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RESEARCH ARTICLE
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A CLINICOEPIDEMIOLOGICAL STUDY OF CUTANEOUS MANIFESTATIONS IN PATIENTS WITH INTERNAL MALIGNANCY AT A TERTIARY CARE CENTRE

Dr. Meet Patel[1], Dr. Manisha Nijhawan[2], Dr. Arvind Verma[3], Dr. Sankalp Awasthi[4*]

[1]Resident, Dept. of Dermatology, Venereology and Leprology, Mahatma Gandhi Medical College and Research Institute, Jaipur, Rajasthan, India
[2]Professor and Head, Dept. of Dermatology, Venereology and Leprology, Mahatma Gandhi Medical College and Research Institute, Jaipur, Rajasthan, India
[3]Professor and Head, Dept. of Dermatology, Venereology and Leprology, Jaipur National University, Jaipur, Rajasthan, India
[4*]Professor, Dept. of Dermatology, Venereology and Leprology, Mahatma Gandhi Medical College and Research Institute, Jaipur, Rajasthan, India

***Corresponding Author:** Dr. Sankalp Awasthi
*Professor, Dept. of Dermatology, Venereology and Leprology, Mahatma Gandhi Medical College and Research Institute, Jaipur, Rajasthan, India

Abstract

Background:
The skin, as the largest organ of the body, can display changes indicative of internal malignancies. These changes, affecting the skin, hair, nails, and mucosa, may be specific or non-specific. They can signal early malignancy, the progression of malignancies, or a compromised immune system. Such manifestations may arise from various causes, including paraneoplastic reactions, skin metastasis, inflammation, infections, or genetic syndromes. This study aims to analyze the patterns of skin conditions associated with internal malignancies.

Material and methods:
Patients with internal malignancies coming to the Dermatology outpatient department or referred by Oncologists with cutaneous manifestations were recruited for this study. After obtaining written consent, a thorough mucocutaneous examination and investigations for malignancies were done. Demographic data was collected, and the frequency and percentage of cutaneous manifestations associated with internal malignancies were calculated.

Results:
Among the 3,741 patients with internal malignancy, 1.47% (55) exhibited cutaneous manifestations. The age of these patients ranged from 3 to 75 years**,** with a mean age of 46.34 years**.** Of the 55 patients showing cutaneous manifestations**,** 54.55% were males and 45.45% were females**.** Overall**,** the most common malignancies observed in patients with cutaneous lesions were leukaemias and lymphomas**,** which accounted for about 34.54% (19 patients)**.** Herpes zoster was the most common dermatosis, observed in 25.45% (14 patients), followed by Herpes labialis in 9.09% (5 patients)**.**

Conclusion:
The study yielded clinically significant insights into specific and non-specific skin manifestations associated with internal malignancies. By understanding these dermatological associations, medical practitioners can enhance their diagnostic accuracy and tailor treatment strategies more effectively.

Keywords: Herpes labialis, Herpes zoster, Leukaemia, Lymphomas, Malignancy, Paraneoplastic reactions

Introduction :
Skin is the largest organ of the human body and can reflect the functioning of internal organs. Manifestations in the skin can be the first sign of a more severe problem, such as an internal malignancy. Several systemic malignancies can present with cutaneous manifestations. Cutaneous manifestations may be the first sign of internal malignancy in some patients. These cutaneous manifestations can arise through direct mechanisms, including local invasion or hematogenous and lymphatic metastasis, or indirectly via paraneoplastic syndromes, which may involve aberrant hormone production or immune-mediated processes or maybe by other poorly understood mechanisms. The incidence varies from 0.7 to 10.4%, as per different studies.[1]
The study aimed to determine the incidence of cutaneous manifestations in malignancy patients, the cause of these manifestations, and the socio-demographic variables associated with them.

Materials and Methods:
It was a cross-sectional observational study approved by an institutional ethical committee with the reference MGMCH/IEC/JPR/2020/74. All diagnosed patients of internal malignancies with skin manifestations attending the Dermatology outpatient department or those referred by the Oncology department from January 2020 to June 2021 were included. Patients not ready to give written consent were excluded from the study. Demographic data and detailed history (clinical, past, family and drug history) were collected. Clinical examination was carried out and photographs were taken with consent. Relevant investigations were carried out.

Results:

Of the 3,741 patients diagnosed with internal malignancy during the study period, 1.47% (55 patients) exhibited cutaneous manifestations. Of these 55 patients, 54.55% (30) were males, and 45.45% (25) were females. The age of patients with cutaneous manifestations ranged from 3 to 74 years, with the most common age group being 31-60 years, comprising 47.27% of the cases [Table 1]. A maximum of 40% (22 patients) were homemakers, and 16.36% (9 patients) were students. In total, 50.90% (28 patients) were from urban areas, and 49.09% (27 patients) were from rural areas. Additionally, 70.91% of patients were literate, while 27.27% were illiterate [Table 2]. Cutaneous infectious manifestations were observed in 29 out of 55 patients, making them the most common type of manifestation at 52.73% [Table 3]. Among these, 25.45% (14 patients) had herpes zoster [Figure 1], followed by herpes labialis in 9.09% of patients. Folliculitis [Figure 2] and scabies were each observed in 3.64% of patients.

Cutaneous inflammatory manifestations were seen in 19 patients, accounting for 34.55% [Table 4]. The most common inflammatory manifestation was acneiform eruption, observed in 5.45% of patients. This was followed by erythroderma, thrombocytopenic purpura, lichen planus [Figure 3], and allergic contact dermatitis, each affecting 2 patients. There was 1 case each of dermatomyositis, pyoderma gangrenosum [Figure 4], chronic urticaria, erythema elevatum diutinum [Figure 5], seborrheic dermatitis, aphthous ulcer and blister beetle dermatitis.

9.09% (5 patients) had premalignant or malignant manifestations [Table 5]. The most common of these was cutaneous metastasis [Figure 6], seen in 2 patients, followed by single cases of mycosis fungoides [Figure 7], lymphomatoid papulosis, and leukemia cutis [Figure 8]. Additionally, 1.81% (1 patient) had an ingrown toenail, and another 1.81% (1 patient) had macular amyloidosis [Table 6].

The most common malignancies observed in patients with cutaneous lesions were leukemias and lymphomas, accounting for 34.54% (19 patients). These were followed by breast carcinoma in 18.18% (10 patients), cervical carcinoma in 9.09% (5 patients), laryngeal carcinoma in 5.45% (3 patients), and monoclonal gammopathy of undetermined significance in 5.45% (3 patients). Other malignancies encountered in our study, in descending order of frequency, included esophageal carcinoma (2 patients), pancreatic carcinoma (2 patients), prostate carcinoma, immune thrombocytopenic purpura, pituitary adenoma, buccal mucosa carcinoma, tongue carcinoma, lung carcinoma, ovarian carcinoma, adrenal adenoma, pheochromocytoma, ependymoma of the spine, and intrahepatic cholangiocarcinoma with cholelithiasis.

Age (years)	**Male**	**Female**
<30	9	4
31-60	16	10
>60	5	11
Total	30 (54.55%)	25 (45.45%)

Table 1: Age and Gender Distribution of Patients with Cutaneous Manifestations

Education Status	**Number of patients out of 55**
Postgraduate	1
Graduate	21
Secondary level	17
Illiterate	15
Other	1

Table 2: Education Status

Manifestations	**Number of patients out of 55**
Herpes zoster	14 (25.45%)
Herpes labialis	5 (9.09%)
Folliculitis	2 (3.64%)
Scabies	2 (3.64%)
Varicella	1 (1.81%)
Pityriasis versicolor	1 (1.81%)
Tinea cruris	1 (1.81%)
Oral candidiasis	1 (1.81%)

Furunculosis	1 (1.81%)
Pyoderma	1 (1.81%)

Table 3: Infections

Manifestations	**Number of patients out of 55**
Acneiform eruptions	3 (5.45%)
Erythroderma	2 (3.63%)
Lichen planus	2 (3.63%)
Thrombocytopenic purpura	2 (3.63%)
Allergic contact dermatitis	2 (3.63%)
Palpable purpura	1 (1.81%)
Dermatomyositis	1 (1.81%)
Pyoderma gangrenosum	1 (1.81%)
Erythema elevatum diutinum	1 (1.81%)
Chronic urticaria	1 (1.81%)
Seborrheic dermatitis	1 (1.81%)
Aphthous ulcers	1 (1.81%)
Blister beetle dermatitis	1 (1.81%)

Table 4: Inflammatory disorders

Manifestations	**Number of patients out of 55**
Cutaneous metastasis	2 (3.63%)
Lymphomatoid papulosis	1 (1.81%)
Leukaemia cutis	1 (1.81%)
Mycosis fungoides	1 (1.81%)

Table 5 : Premalignant /Malignant disorders

Manifestations	**Number of patients out of 55**
Ingrown toenail	1 (1.81%)
Macular amyloidosis	1 (1.81%)

Table 6: Others

Figure 1: Multiple grouped fluid filled vesicles and bulla over erythematous base involving left side of T2 dermatome suggestive of Herpes Zoster seen in patient having carcinoma of epiglottis

Figure 2: Folliculitis seen over the abdomen in a patient with carcinoma prostate

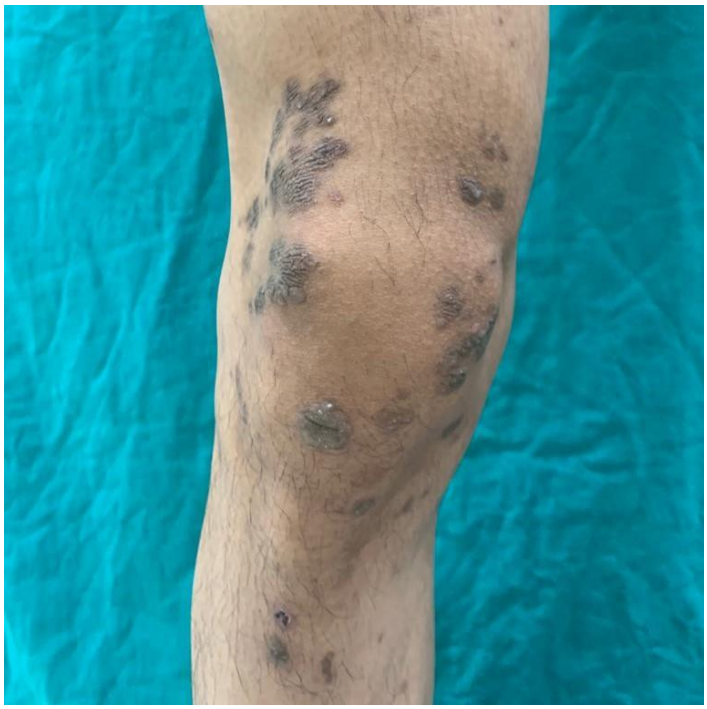

Figure 3: A patient with peripheral T cell lymphoma presented with multiple well defined violaceous plaques of varying sizes present around the left knee suggestive of lichen planus

Figure 4: A patient of Monoclonal Gammopathy of Undetermined Significance presented with a single well-defined ulcer with an erythematous base and surrounding violaceous border present over the lateral part of the left breast suggestive of Pyoderma Gangrenosum

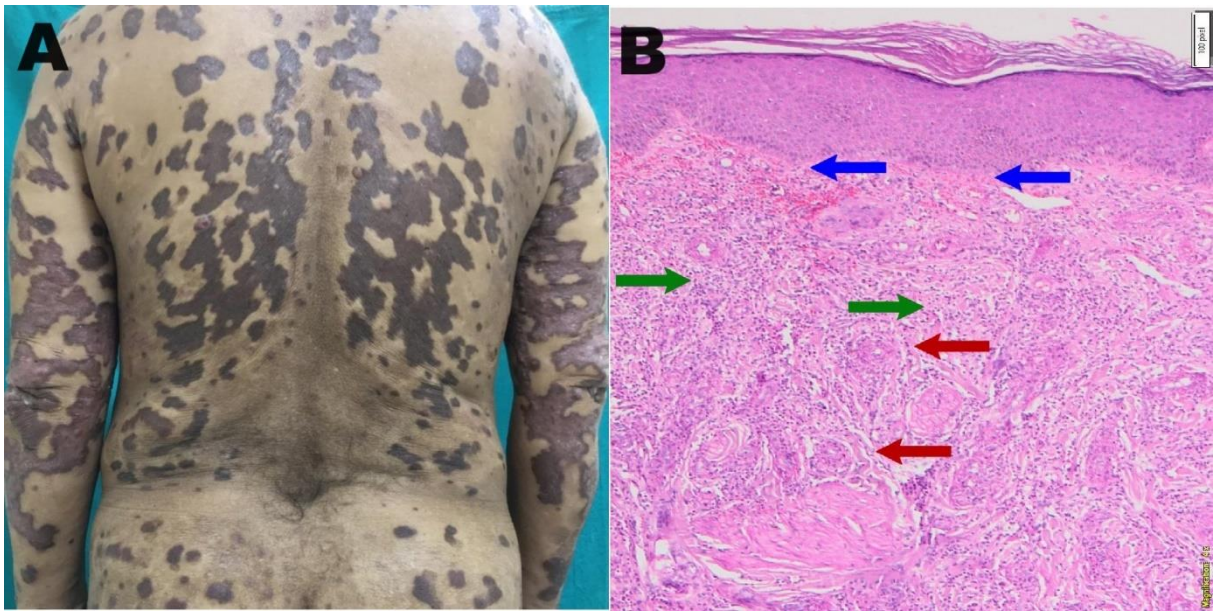

Figure 5: A) Another patient of Monoclonal Gammopathy of Undetermined Significance presented with multiple well defined discrete to confluent violaceous atrophic plaques of varying sizes present over the back and extensor surface of bilateral arms and forearms, biopsy suggestive of Erythema Elevatum Diutinum. B) Histopathology of Erythema Elevatum Diutinum showing leukocytoclastic vasculitis (red arrow) with mixed infiltration including neutrophils, lymphocytes, histiocytes, plasma cells and eosinophils (green arrow), Perivascular fibrosis in onion skinning pattern, Relative sparing of papillary dermis (blue arrow) (haematoxylin and eosin stain 4x magnification)

Figure 6: A patient with breast cancer presented with cutaneous metastasis (Carcinoma en cuirasse)

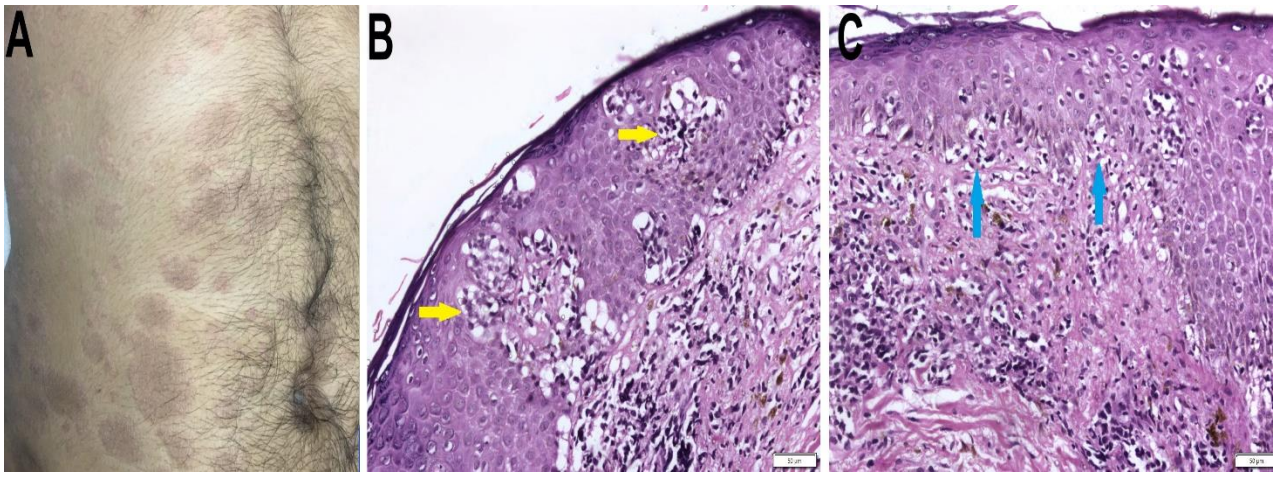

Figure 7: A) Multiple well defined erythematous to hyperpigmented plaques of varying size with overlying scaling present over abdomen, biopsy suggestive of mycosis fungoides Histopathology of mycosis fungoides showing B) Pautrier microabscesses in epidermis (yellow arrow) (hematoxylin and eosin stain 10x magnification) C) Intraepidermal lymphocytes out of proportion with spongiosis (epidermotropism) (blue arrow), papillary dermis exhibiting lymphoid infiltrate (hematoxylin and eosin stain, 10x magnification)

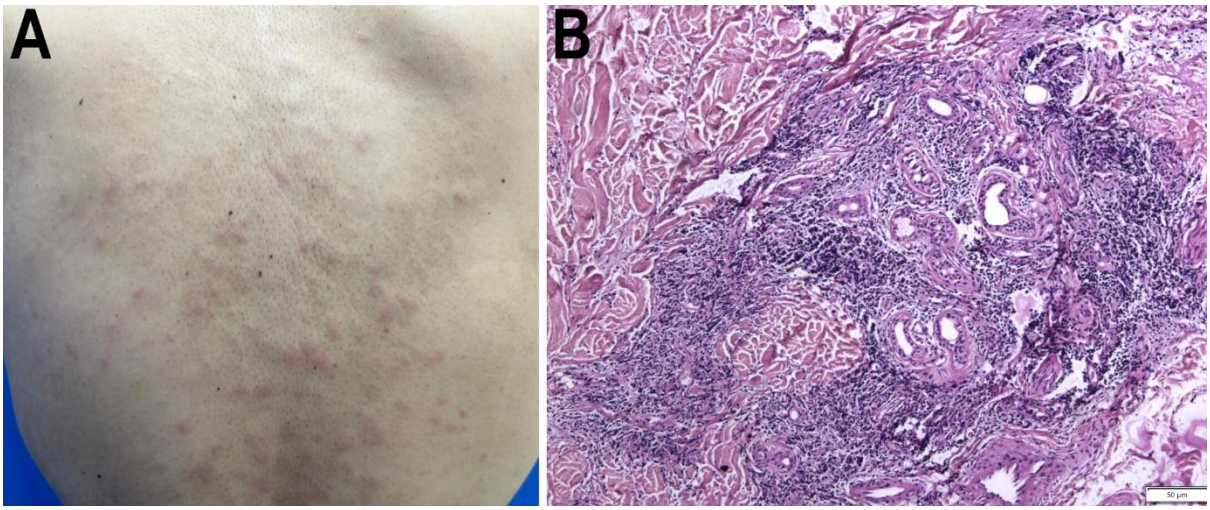

Figure 8: A) Patient with Acute Myeloid Leukaemia presented with multiple erythematous discrete to confluent papules and plaques over the trunk, biopsy suggestive of leukaemia Cutis. B) Histopathology of leukaemia cutis showing atypical monotonous population of cells in sheets around vessels and appendageal structures, interspersed with chronic inflammatory infiltrate (hematoxylin and eosin stain, 100x magnification)

Discussion:

Skin can provide insight into the health of internal organs, and changes in appearance may indicate underlying health issues. Cutaneous changes can occur for various reasons, including direct tumor invasion, distant metastasis, paraneoplastic phenomena, chemotherapy, or radiotherapy.

The risk of developing cancer significantly increases with age. In our study of 55 cases with internal malignancies and cutaneous manifestations, the age group most affected was those over 60 years old, accounting for 30.90% of cases. The following most affected age groups were those between the ages of 51-60 years (18.18%) and 41-50 years (16.36%). While these manifestations can occur at any age, they are most common during or after the fifth decade of life. This finding is consistent with previous studies, such as Ayyamperumal et al.[2], who also observed that most patients in their studies were over 50 years old. Of the 55 cases displaying cutaneous manifestations, 54.56% were males, and 45.45%

were females. Rajagopal et al.[3] also noted a higher prevalence of cutaneous manifestations in males in their study.

In the present study, 70.90% of patients were literate. Of these, 30.91% had completed education up to the secondary level, 38.18% were graduates, and 1.81% were post-graduates. On the other hand, 27.27% of patients were illiterate. One case was 3 years old and was categorized as others. Bandyopadhyay G et al.[4] suggested that individuals with higher levels of education are more aware of the importance of regular check-ups and consequently, are more likely to detect and address medical conditions at an early stage. In contrast, illiterate individuals often present at later stages of malignancy, resulting in a higher risk of mortality.

Malignancy is a major cause of death and illness worldwide and its burden is expected to increase in the future. Despite the existence of over 200 different types of malignancies, many aspects of the disease are still not well understood.[5] In present study, the most common malignancies were leukemias and lymphomas, accounting for 34.54% of cases. Breast carcinoma was the next most common with 18.18% of cases, followed by cervical carcinoma with 9.09% of cases. Ayyamperumal et al.[2] observed that the most common malignancies in their study were leukemia and lymphomas, followed by breast carcinoma. In males, leukemia was the most common malignancy producing cutaneous manifestations, accounting for about 36.67% of cases. In females, breast carcinoma was the most common malignancy causing cutaneous manifestations, accounting for 40% of cases.

Cutaneous manifestations of internal malignancies can take many different forms. They may be caused by metastasis to the skin, or they may be part of a syndrome that encompasses proliferative and inflammatory dermatoses, genodermatoses, inherited immunodeficiency syndromes, or hormone-secreting tumors**.** These cutaneous manifestations are only a small part of the overall picture of internal malignancy.[3] In our study, various inflammatory manifestations were present. Three cases of acneiform eruptions were found, each primarily diagnosed with pituitary adenoma, adrenal adenoma and B-ALL. Hormonal profiles showed increased androgen levels in the pituitary and adrenal adenoma patients**.** Our findings were consistent with studies by Allen MJ et al.[6] and Mahmood E et al.[7], who reported that glucocorticoid-producing adrenal tumours could present with acne. Further on in our study, we found two cases, each of which was erythroderma, lichen planus, thrombocytopenic purpura, and allergic contact dermatitis, as other inflammatory manifestations. Additionally, we found one case each of palpable purpura, dermatomyositis, pyoderma gangrenosum, erythema elevatum diutinum, chronic urticaria, seborrheic dermatitis, aphthous ulcer and blister beetle dermatitis.

Changes in the host's immune function due to the underlying cancerous process or its treatment have been associated with an increased risk of infections.[8] Literature suggests that disseminated herpes zoster is often linked with underlying malignant diseases.[2] In our study, herpes zoster was identified as the most common infectious dermatosis, observed in 14 cases, 25.45% of the patients. This is similar to the findings of a study conducted by Jinal Tandel et al.[9] The reason for the correlation between herpes zoster and malignancy is their common link to immunosuppression. Herpes labialis was the second most common infection, affecting 5 patients, 9.09% of the cases. Other identified infections included folliculitis, scabies, varicella, pityriasis versicolor, tinea cruris, oral candidiasis, furunculosis and pyoderma.

Dermatoses specific to malignancies can be attributed to cutaneous metastasis**.** Some of these changes are detected early, suggesting a strong correlation with malignancy, while others appear later in the course of the malignancy, indicating either dissemination or immunosuppression.[10] There were two instances of cutaneous metastasis in female patients with a history of breast carcinoma. These findings align with the reports by Culver et al.[11] and Ameer et al.[12] Our study also included two cases of

Cutaneous T-cell Lymphoma (CTCL). In one case, a skin biopsy of the lesion was performed considering the possibility of mycosis fungoides. The presence of Pautrier's micro abscesses and epidermotropism suggested mycosis fungoides. Mycosis fungoides (MF) is the most prevalent type of cutaneous T-cell lymphoma, representing about 40% of all cutaneous lymphomas and 54%–65% of cutaneous T-cell lymphomas.[13,14] The second case involved a 62-year-old female with a history of CTCL who was diagnosed with lymphomatoid papulosis. Pulitzer et al. described a similar case in their study.[15] Our study found a case of Acute Myeloid Leukemia (AML) with leukemia cutis, similar to a case reported by Rao et al.[16] Leukemia cutis is linked to a poor prognosis in AML patients and may need thorough monitoring and aggressive treatment.[17]

The study's limitation is the relatively small sample size with cutaneous manifestations, which may limit the generalizability of the findings. Additionally, the study was conducted at a single tertiary care center, which could introduce a selection bias and may not fully represent the broader population.

Conclusion:

This study highlights the broad spectrum of cutaneous manifestations and their significant pathological associations in patients with internal malignancies. It emphasizes the crucial role of dermatological evaluations in these individuals, as skin manifestations often provide valuable insights into the underlying malignancy and its progression. The relationship between skin disorders and internal cancers is complex, as evidenced by cases of metastasis and specific dermatoses such as mycosis fungoides, lymphomatoid papulosis, and leukemia cutis. The notably high prevalence of infectious dermatoses, particularly herpes zoster and herpes labialis, in immunosuppressed patients further underscores the importance of a multidisciplinary approach that addresses the malignancy and its dermatological consequences. Also, this study's rare conditions, such as Erythema elevatum diutinum, associated with hematological malignancies, should not be overlooked. Healthcare providers must remain vigilant to cutaneous manifestations in patients with internal malignancies, as these can serve as early indicators of disease, aid in diagnosis, and guide the comprehensive management of malignancies.

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