNAL MALIGNANCY

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ABSTRACT**BACKGROUND**

Paraneoplastic dermatoses are rare dermatological entities that are difficult to diagnose. However, when identified, facilitate the diagnosis of underlying malignancy. Malignancies affecting the internal organs display cutaneous manifestations in the form of nonspecific lesion (Paraneoplastic dermatoses).

This aim is to study the frequency with which paraneoplastic dermatoses are associated with internal malignancy.

MATERIALS AND METHODS

100 cases of internal malignancy confirmed by biopsy were taken for study from August, September, October, November 2013 -4 months' duration. These patients were attending Oncology Outpatient and Inpatient Department at Father Muller Medical College Hospital, Mangalore.

RESULTS

Paraneoplastic dermatoses seen in 19 cases. Acquired ichthyosis was common and seen in 10 cases, generalised pruritus seen in 3 cases, herpes zoster seen in 3 cases. Acanthosis nigricans, palmar plantar keratoderma, petechial haemorrhage seen one each in carcinoma breast, carcinoma lung, acute lymphatic leukaemia respectively. Herpes zoster shows multidermatomal involvement in one case. One case of acute lymphatic leukaemia had both generalised pruritus and acquired ichthyosis

CONCLUSION

Paraneoplastic dermatoses have associated with neoplasms. Recognition of dermatoses may lead to early diagnosis and treatment of underlying malignancy.

KEYWORDS

Paraneoplastic Dermatoses, Skin Manifestations, Malignancy.

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BACKGROUND

Paraneoplastic dermatoses are ailments that arise in association with malignancy elsewhere in the body. These dermatoses represent a heterogeneous group of clinical manifestations, which might appear in association with a malignancy. They are the second most common paraneoplastic disease after the endocrinological paraneoplastic syndromes. Paraneoplastic dermatoses are characterised by diverse range of cutaneous changes, some of which appear benign. Therefore, they may go unnoticed by the physician.¹

The criteria for a certain set of skin diseases to be considered as paraneoplastic dermatoses is shown in Table 1. In fact, the first two criteria (Major criteria) are sufficient to consider a dermatoses as paraneoplastic.¹

The frequency with which some benign dermatoses are associated with underlying malignancy suggests that this is not random; however, in most cases it is difficult to demonstrate a cause effect relationship with primary tumour. The current literature suggests that these phenomena are the result of interaction between the tumour, some mediator factors and the involved tissue. The mediators are generally polypeptides, hormones, cytokines, antibodies and growth factors. These mediator factors interfere with cell to cell communication, resulting in an increase of cellular activity. More than 40 dermatoses are found to be reported as neoplastic. The paraneoplastic dermatoses might be categorised in three different groups (Table 2).

Skin is indirectly involved in paraneoplastic dermatoses.²

Paraneoplastic diseases may be defined as hormonal, neurological or haematological disturbances and as clinical and biochemical imbalances associated with the presence of malignancies without direct association with primary tumour invasion or metastasis. The skin may provide the doctor with signs that are suggestive of systemic disease, contributing to the diagnosis of many diseases, including malignancies. Skin may be directly or indirectly involved in malignancy. Direct involvement implies the presence of tumour cells in the skin caused by direct tumour extension or metastasis. Indirect involvement is caused by verity of factors (Inflammatory, proliferative or metabolic factors) related to neoplasia, such as polypeptides, hormones, cytokines, antibodies or growth

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factors that act as mediators, interfering with cell communication and consequently, with its activity. In this case, there is no presence of neoplastic cells in the skin, and this involvement is considered as dermatologic paraneoplastic syndrome.³

Type of Criteria	Diagnostic Criteria
Major	Both conditions begin almost at the same time.
Major	Both conditions follow a parallel course.
Minor	Neither the presentation nor the course of the disease depends on each other.
Minor	A specific tumour produces a characteristic cutaneous manifestation
Minor	The dermatoses are not common in general population
Minor	There is high percentage of association between both conditions

Table 1. Curth's Criteria to Diagnose Paraneoplastic Dermatoses

Type of Paraneoplastic Dermatoses	Characteristic	Paraneoplastic Dermatoses
Mandatory	Always or very frequently are Paraneoplastic	Acanthosis Nigricans, Erythema Gyratum Repens, Paraneoplastic Acrokeratosis, Hypertrichosis Lanuginosa Acquisita, Necrolytic Migratory Erythema, Paraneoplastic Pemphigus.
Optional	Appearance may or may not be Related to Malignancy	Migratory Thrombophlebitis, Sweet's Syndrome, Dermatomyositis, Pyoderma Gangrenosum, Erythema Annular Centrifugum, Leser-Trelat Syndrome
Occasional	Sign and Symptoms Rarely Appear related to Malignancy	Amyloidosis, Cryoglobulinaemia, Hyperpigmentation, Ichthyosis, Herpes Zoster.

Table 2. Classification of Paraneoplastic Dermatoses

This review focuses on the recognition, diagnosis, and clinicopathologic findings of cutaneous changes associated with malignancies. A Medline search (Of reference words paraneoplastic and dermatosis or skin) and a survey of major review articles yield more than 40 dermatoses reported to be paraneoplastic. We have selected the 16 dermatoses that have strongest association with internal malignancy (i.e. the highest apparent causal relationship or the mostly closely parallel course) and that specific enough clinically and pathologically for practical dermatologic or dermatopathologic recognition (Table 3). In addition, as indicated by their frequent mention in the dermatological literature, a few entities are included for their historical significance to the field. We have excluded conditions that are too nonspecific to be of diagnostic value.

Relative time of presentation and the demographics of each condition are specifically addressed in the context of the internal malignancy.

1	Acanthosis Nigricans	2	Acquired Ichthyosis	3	Triple Palm	4	Leser-Trelat Sign
5	Bazex Syndrome	6	Dermatomyositis	7	Paraneoplastic Pemphigus	8	Erythema Gyratum Repens
9	Necrolytic Migratory Erythema	10	Sweet's Syndrome	11	Pyoderma Gangrenosum	12	Multicentric Reticulo Histocytosis
13	Necrobiotic Xantho-granuloma	14	Scleromyxoedema	15	Cutaneous Amyloidosis	16	Hypertrichosis Lanuginosa Acquisita

Table 3. Paraneoplastic Dermatoses in Internal Malignancy

For conceptual organisation, the paraneoplastic dermatoses discussed have been classified into following clinicopathological categories- 1) Paposquamous (Epidermal proliferative) disorders- Acanthosis nigricans, acquired ichthyosis, triple palm, Leser-Trelat sign, Bazex syndrome. 2) Interface dermatitides- Dermatomyositis, paraneoplastic pemphigus. 3) Reactive erythema- Erythema gyratum repens, necrolytic migratory erythema. 4) Neutrophilic dermatoses- Sweet's syndrome, pyoderma gangrenosum. 5) Dermal proliferative disorder- Multicentric reticulohistocytosis, necrobiotic xanthogranuloma. 6) Depositive disorder- Scleromyxoedema, cutaneous amyloidosis. 7) Other dermatoses- Hypertrichosis lanuginosa acquisita.

MATERIALS AND METHODS

Ethical committee approval from the institution was obtained and informed consent from the patient was taken.

100 cases of histopathologically proved malignancy of all age group of varying duration involving different body organs attending oncology outpatient and inpatient department were randomly taken for the present study. Detailed history about duration of malignancy and skin changes were recorded. Cutaneous and systemic examination was done; findings were recorded in proforma for analysis and interpretation of data. Data collected is compared with similar studies conducted elsewhere.

RESULTS

Out of 100 malignancy, 19 cases of paraneoplastic dermatoses were seen (19%), 10 male, 9 female. 5 patients were in the age group of 60-70 years, 4 patients were in the age group of 50-60, 4 patients' age was between 40-50 years, 5 patients were in the age group of 30-40 years, 1 patient age was between 20-30 years, Paraneoplastic dermatoses seen in 19 cases. 1) Acquired ichthyosis was commonly seen in 10 cases. 4 in Hodgkin's lymphoma, 1 in non-Hodgkin's lymphoma, 2 patients in acute lymphatic leukaemia, 2 in carcinoma of stomach, 1 in carcinoma of oesophagus. 2) Generalised pruritus seen in 3 cases, one each seen in hepatocellular carcinoma, acute lymphatic leukaemia, carcinoma pancreas. 3) Herpes zoster seen in 3 cases, 2 in carcinoma breast, 1 in carcinoma cervix. 4) Acanthosis nigricans, palmar plantar keratoderma, petechial haemorrhage seen one each in carcinoma breast, carcinoma lung, acute lymphatic leukaemia respectively.

Herpes zoster multidermatomal involvement seen in one case. One case of acute lymphatic leukaemia had both acquired ichthyosis and generalised pruritus.

DISCUSSION

The clinical characteristics of paraneoplastic dermatoses in our country seem to be same as that of developed countries.^{1,4,5}

Three non-specific skin changes were found with increased predilection in patients with malignant diseases as compared to controls and those were acquired ichthyosis, generalised pruritus and herpes zoster. All the cases of acquired ichthyosis and generalised pruritus were common in Hodgkin’s lymphoma as reported by other workers.^{1,2,5,6,7,8,9}

Acanthosis nigricans maligna was the first dermatoses associated with malignant process being perhaps the best known among all association.³

In our study, the more common paraneoplastic dermatoses was acquired ichthyosis seen in 10 cases. Four seen in Hodgkin’s lymphoma, one in non-Hodgkin’s lymphoma, two in acute lymphatic leukaemia, two in carcinoma stomach, one in carcinoma oesophagus. Correlates with study of Rajgopal et al. Table 4.

Of the nonspecific lesions, herpes zoster was the most common (11 patients) followed by generalised pruritus, multiple eruptive seborrhoeic keratoses, bullous disorders, erythroderma, flushing, purpura, systemic lupus erythematosus, pyoderma gangrenosum, insect bite allergy and lichenoid dermatitis.⁷

In this study, generalised pruritus seen in three cases .One each in hepatocellular carcinoma, acute lymphatic leukaemia, carcinoma Pancreas. Correlates with study of Rajagopal et al, A. Ayyamperumal et al. One case of acute lymphatic leukaemia shows both acquired ichthyosis and generalised pruritus.

Among the non-specific skin manifestations with internal malignancy, herpes zoster (27%) came first. carcinoma of breast was the most common malignancy associated with herpes zoster, while carcinoma of the cervix (18%) was the second. Among 11 patients, 6 had single dermatomal involvement, 2 had disseminated and 3 had multidermatomal involvement. According to literature, herpes zoster is commonly associated with underlying malignant disease.^{7,8}

In this study, herpes zoster seen in three cases. Two in carcinoma breast, one in carcinoma cervix. One case shows multidermatomal involvement. Correlates with study of A. Ayyamperumal et al. Acanthosis nigricans associated with malignancy was reported by Pollitzer S.¹⁰ More than 1000 cases have been reported¹¹ by Seduno HO et al.

In our study, acanthosis nigricans, palmar plantar keratoderma, petechial haemorrhage seen one case each in carcinoma breast, carcinoma of lung, acute lymphatic leukaemia respectively,^{3,5} correlates with study of Silva JA et al, Chung VQ et al.

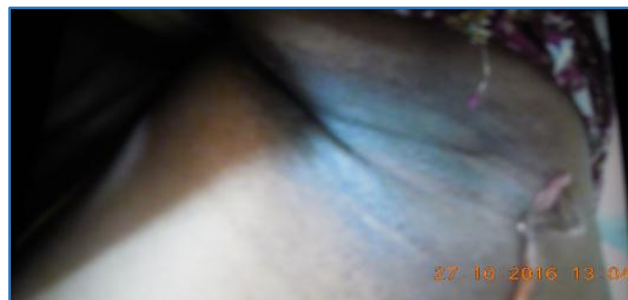


Figure 1. Acanthosis Nigricans in Carcinoma of Breast



Figure 2. Acquired Ichthyosis in Hodgkin’s lymphoma



Figure 3. Acquired Ichthyosis of Forearm in Acute Lymphatic Leukaemia

Sl. No.	Dermatological Diagnosis	Age (Years)	Gender	Malignant Tumour
1	Acquired Ichthyosis	51	Male	Hodgkin’s Lymphoma
2	Acquired Ichthyosis	61	Male	Hodgkin’s Lymphoma
3	Acquired Ichthyosis	61	Male	Hodgkin’s Lymphoma
4	Acquired Ichthyosis	62	Male	Hodgkin’s Lymphoma
5	Acquired Ichthyosis	25	Female	Non-Hodgkin’s Lymphoma
6	Acquired Ichthyosis	56	Male	Ca Oesophagus
7	Acquired Ichthyosis	33	Male	ALL
8	Acquired Ichthyosis	58	Male	Ca Stomach
9	Acquired Ichthyosis	59	Male	Ca Stomach
10	Acquired Ichthyosis	31	Female	ALL

11	Generalised Pruritus	37	Female	Ca Pancreas
12	Generalised Pruritus	45	Female	Ca Stomach
13	Generalised Pruritus	36	Male	ALL
14	Herpes Zoster	45	Female	Ca Breast
15	Herpes Zoster	47	Female	Ca Breast
16	Herpes Zoster	61	Female	Ca Cervix
17	Acanthosis Nigricans	47	Female	Ca Breast
18	PPK	67	Male	Ca Lung
19	Petechial Haemorrhage	36	Male	ALL
Table 4. Paraneoplastic dermatoses and underlying malignancy				

CONCLUSIONS

Paraneoplastic dermatoses is important to both clinician and pathologist alike as recognition of such condition offers opportunity for early diagnosis and treatment of internal malignancy and monitoring for tumour recurrence and insight into pathophysiology which may yield possible clue to treatment.

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