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Beyond the Tumor: Cutaneous Manifestations of Paraneoplastic Syndromes

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Abstract

The skin is the most visible organ of the human body and the second largest, surpassed only by the endothelium. Its functions extend beyond aesthetics, as it is considered the primary protective barrier against external agents such as microorganisms, corrosive substances, ultraviolet radiation, and other harmful vectors. It also plays crucial roles in preventing total body water loss and regulating temperature. This physical, immunological, and chemical barrier is essential for homeostasis and overall well-being. Additionally, the skin can serve as an early indicator of underlying neoplasms, being the epicenter of multiple manifestations of paraneoplastic syndromes. These syndromes represent a heterogeneous group of clinical manifestations caused by the release of substances by tumor cells or the body's immune response to them. Paraneoplastic skin manifestations, such as acanthosis nigricans, Leser-Trélat syndrome, or necrolytic migratory erythema, are examples of how the skin can reflect systemic alterations related to cancer. The importance of the skin in this context lies in its accessibility for clinical evaluation and its ability to provide critical diagnostic clues. An attentive physician can identify cutaneous signs that act as "red flags", guiding early cancer detection and potentially improving patient prognosis. Therefore, the skin is not only a barrier but also a reflection of internal health, playing a vital role in diagnosing systemic diseases and clinical oncology.

Keywords

Paraneoplastic, Skin, Neoplasia, Oncology

1. Introduction

Paraneoplastic syndromes represent a complex group of clinical manifestations associated with hormonal, hematological, neurological, or metabolic disorders resulting from interactions between underlying neoplastic processes and host immune responses [1]. These alterations are not a direct consequence of tumor invasion or metastasis but rather systemic mechanisms reflecting the presence of malignancy [1] [2]. Within this group, dermatological manifestations hold a prominent place, often being the first visible signs of underlying cancer [3]. These skin changes can provide valuable clues for early diagnosis, disease progression assessment, and, in some cases, even prognosis [1]-[3].

Over 50 dermatological manifestations associated with malignancies have been documented in the literature, highlighting the importance of clinical recognition of these findings [3] [4]. These manifestations can arise at various stages of the disease: before cancer diagnosis, during disease progression, or even in advanced stages post-treatment [4]. This temporal variability underscores the need for a comprehensive clinical approach that considers these manifestations as potential markers of underlying neoplasms.

The interest in the relationship between skin diseases and neoplastic processes dates back to the 19th century [1] [3]. Austrian dermatologist Ferdinand Ritter von Hebra first proposed a possible connection between cutaneous hyperpigmentation and visceral cancers [5]. Decades later, in 1900, Dr. Hollander established the relationship between the spontaneous appearance of seborrheic keratosis and visceral cancer, solidifying this condition as a paraneoplastic manifestation [6]. In 1976, German-American dermatologist Helene Ollendorff Curth developed a set of diagnostic criteria to determine the association between skin manifestations and internal neoplasms (**Table 1**) [1]. These criteria, still widely used for their versatility, include aspects such as the timing of lesion appearance and its correlation with the underlying malignancy. However, they do not cover all possible presentations, emphasizing the need for a high clinical suspicion [1] [6] [7].

The skin acts as a mirror of the body's systemic conditions, and its detailed study can reveal critical clues about underlying diseases (**Figure 1**) [7]. Recognizing paraneoplastic dermatological manifestations should prompt a thorough evaluation to identify underlying malignancies, guiding clinicians in implementing a multidisciplinary approach to optimize patient management (**Table 2**). Ultimately, a correct interpretation of these signals can contribute to early diagnosis, improved prognosis, and enhanced patient quality of life [7] [8].

Table 1. Curth's criteria or postulates.

	Curth's Criteria
	Major Criteria:
1.	Simultaneous onset of the neoplasm and dermatosis.
2.	Parallel development of both conditions.
	Minor Criteria:
1.	The condition is not recognized as part of a genetic syndrome.
2.	A specific tumor is associated with a specific dermatosis.
3.	The presented cutaneous dermatosis is uncommon.
4.	There is a statistically significant association between the skin lesions and the type of neoplasm.

Adapted from: Curth HO. Skin lesions and internal carcinoma. In: Andrade R, editor. Cancer of the skin: biology, diagnosis, management. Philadelphia: Saunders; 1976.

2. Epidemiology

Paraneoplastic syndromes are rare entities, and although exact statistical data are unavailable, they are estimated to occur in approximately 7% to 15% of malignancies [9] [10]. Their incidence ranges from 1 to 8 cases per 100,000 inhabitants annually, with a global prevalence of around 4 cases per 100,000 inhabitants. These syndromes can occur at any age, with no specific predilection for sex or race [6]. They are primarily associated with solid tumors, most commonly lung, breast, and colon cancers, highlighting the importance of timely and accurate diagnosis in these clinical contexts [10].

3. Pathophysiology

Paraneoplastic syndromes arise from the complex interaction between the tumor and the host, unrelated to tumor invasion or metastasis [10]. Their pathophysiology involves multiple biological mechanisms, including the release of growth factors, cytokine production, systemic inflammatory responses, and autoimmune reactions [1] [6].

One of the primary mechanisms is the release of growth factors and humoral products by tumor cells [3] [4]. For example, certain tumors secrete hormones or hormone-like peptides, such as ectopic adrenocorticotropic hormone (ACTH) production in small cell lung carcinoma, leading to Cushing's syndrome [2] [4] [6]. Other tumors may release transforming growth factors (TGF), insulin-like growth factor 1 (IGF1), fibroblast growth factor (FGF), and alpha-melanocyte-stimulating hormone (MSHα), which are implicated in cutaneous manifestations like acanthosis nigricans and Leser-Trélat syndrome [3] [6].

Cytokines play a crucial role in paraneoplastic skin manifestations by mediating processes such as inflammation, cell proliferation, and tissue remodeling. Molecules like TGF-α and IL-6 stimulate epidermal proliferation and keratinocyte and fibroblast differentiation, contributing to conditions like acanthosis nigricans, while pro-inflammatory cytokines like TNF-α and IL-1 induce chronic inflammation, as seen in Sweet's syndrome [6]. Additionally, factors like vascular endothelial growth factor (VEGF) promote angiogenesis, present in syndromes like Bazex,

and others, such as IL-10, modulate immune responses that favor characteristic lesions in paraneoplastic dermatomyositis [3] [11] [12].

Finally, autoimmune processes are closely related to paraneoplastic syndromes. Aberrantly expressed proteins by tumor cells, known as onconeural antigens, can trigger a cross-reactive immune response affecting normal tissues [6] [12] [13].

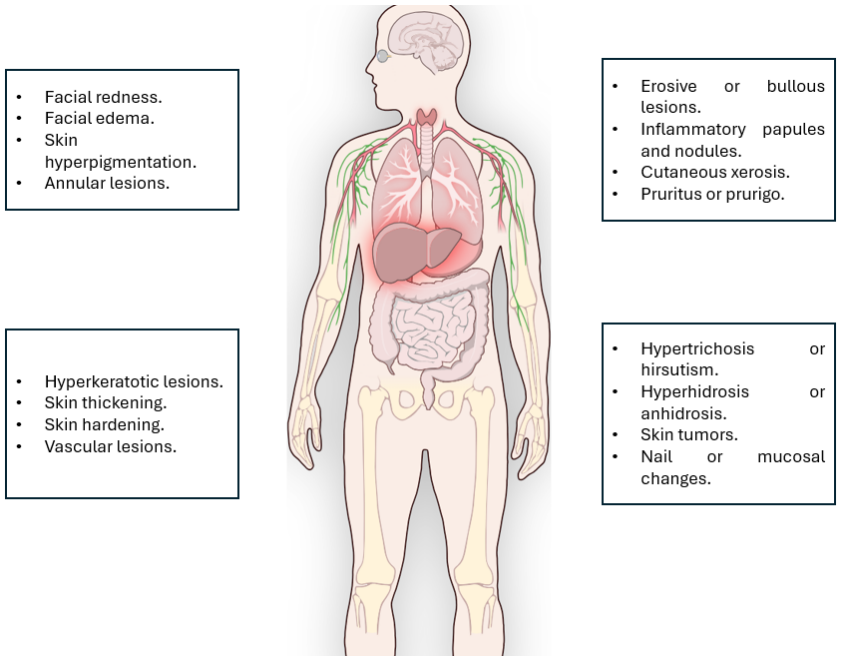

Figure 1. Changes that should alert to possible underlying neoplasms. Source: Prepared with BIOART resources.

Table 2. Some of the main paraneoplastic cutaneous manifestations.

Paraneoplastic Syndromes Associated with Occult Neoplasms			
Disorder	**Clinical Findings**	**Main Associated Malignancy**	**Histologically**
Acanthosis Nigricans	Symmetric hyperkeratosis, papillomatosis, and hyperpigmentation in anatomical fold areas.	Gastric adenocarcinoma.	Hyperkeratosis, papillomatosis, and thickening of the spinous layer are observed.
Paraneoplastic Acrokeratosis	Psoriasiform scaling lesions on surfaces, primarily affecting the nasal bridge and auricle.	Squamous cell carcinoma of the aerodigestive tract.	Hyperkeratosis, acanthosis, parakeratosis, vacuolar degeneration of basal cells, and a perivascular lymphocytic infiltrate.
Dermatomyositis	Violaceous poikiloderma in sun-exposed areas, heliotrope rash, nail fold telangiectasias, Gottron's papules, proximal muscle weakness.	Lung, ovarian, nasopharyngeal, and gastrointestinal cancers.	Vacuoles in the dermis, epidermal atrophy, interstitial mucin deposits, and a diffuse lymphocytic infiltrate.
Erythema Gyratum Repens	Annular, erythematous, pruritic, and scaly lesions with a "wood grain" pattern.	Lung, breast, and esophageal cancers.	Moderate hyperkeratosis, parakeratosis, acanthosis, and spongiosis are observed, along with a mononuclear perivascular inflammatory infiltrate in the dermis

Continued

Necrolytic Migratory Erythema	Vesicular, bullous, or superficial erosive skin lesions.	Pancreatic neuroendocrine tumors [Glucagonoma].	Edema, epidermal hyperplasia, perivascular inflammation with lymphocytic infiltrate, parakeratosis, and necrosis.
Scleredema	Induration of cervicofacial skin, trunk, or upper extremities, with progressive nature.	Multiple myeloma, lymphomas.	Dermis with mucin and collagen deposits, without an increase in fibroblast numbers.
Acquired Hypertrichosis Lanuginosa	Appearance of unpigmented, fine, long, and easily detachable lanugo-type hair.	Lung, breast, and colorectal cancers.	Hair grows horizontally or parallel to the epidermis.
Leser-Trélat Sign	Sudden onset of diffuse seborrheic keratosis.	Colorectal, gastric, and breast cancers; less commonly, hematologic neoplasms.	The keratoses present hyperkeratosis, acanthosis, and papillomatosis, with basaloid and squamous cells, horn cysts, and melanocytic pigmentation.
Paraneoplastic Pemphigus	Mucosal erosions with associated stomatitis or vesicles.	Non-Hodgkin lymphoma, leukemias, Castleman disease.	Intraepithelial acantholysis with a band-like lymphohistiocytic infiltrate is observed
Pityriasis Rotunda	Circular scaly patches on the torso and proximal regions of the extremities.	Hepatocellular carcinoma, prolactinoma.	Uniform basal layer pigmentation, orthokeratotic hyperkeratosis, focal agranulosis, or hypogranulosis in the affected area.
Sweet's Syndrome	Appearance of erythematous or violaceous plaques and nodules on the skin, accompanied by fever and general malaise.	Hematologic neoplasms.	Dense, mature neutrophilic infiltrate is found in the mid-dermis, associated with variable degrees of edema, and absence of leukocytoclastic vasculitis

4. Acanthosis Nigricans

Acanthosis nigricans is a cutaneous manifestation classified into two main forms: benign, which accounts for 80% of cases and is closely associated with insulin resistance and obesity, and malignant, a less common but clinically significant variant [14].

Malignant acanthosis nigricans was the first dermatosis described with a clear relationship to underlying malignancies [1] [7]. It affects men and women equally, with no known racial or hereditary predisposition [7]. Its onset is usually sudden, with extensive, severe, and rapidly progressive skin involvement [14] [15]. Clinically, it is characterized by symmetric hyperpigmentation in areas such as the axillae, neck, submammary, inguinal, and cubital fossae, potentially extending to other body parts [16]. Lesions often present with skin tags and hyperkeratotic plaques and may be accompanied by pruritus. In advanced cases, it can affect the palms, a condition known as acanthosis palmaris, manifested by darkened, hardened, and rough palms [6] [14] [16].

Histologically, hyperkeratosis, papillomatosis, and thickening of the spinous layer are observed. Interestingly, the characteristic hyperpigmentation is not due to melanin deposits but is related to hyperkeratotic changes [1] [7].

This condition can appear simultaneously with or precede the diagnosis of an underlying neoplasm. An association of up to 90% with intra-abdominal tumors

has been identified, with gastric adenocarcinomas being the most common, representing 70% to 90% of cases [1] [6] [7] [16]. Less commonly, it is associated with cancers of the pancreas, liver, intestine, ovary, kidney, breast, thyroid, and gallbladder, as well as hematologic neoplasms in rare cases [1] [16].

5. Paraneoplastic Acrokeratosis

Acrokeratosis paraneoplastica, or Bazex syndrome, was first described in 1965 by French dermatologist André Bazex and colleagues as a clinical marker of malignancy [1] [6]. This syndrome is a rare dermatosis characterized by specific skin lesions frequently associated with malignant tumors, especially of the upper aerodigestive tract [17]. Bazex proposed a classification into three clinical stages, reflecting disease progression:

- Initial stage: Erythema and psoriasiform scaling appear, mainly on the fingers, toes, and the margin of the helix. These lesions have a characteristic violaceous color. Additionally, nail changes such as subungual hyperkeratosis and onycholysis may be observed [17].
- Second stage: Scaling progresses, affecting the entire surface of the hands and feet, resulting in violaceous keratoderma with an edematous texture and a honeycomb-like pattern.
- Third stage: Skin lesions extend beyond the extremities, involving additional areas such as the knees, legs, and arms [17].

Histological features include hyperkeratosis, acanthosis, parakeratosis, vacuolar degeneration of basal cells, and a perivascular lymphocytic infiltrate. These characteristics are useful for confirming the diagnosis when clinical suspicion exists [6] [7] [18].

Skin lesions may precede the diagnosis of an underlying neoplasm by 2 to 12 months, making Bazex syndrome a valuable early marker of malignancy [19]. Approximately 80% of cases are associated with tumors of the upper aerodigestive tract, such as those affecting the oral cavity, larynx, pharynx, trachea, esophagus, and lungs [17] [18]. Among these, squamous cell carcinoma is the most frequently related type [1] [6] [7] [17].

6. Dermatomyositis

Dermatomyositis is a complex clinical condition characterized by proximal muscle weakness associated with inflammatory myopathy, predominantly in the extensors, along with violaceous poikiloderma in sun-exposed areas. Other findings include nail bed alterations and heliotrope rash, considered its most distinctive semiological sign [12].

The link between dermatomyositis and malignancy was first described in 1916 by Dr. Stretz, who identified this association in a patient with gastric carcinoma [1] [7]. Since then, this relationship has been consolidated, especially in populations from Northern Europe and East Asia [20].

Clinical indicators suggesting malignancy in the context of dermatomyositis in-

clude rapid disease progression, cutaneous necrosis, absence of Raynaud's phenomenon, and elevated erythrocyte sedimentation rate [20] [21].

Histologically, vacuoles in the dermis, epidermal atrophy, interstitial mucin deposits, and a diffuse lymphocytic infiltrate are observed. In muscle biopsy, findings include type II fiber atrophy, necrosis, hypertrophy, regeneration, and centralization of nuclei in the sarcolemma [1] [7].

Although dermatomyositis shows a strong association with adenocarcinomas, a thorough search for possible etiologies is recommended for adequate management [1] [7] [20] [21].

7. Erythema Gyratum Repens

Erythema gyratum repens is an atypical paraneoplastic dermatosis considered highly specific for underlying malignancies [22]. It was first described in 1952 by Dr. Gammel, who reported undulating erythematous lesions with marginal scaling in a patient later diagnosed with breast adenocarcinoma [23].

Lesions present a "wood grain" or "cypress" pattern, are annular, erythematous, pruritic, and scaly, with rapid progression of up to one centimeter per day [22]-[24].

Histologically, moderate hyperkeratosis, parakeratosis, acanthosis, and spongiosis are observed, along with a mononuclear perivascular inflammatory infiltrate in the dermis [1] [6] [7].

Erythema gyratum repens are present in 82% to 84% of cases of underlying malignancy, most frequently in lung cancer, followed by esophageal and breast cancer. Exceptionally, it has been associated with multiple myeloma, as reported in the literature [6] [22]-[24].

8. Necrolytic Migratory Erythema

Necrolytic migratory erythema is a paraneoplastic dermatosis common in individuals over 45 years old, with a peak incidence in the sixth decade of life [25]. It was first described by Becker and colleagues in 1942 [1] [6] [7]. Clinically, it is characterized by scaly, erythematous, irregular patches with centrifugal growth, accompanied by superficial erosions and vesiculobullous lesions [25] [26]. The most affected areas include the perineum, distal extremities, lower abdomen, and face [26].

Systemic manifestations include hyperglycemia, weight loss, diarrhea, abdominal pain, and neuropsychiatric symptoms. Additionally, there is an increased risk of thromboembolic events, such as deep vein thrombosis or pulmonary embolism, with an incidence of 24% [1]. Frequent infections, mainly by *Candida albicans* and *Staphylococcus aureus*, can complicate the diagnosis by mimicking chronic infectious processes [27].

Histologically, findings include edema, epidermal hyperplasia, perivascular inflammation with lymphocytic infiltrate, parakeratosis, and necrosis [1] [6] [7].

Necrolytic migratory erythema is closely related to pancreatic neuroendocrine

tumors, especially glucagonoma, present in 70% of cases. Its identification is crucial as an early marker, as treatment of the underlying neoplasm results in rapid resolution of skin manifestations [25]-[27].

9. Scleredema

Scleredema is an uncommon dermatosis, primarily associated with metabolic conditions such as diabetes mellitus. However, its occurrence as a paraneoplastic dermatosis in the context of lymphomas and multiple myeloma has been documented [28]. It was first described in 1752 by Curzio, and in 1902, Buschke consolidated the condition by describing progressive hardening of the neck skin in a patient who had presented with a flu-like illness [1] [6].

Clinically, it is characterized by indurated edema in the neck and dorsal region, which can progress to sclerosis and involve larger body areas. Three main variants are recognized:

- Buschke's description: Preceded by a febrile illness of infectious or other etiology.
- Karokowski's description: Associated with endocrinopathies, most commonly diabetes mellitus.

Indeterminate description: Progressive presentation without an identifiable underlying disease.

Differential diagnoses include scleromyxedema and scleroderma. Histologically, an expanded dermis with mucin and collagen deposits is observed, without an increase in fibroblast numbers, helping to differentiate it from other pathologies. It may be associated with systemic involvement, affecting the liver, heart, eyes, and bones [7] [28].

Treatment focuses on the underlying neoplasm, although systemic interventions may be required in some cases. It is frequently associated with multiple myeloma and lymphomas [6].

10. Acquired Hypertrichosis Lanuginosa

Acquired hypertrichosis lanuginosa was described as a paraneoplastic dermatosis by Turner in 1865, in a patient with breast cancer who developed thick, short, soft, and white hair [6]. Since then, reports have been scarce but consistently associated with a poor prognosis. Most cases have been recorded in women [1].

Clinically, it is characterized by the appearance of thin, white, and soft hair, similar to lanugo, predominantly on the face and with a craniocaudal distribution. Trichomegaly is another frequent manifestation [29]. The gradual onset of this condition usually precedes the diagnosis of the underlying neoplasm by 2.5 to 3 years, delaying its identification [30]. Other manifestations include weight loss, diarrhea, and lymphadenopathy [1].

Histologically, the hair grows horizontally or parallel to the epidermis, in contrast to the usual vertical growth. Hair follicles present immature sebaceous ducts [7].

It is closely related to lung and colorectal neoplasms, although it has also been described in breast and ovarian cancers [29] [30].

11. Leser-Trélat Sign

The Leser-Trélat sign is a paraneoplastic dermatosis characterized by the sudden and progressive appearance of multiple seborrheic keratoses with verrucous features [31] [32]. These lesions are usually located on the chest and back but may also be found on the neck, axillae, face, and abdomen [33]. The lesions are brown or black and tend to respond favorably to treatment of the underlying neoplasm [31].

It was first described by Hollander in 1900, who named it in honor of Edmund Leser and Ulysses Trélat, who had previously linked cherry angiomas to neoplastic diseases [31].

Diagnostic criteria, such as those proposed by Fink *et al.*, suggest that the appearance of 20 or more seborrheic keratoses within six months is highly suggestive of this condition [34].

Histologically, the keratoses present hyperkeratosis, acanthosis, and papillomatosis, with basaloid and squamous cells, horn cysts, and melanocytic pigmentation. These findings do not differ between benign forms and the Leser-Trélat sign [33] [35].

It is mostly associated with adenocarcinomas of gastric, colorectal, breast, or lung origin, although it can also occur in hematologic neoplasms [31].

12. Paraneoplastic Pemphigus

Paraneoplastic pemphigus was established as a clinical entity in 1990 by Anhalt et al. It shows no significant differences between sexes, and it is estimated that two-thirds of patients have a recognized neoplasm at the onset of the disease [36].

Among the main clinical manifestations, the most frequent and disabling is persistent stomatitis, often associated with glossitis [1] [6]. There may also be involvement of the oropharynx, nasopharynx, esophagus, and anogenital region [7]. Up to 70% of patients may present ocular involvement. As the disease progresses, lesions extend to the head, trunk, and upper extremities, characterized by erythema, blisters, and plaques [37] [38].

Diagnostic criteria proposed by Helm and Camisa include:

- Major criteria: Polymorphic skin eruption, concomitant internal neoplasm, characteristic immunoprecipitation findings with serum.
- Minor criteria: Deposits of immunoreactants in intercellular spaces and the basement membrane on direct immunofluorescence, acantholysis in biopsy from at least one anatomical site, and staining of rat bladder transitional epithelium on indirect immunofluorescence.

The diagnosis requires the presence of three major criteria or two major and one minor criterion [38].

Histologically, intraepithelial acantholysis with a band-like lymphohistiocytic

infiltrate is observed [6] [7]. On direct immunofluorescence, deposits of IgA, IgG, and C3 are found. Additionally, autoantibodies against desmoglein 3 and, less frequently, against periplakin, envoplakin, desmoplakins I and II, and A2ML1 have been identified [1] [3] [6].

Paraneoplastic pemphigus, which usually present between the fifth and eighth decades of life, is associated in 80% of cases with hematologic neoplasms such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease. It may also be related to solid tumors like lung, colon, or stomach cancer [36]-[38].

13. Pityriasis Rotunda

Pityriasis rotunda is a rare dermatosis characterized by alterations in keratinization, with oval, scaly plaques with well-defined borders, which may be hypo- or hyperpigmented compared to the surrounding skin. The lesions, usually located on the trunk, are multiple, may coalesce, and show no inflammation or pruritus [39].

First described by Dr. Toyama in 1906 in Japanese patients, it is classified into:

- Type I: Presentation in Black or Asian patients over 60 years old, associated with neoplasia or systemic disease.
- Type II: Presentation in White patients under 30 years old, with familial association.
- It predominates in darker skin types, and the most frequent age of presentation is between 20 and 45 years [6] [7].

Histologically, uniform basal layer pigmentation, orthokeratotic hyperkeratosis, focal agranulosis, or hypogranulosis in the affected area may be found [7].

Although it can occur in the presence of non-neoplastic diseases such as tuberculosis, leprosy, or hepatic or pulmonary diseases, it has been described in association with solid tumors, especially hepatocellular, gastric, esophageal, and prostate carcinomas, as well as multiple myeloma and chronic lymphocytic leukemia [1] [6] [7] [39].

14. Sweet's Syndrome

Sweet's syndrome was first described in 1964 by Dr. Robert Douglas Sweet as an "acute febrile neutrophilic dermatosis". It is the most frequent neutrophilic dermatosis, characterized by neutrophilic infiltrate, fever, and painful skin lesions such as papules, nodules, or erythematous plaques [40] [41].

This dermatosis has three types of presentation: classic or idiopathic, malignancy-associated, and drug-induced. Additionally, major and minor diagnostic criteria have been established, requiring the presence of 2 major and at least 2 minor criteria for diagnosis [6] [40] [41].

- Major criteria: Sudden onset of painful erythematous lesions and histopathological findings of dense neutrophilic infiltrate without leukocytoclastic vasculitis.

- Minor criteria: Fever [>38˚C], association with malignancy, inflammatory diseases, infections, or pregnancy, response to treatment with corticosteroids or potassium iodide, and paraclinical alterations [elevated ESR, increased CRP, leukocytosis >8000, neutrophilia >70%].

Histologically, a dense, mature neutrophilic infiltrate is found in the mid-dermis, associated with variable degrees of edema, and absence of leukocytoclastic vasculitis [7].

It is estimated that around 25% of patients with Sweet's syndrome have an underlying neoplasm, usually hematologic, with acute myeloid leukemia being the most frequent in up to 42% of cases, while association with solid tumors is rare [6] [40] [41].

15. Conclusion

Paraneoplastic cutaneous syndromes represent highly relevant clinical manifestations in medical practice, as they can serve as early signals of an underlying neoplasm. Recognizing the clinical and semiological features of these skin alterations is essential for identifying specific patterns that guide accurate diagnosis. Early detection of these syndromes not only allows for timely intervention but also significantly improves patient prognosis by facilitating early management of the underlying disease. Therefore, it is imperative to strengthen medical training in this area and promote clinical research to expand knowledge about these complex interactions between the skin and neoplasms.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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