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Cutaneous paraneoplastic syndromes. Dermatological manifestations associated with malignancies

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ABSTRACT:

Introduction and purpose: Paraneoplastic syndromes (PS) are conditions associated with malignant tumours whose mechanism of onset is not fully understood. It is postulated that it's pathophysiology may involve metabolic, endocrine, haematological changes and autoimmune reactions. The aim of this study is to describe cutaneous PS that nearly always occur with neoplasms. The work aims to give an overview of their clinical manifestations and to indicate the neoplasms they are most commonly associated with.

Description of the state of knowledge: Several types of cutaneous PS are almost always associated with malignancies. These include conditions like acroceratosis paraneoplastica, paraneoplastic pemphigus, erythema gyratum repens, acquired hypertrichosis lanuginosa, necrolytic migratory erythema, tripe palms, and syndromes such as AESOP syndrome, ectopic ACTH syndrome, and carcinoid syndrome. These dermatoses present a wide range of clinical features, including skin lesions that vary in appearance, severity, and location, and they are linked to different types of tumors. The connection between cutaneous PS and underlying neoplasms involves various potential pathophysiological mechanisms. However, the exact processes driving these relationships remain unclear and are the subject of ongoing research.

Conclusions: Awareness of cutaneous PS is crucial for early malignancy detection. Timely identification of these skin manifestations allows for quicker diagnosis and treatment of underlying neoplasm, significantly improving the patient's prognosis.

KEY WORDS: cutaneous paraneoplastic syndromes; paraneoplastic conditions, skin manifestations; neoplasm

INTRODUCTION:

Paraneoplastic syndromes constitute a group of conditions that are associated with the presence of a malignant tumor in the body, independent of its local growth or the presence of its distant metastases [1]. The pathogenesis of skin lesions in paraneoplastic syndromes remains poorly understood. It is postulated that the potential etiologies of these lesions may include metabolic, endocrine and hematological disorders induced by the tumor. Additionally, growth factors are believed to play a crucial role in the development of these conditions and in some cases, they may be linked to an autoimmune response [2].

Helene O. Curth proposed six criteria that discuss the relationship between skin manifestations and internal malignancies. These criteria include [3]:

1. Both conditions start simultaneously
2. Both conditions runs in parallel
3. The condition is not considered to be within a genetic syndrome
4. A particular neoplasm is associated with a particular dermatosis
5. The skin disorder is not common
6. There is a high percentage of association between the two conditions

The temporal relationship between cutaneous manifestations and the underlying malignancy is variable. The dermatosis may present once the malignancy is well developed and clinically evident, may be the first sign of a small undiagnosed tumour, or may precede the onset of the neoplasm [4].

Cutaneous manifestations can facilitate early diagnosis of a previously asymptomatic neoplasm, allowing prompt treatment initiation and potentially prolonging the patient's life. Moreover, these skin changes can provide insights into the effectiveness of ongoing therapy and may serve as an early indicator of tumour recurrence after treatment completion [2,5].

According to Bologna, the paraneoplastic syndromes can be divided into the following categories [6]:

Association with neoplasm in most or all cases	Bazex syndrome Carcinoid syndrome Erythema gyratum repens Acquired hypertrichosis lanuginosa Paraneoplastic pemphigus	AESOP syndrome ACTH syndrome Glucagonoma syndrome Tripe palms
Strong association with neoplasm in a subset of cases	Acanthosis nigricans Anti-laminin 332 mucous membrane pemphigoid Dermatomyositis Neutrophilic dermatoses	
Association with a monoclonal gammopathy	Acquired angioedema due to C1 esterase inhibitor dysfunction Cryoglobulinemia, type I Normolipemic plane xanthoma Necrobiotic xanthogranuloma	Amyloidosis POEMS syndrome Schnitzler syndrome Scleromyxedema
PD that may be associated with cancer in a subset of patients	Cutaneous small vessel vasculitis Dermatitis herpetiformis Multicentric reticulohistiocytosis Eruptive disseminated porokeratosis JXGs in the setting of NF1	Acquired ichthyosis Exfoliative erythroderma Mycosis fungoides Porphyria cutanea tarda
Association with cancer is controversial	Sign of Leser–Trélat	

This review focuses on cutaneous paraneoplastic syndromes that in most or all cases occur in association with neoplasms.

1. Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) is a rare and severe autoimmune bullous disease. It affects multiple areas of the skin and mucous membranes, as well as internal organs, and is therefore also termed as PAMS - paraneoplastic autoimmune multiorgan syndrome [7]. The disease

primarily affects individuals between the ages of 45 and 70, though it can sometimes be seen in children and adolescents [8]. Only 450 cases of the disease have been described worldwide, presenting with equal frequency in men and women [9].

The disease is characterised by the presence of painful, haemorrhagic mucosal erosions and polymorphous skin lesions presenting as erythematous, erythematosquamous or bullae [2,9]. Mucosal erosions and ulcerations may occur in the nasopharynx, tongue, vermilion of the lips, conjunctiva and anogenital region. Lesions on the lips resemble those seen in erythema multiforme and Stevens-Johnson syndrome. The typical presentation of the skin lesions is on the upper part of the body, although they can occur on any area of the skin [8]. The skin lesions have features of pemphigus vulgaris, bullous pemphigoid, lichen planus, erythema multiforme and GVHD [2]. PNP can involve other organs besides the skin, most commonly the respiratory system and the gastrointestinal tract. Occupation of the respiratory tract, which is particularly seen in the youngest patients, is associated with a high mortality rate [8]

Anhalt et al. were the first to define five diagnostic criteria for paraneoplastic pemphigus [10]. Later, other modified diagnostic criteria have been suggested [11]. In 84% of cases, PNP is co-associated with hematological neoplasms. These include, in order of prevalence: non-Hodgkin's lymphoma (38,6%), chronic lymphocytic leukemia (18,4%), Castelman's disease (18,4%), thymoma (5,5%), Waldenström's macroglobulinemia (1,2%), Hodgkin's lymphoma (0,6%) and monoclonal gammopathy (0,6%) [12,13] Castelman's disease is the most frequently diagnosed associated neoplasm in children. Other, non-hematological neoplasms found in patients are epithelial carcinomas (8.6%), mesenchymal sarcomas (6.2%) and melanoma (0.6%) [13]. Usually, the malignancy is diagnosed before the onset of PNP, but in 30% of individuals, PNP is the first sign that leads to the identification of an occult tumour. In addition, in 10% of patients no neoplasm is found, but in these cases oncological vigilance is essential [13,14].

2. Acroceratosis paraneoplastica

Acroceratosis paraneoplastica (APB) known as Bazex syndrome is a rare dermatological condition that usually occurs in men aged between 40 and 70 years [15]. It is characterised by the presence of acral psoriasis-like skin lesions associated with the presence of a neoplasm, most commonly squamous cell carcinoma (SCC) of the upper respiratory and gastrointestinal tract [16,17]. In most cases, the skin lesions appear before the diagnosis of cancer and tend to resolve after successful neoplastic treatment [16].

Bazex syndrome typically manifests as symmetrical psoriasis-like lesions, located in acral areas such as nose, ears, hands and feet. The lesions are characterized by intense violet erythema, erosions, crusts, and hyperkeratotic papules. A distinctive feature is the thickening of the skin on the soles, sparing the central region, which can aid in diagnosis. Furthermore, nail abnormalities, resembling those seen in psoriasis, are frequently observed and may even precede other clinical signs. The cutaneous lesions may be asymptomatic; however, some patients can experience pruritus or pain [16].

The pathogenesis of Bazex syndrome is currently not fully understood, but there are several theories attempting to explain the mechanism of the disease. One hypothesis suggests the occurrence of cross-reactivity, in which immune cells, reacting to the growth of a tumour, initiate an invasion of keratinocytes. Another theory posits that tumours produce growth factors such as EGF (epidermal growth factor), IGF-1 (insulin-like growth factor 1) and TGF-α (transforming growth factor alpha), which stimulate hyperproliferation of epidermal and epithelial cells, leading to the development of cutaneous lesions observed in APB. One further concept relates specifically to lung SCCs, which can induce a Th2 immune shift. This results in increased production of cytokines, particularly IL-4, IL-5 and IL-13, which subsequently stimulate epidermal growth factor receptor (EGFR) expression on keratinocytes. This process can lead to the appearance of psoriasis-like cutaneous lesions characteristic for the Bazex syndrome [17].

As previously mentioned, APB is most commonly associated with SCC of the upper respiratory and upper gastrointestinal tract, involving locations such as the oral cavity, pharynx, larynx, trachea and oesophagus. The literature also describes the association of Bazex syndrome with other malignancies, including lung cancer (SCC and adenocarcinoma), colorectal adenocarcinoma, ductal breast cancer, biliary tract cancer, genitourinary tumours, Hodgkin's lymphoma and other lymphomas [16–18].

3. Tripe palms

Tripe palms (TP) are also known as acanthosis palmaris, pachydermatoglyphy, palmar hyperkeratosis, palmar keratoderma and acanthosis nigricans of the palms [19]. This skin condition is commonly linked to the Leser-Trélat sign and acanthosis nigricans maligna (ANM), with some experts viewing it more as a subtype of ANM rather than a distinct disorder. It

primarily occurs in adults, showing a higher prevalence among men, who account for 63% of reported cases [1].

TP is characterised by yellowish, velvety, thickened palms with strongly marked dermatoglyphs. Skin lesions resemble the surface of intestinal villi [19]. Histologically, hyperkeratosis, acanthosis and perivascular deposition of mucin in the dermis is shown [1]. In 90% of cases, TP is associated with an underlying malignancy. Lung and gastric cancers were the most frequently identified, accounting for 50% of the cases. Breast and genitourinary cancers were also linked to TP [1,19].The diagnosis of TP usually precedes the identification of a neoplasm or neoplastic recurrence [19].

Physiologically, it is hypothesized that neoplastic cells secrete EGF-α and TGF-α, playing a key role in the process. Both histological and physiological features of AP closely resemble those of ANM, indicating a potential relationship between the two conditions [1].

4. Erythema gyratum repens

Erythema gyratum repens (EGR) is a rare paraneoplastic syndrome that was first described by John Gammel in 1952. The report concerned a 55-year-old female patient who presented with figurate erythema, which subsequently led to the diagnosis of breast adenocarcinoma [20]. The disease is most prevalent in Caucasian men over 60 years of age. Men tend to develop the condition twice as often as women. Typically, the diagnosis of EGR precedes the malignancy detection by 4 to 9 months [21]. Previously, EGR was considered an obligatory cutaneous paraneoplastic syndrome. However, research conducted by Rangioletti et al. suggests that EGR should be classified as a non-obligatory paraneoplastic syndrome. Their study demonstrated that 70% of EGR cases were associated with neoplasms, while 30% had no such connection [22].

EGR is characterized by concentric erythematous bands that resemble wood grain. The cutaneous lesions appear on the trunk and proximal parts of the extremities, usually sparing the hands, feet, and face. Most patients experience severe pruritus. Some reports also mention presence of palmoplantar hyperkeratosis, ichthyosis, and vesicular or bullous lesions. The dermatitis develops rapidly, increasing in size by about 1 cm per day [23].

In the differential diagnosis, the following conditions should be considered: resolving pityriasis rubra pilaris, ichthyosis, syphilis, lupus erythematosus, autoimmune blistering diseases, neutrophilic dermatoses, and cutaneous T-cell lymphoma [24]. The most commonly

associated neoplasms include bronchial, esophageal and breast cancer [21,25]. There have also been cases of EGR patients diagnosed with other malignancies such as: cervix, tongue, stomach, pharynx, bladder, prostate, uterus, colon, rectum, and pancreatic cancer [21]. Effective treatment of the underlying neoplasia often leads to the complete resolution of the lesions [25]. While the exact pathogenesis of paraneoplastic EGR remains unclear, it is believed to involve an immune response triggered by the tumour. This theory is supported by deposits of immunoglobulin G, C3, and C4 in the basement membrane revealed by the direct immunofluorescence (DIF) [22].

5. Necrolytic migratory erythema

Necrolytic migratory erythema (NME) occurs in approximately 70% of patients with glucagonoma syndrome, a clinical condition associated with a neuroendocrine tumour originating from the alpha cells of the pancreatic islets [26]. Glucagonoma syndrome is characterized by the pathological effects of elevated glucagon secretion by the tumour, presenting with a classic triad of diabetes mellitus, significant weight loss and NME. Other possible symptoms include diarrhea, angular stomatitis, cheilitis, deep vein thrombosis, normochromic normocytic anemia, and neuropsychiatric disturbances. Less commonly, patients may present with reversible dilated cardiomyopathy, acute heart failure, or ocular scotomas [1,27]. NME is more commonly observed in women in the fifth decade of life, with an average age of onset of 52 years. As the dermatosis is often the first manifestation of glucagonoma syndrome, its early recognition is crucial to facilitate prompt diagnosis and initiation of appropriate treatment for the underlying neoplasm [1]. Although dermatosis is characteristic of glucagonoma syndrome, it is not exclusive to this condition. It may also be associated with nutritional deficiencies secondary to previous abdominal surgery, alcoholism, anorexia nervosa, cystic fibrosis and celiac disease [27]. Rarely, NME has been seen in patients with multiple endocrine neoplasia type 1 (MEN1) and other malignancies, such as small-cell lung cancer, liver cancer, insulin-secreting tumours and duodenal neoplasms [1,27].

NME lesions develop over approximately two weeks and are characterized by spontaneous exacerbations and remissions. Initially appearing as erythematous vesicles and bullae, they gradually evolve into patches or plaques with central blistering, followed by erosion, crusting, and healing that often leaves residual hyperpigmentation. The lesions can be widespread but are typically located in areas subjected to pressure and friction, such as the perineum, groin,

intergluteal region, lower abdomen, thighs, fingers and lower extremities. They may also appear in the perioral region. Common associated manifestations include angular cheilitis, glossitis, and stomatitis. The skin lesions are intensely pruritic and painful [27–29]. Complications with infections caused by *Candida albicans* or *Staphylococcus aureus* are frequent in NME, often resulting in misdiagnoses of chronic candidiasis. Many patients report prior ineffective treatments with antibiotics and antifungal agents before receiving an accurate diagnosis [1].

The pathogenesis of NME has not been fully elucidated. It has been suggested that the development of skin lesions is the result of excessive glucagon levels and deficiencies of zinc, amino acids and free fatty acids. It is postulated that elevated glucagon levels induce prolonged glycogenolysis and gluconeogenesis, which can cause a depletion of epidermal proteins, resulting in necrolysis. Moreover, glucagon is thought to have a direct role in the pathogenesis of skin lesions. Clinical studies indicate that the supplementation of amino acids and the normalization of glucagon levels in affected patients contribute to the rapid resolution of skin lesions [28].

6. Acquired hipertrichosis lanuginosa

Acquired hipertrichosis lanuginosa (AHL) is a rare paraneoplastic dermatosis first described by Turner in 1865 in a woman with breast cancer [30]. Since then, it has been called “malignant down”, indicating its association with advanced neoplasms. It predominantly affects women between 40 and 70 years of age [31]. The most commonly associated neoplasms are bronchopulmonary (32%) and gastrointestinal (26%) malignancies [32]. Other reported neoplasms are breast, uterus, bladder, ovary, gallbladder, pancreas, liver, kidney, parotid gland, cervical and prostate carcinomas, lymphoma, leukemia, melanoma, and Ewing's sarcoma [31–33]. HLA is typically diagnosed up to 5 years before or up to 8 years after the detection of malignancy. Unfortunately, at the time of HLA diagnosis, majority of patients present with metastases, which significantly worsens the prognosis [31]. If the tumour is successfully treated, AHL frequently resolves [31,33,34].

In the course of the disease, a sudden and rapid growth of lanugo-type hair in a craniocaudal direction is observed [31]. Hair typically appears on the face, trunk, and limbs, while usually sparing the palms, soles, suprapubic and genital areas. Reported associated symptoms observed in this condition include burning glossitis, hypertrophy of lingual papillae, oral hyperpigmentation, trichomegaly, alterations in taste and smell, diarrhea, lymphadenopathy,

and weight loss [32]. Additional dermatological manifestations reported in AHL include scleroderma, seborrheic keratoses, florid cutaneous papillomatosis, acanthosis nigricans, palmoplantar hyperkeratosis, acquired ichthyosis and Leser-Trélat sign [31,32].

The pathogenesis of paraneoplastic AHL is not fully understood. It is hypothesized that cytokines produced by tumours stimulate the proliferation of hair follicle cells. In lung tumours, the production of fibroblast growth factors (FGFs) has been observed, which are known to influence hair growth. Additionally, other growth factors produced by epithelial tumours, such as Wingless proteins and β-catenin, also play a role in promoting hair follicle development [34]. AHL should be distinguished from hypertrichosis resulting from endocrine or metabolic disorders such as anorexia nervosa, AIDS, brain injury, hypothyroidism, polymyositis, porphyria cutanea tarda, primary biliary cirrhosis, shock, or systemic lupus erythematosus. Additionally, it must be differentiated from medication-induced hypertrichosis, which can occur with the use of drugs like corticosteroids, cyclosporine, diazoxide, interferon-α, minoxidil, penicillin, phenytoin, spironolactone, streptomycin, and zidovudine [33].

7. Ectopic ACTH syndrome

Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) occurs in approximately 20% of patients with ACTH-dependent Cushing's syndrome (CS) and accounts for about 10% of all cases of CS. EAS is caused by tumours that secrete excessive amounts of ACTH, and it can be associated with nearly any neuroendocrine or non-endocrine tumour. However, it is most frequently linked to bronchial carcinoids, small cell lung carcinomas (SCLCs), pancreatic and thymic carcinoids, thyroid medullary carcinomas, and pheochromocytomas [35].

The dermatological manifestations of EAS closely resemble those of ACTH-dependent CS and include skin thinning, easy bruising, weight gain, facial fullness, and generalised hyperpigmentation [36,37]. The degree of skin hyperpigmentation varies depending on several factors, including the type of ACTH-secreting tumour, ACTH levels, and the speed of onset and severity of EAS. It can occur both before and after the tumour is diagnosed. Diffuse skin hyperpigmentation with elevated ACTH requires a broad differential diagnosis, including Addison's disease, Nelson's syndrome, and Cushing's syndrome, which result from pituitary tumours or ectopic ACTH-secreting non-pituitary neoplasms [36].

8. Carcinoid syndrome

Carcinoid syndrome (CS) is a paraneoplastic syndrome associated with the presence of neuroendocrine tumours (NETs). The pathogenesis of the symptoms is due to the secretion by the tumours of over 40 humoral substances, such as histamine, tachykinins, kallikrein, prostaglandins or serotonin, with serotonin being thought to play the predominant role in the clinical manifestations [38].

NETs can develop in a variety of locations including the bronchi, gonads, thymus or gastrointestinal tract [39]. Carcinoid syndrome is most commonly associated with NETs originating in the midgut, particularly in the presence of liver metastases. This occurs because biologically active substances secreted by the tumor bypass hepatic metabolism, avoiding inactivation. As a result, these substances enter the systemic circulation directly, leading to the clinical manifestations of CS. Less frequently, it can occurs in cases of lung carcinoids, NETs originating from the pancreas or ovaries, and metastatic small bowel NETs with extrahepatic disease. [40].

Symptoms that can be found in this condition include diarrhea (78%), cutaneous flushing (78%), wheezing/ asthma-like symptoms (12%) and pellagra-like skin lesions with hyperkeratosis and pigmentation (1%)[41]. Flushing can take a variety of clinical forms. It most commonly presents as recurrent episodes of sudden erythema, usually lasting a few minutes and affecting mainly the face, neck or upper trunk. Characteristically, there is no accompanying sweating. Triggers may include physical exertion, alcohol or tyramine-rich foods, such as kiwi, chocolate, banana, nuts, and avocado. A less common form is atypical flushing, which presents as a purplish erythema. This type of lesion lasts for several hours and may also occur on the extremities. Next condition is pellagra, resulting from niacin (vitamin B3) deficiency, which in CS is caused by excessive synthesis of tryptophan or chronic secretory diarrhea. Symptoms of pellagra include dermatitis, diarrhea and, in severe cases, dementia. Patients may also complain of severe pruritus [39,40]. Other manifestations of CS include cardiac symptoms (40%) such as tricuspid stenosis, pulmonary regurgitation, pulmonary stenosis and mitral regurgitation. There may also be cognitive disorders and other conditions such as rheumatoid arthritis, arthralgia, ophthalmic flushing leading to vascular occlusion and a range of problems associated with increased fibrosis [41].

9. Adenopathy and Extensive Skin patch Overlying a Plasmacytoma syndrome

Adenopathy and Extensive Skin patch Overlying a Plasmacytoma (AESOP) syndrome is a rare cutaneous paraneoplastic syndrome first described by Lipsker in 2003 [42].
Skin lesions appear as a large 5-10cm in diameter patch or plaque that gradually expands. It is associated with an underlying plasmacytoma and typically located on the rib cage, sternum, or scalp [43,44]. Cutaneous findings are classified into two variants. The first is the classic form, characterized by a smooth, shiny red or brown patch with inappropriately visible skin vessels. The second is the morphea-like variant, presenting as a plaque with folded skin [43]. Typically, regional lymphadenopathy develops within a few months after the appearance of skin lesions [45]. As it is an initial manifestation of POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-Protein, Skin changes), a life-threatening condition, early diagnosis is crucial and potentially lifesaving [43].

The exact mechanism of skin lesion formation is not fully elucidated. It has been hypothesised that cutaneous findings may arise secondary to the action of angiogenic growth factors, such as VEGF, and cytokines, including interleukin-1β, TNF-α and interleukin-6, produced by plasmacytoma. Successful treatment of the plasmacytoma often results in the resolution of the skin changes within a few months and in the disappearance of the POEMS symptoms [45].

CONCLUSIONS

It is crucial to be aware that certain skin lesions may be associated with neoplasms. This review discusses cutaneous paraneoplastic syndromes, which are almost always associated with malignancy, making their awareness extremely important in clinical practice. Early identification of these dermatoses can facilitate prompt oncological diagnosis, enabling the rapid initiation of treatment, thereby significantly improving prognosis and potentially saving patients' lives.

DISCLOSURES

Author's contribution:

Conceptualization, PP, MG; methodology, PP, MK; software, PP; check, MZ; formal analysis, PP; investigation, PP, MG; resources, MG, MZ; data curation, MZ, MK; writing - rough

preparation, PP; writing - review and editing, MK; MZ; visualization, MG; supervision, MK; project administration, PP; All authors have read and agreed with the published version of the manuscript.

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