REVIEW

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Paraneoplastic dermatoses

Stephanie Natasha DJUANDA[1], Willy SANDHIKA[2]

[1]Faculty of Medicine, University of Surabaya, Surabaya, East Java, Indonesia
[2]Faculty of Medicine, Airlangga University, Surabaya, East Java, Indonesia

ABSTRACT

The skin is a window to changes deep organ. Several skin lesions indicate a deep organ malignancy. An abrupt onset of multiple seborrheic keratosis indicates a deep organ malignancy, acanthosis nigricans can be a sign of malignancy at another organ. There is a form of pemphigus that occurs in corresponding to lymphoma or other neoplasm. Dermatomyositis is an autoimmune disease that involves skin and muscle, however it can be a sign to other organ malignancy. Sweet syndrome can indicate a myeloproliferative or lymphoproliferative disorder. Pyoderma gangrenosum can be a sign to other neoplastic disease. Understanding skin lesion would help us to seek and identify other organ malignancy in early stage.

Keywords: neoplasm, paraneoplastic syndrome, malignancy, skin

Abbreviations:

AN	– Acanthosis nigricans	SLE	– Systemic lupus erythematosus	MPDs	– myeloproliferative disorders
ANA	– Anti-nuclear antibody			LPDs	– lymphoproliferative disorders
DEJ	– Dermoepidermal junction	TEN	– Toxic epidermal necrosis	PG	– pyoderma gangrenosum
DM	– Dermatomyositis	Anti-dsDNA	– anti-double stranded deoxyribonucleic acid	IL	– interleukin
HE	– hematoxylin eosin			TNF	– Tumor necrosis factor
HIV	– Human Immunodeficiency virus	G-CSF	– Granulocyte-Colony stimulating factor	PMN	– polymorphonuclear
				IFN	– interferon
MCP	– metacarpophalangeal	CKMB	– Creatinin Kinase-MB	AML	– acute myelogenous leukemia
PCOS	– Polycystic ovary syndrome	CPK	– Creatine Phosphokinase	IBD	– inflammatory bowel disease
PNP	– Paraneoplastic Pemphigus	LDH	– Lactate Dehydrogenase	MMP	– matrix metalloproteinase
SJS	– Stevens-Johnson syndrome	SS	– Sweet syndrome		

INTRODUCTION

Paraneoplastic syndrome is the symptoms of a malignant tumor, apart from the symptoms of the tumor itself. This is neither a symptom of a primary tumor nor a metastatic tumor. In general, symptoms of paraneoplastic syndrome arise because tumor cells actively produce certain hormones. However, some tumors that do not produce hormones can also cause symptoms of paraneoplastic syndrome.

The skin, as one of the outermost organs, can be a manifestation of paraneoplastic syndrome. There are several tumors in internal organs that may have an unclear presentation but give symptoms of paraneoplastic syndrome on the skin, known as paraneoplastic dermatoses.

CONTENT

This article will discuss several paraneoplastic syndromes with skin manifestations.

Seborrhoeic keratosis and Leser-Trélat sign

Seborrhoeic keratosis is a benign tumor on the skin that is common, especially in the elderly. These tumors

Corresponding author:
Willy Sandhika
E-mail: willysand@fk.unair.ac.id

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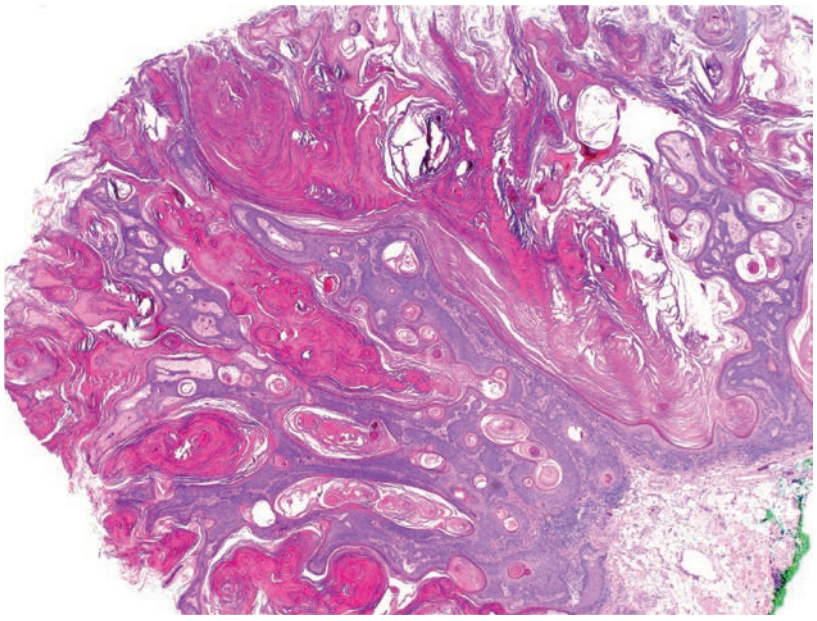

FIGURE 1. *Histopathology feature of Leser Trélat sign. The microscopic feature are same as seborrhoeic keratosis, with hyperkeratosis, papillomatosis and pseudohorn cyst (HE, 100x) [9]*

can sometimes present an asymmetric appearance similar to malignant melanoma. Microscopic examination can clearly differentiate seborrhoeic keratosis from malignant melanoma. In seborrhoeic keratosis, there are no signs of anaplasia [1].

Seborrhoeic keratoses are only a proliferation of mature squamous epithelial cells, which can be accompanied by the formation of excessive keratin material. This tumor is not a premalignant lesion. However, the presence of a lot of seborrheic keratosis can be a sign of malignancy in the internal organs, known as the Leser-Trélat sign. The neoplasm most often associated with Leser-Trélat sign is gastric adenocarcinoma [2], but apparently this sign is also found in other malignancies, namely lymphoproliferative disorders, lungs, bladder, breast and ovarian tumors [2-5].

However, it's important to note that Leser-Trélat sign is rare and does not always indicate the presence of cancer. Inamadar and Palit reported a case of Leser-Trélat sign, which occurred in a 32-year-old man with HIV infection. This patient experienced multiple eruptions of papules on the head, neck, and trunk within 3 weeks [6]. Hsu et al. reported the incidence of Leser-Trélat signs in post-heart transplant patients who were taking immunosuppressant drugs [7]. These two cases show that the immune system also plays a role in the occurrence of these signs. Therefore, it is very important for individuals who experience multiple seborrheic keratoses to undergo a thorough evaluation to determine the cause.

Histopathology examination of a biopsied seborrheic keratosis from a patient suspected to exhibit the Leser-Trélat sign does not show any significant difference compared to a seborrheic keratosis in a patient without underlying malignancy (Figure 1) [8,9].

Acanthosis Nigricans (AN)

AN is a skin condition characterized by thickened, dark, velvety patches of skin, especially in intertriginous areas, such as the axilla and the neck. A generalized pruritus and mucosal involvement can be found [2,10]. While AN can be associated with certain malignancies, including deep organ malignancies, it is more commonly associated with non-cancerous conditions such as obesity, insulin resistance, hormonal disorders like PCOS, and certain medications [2].

In cases where AN is associated with malignancy, it often occurs in the context of adenocarcinomas, particularly gastric cancer or certain types of adenocarcinomas of the gastrointestinal tract. AN also can be found in other adenocarcinoma in diverse sites, include uterine, liver, intestine, pancreas, thyroid, ovary, kidney, breast, lung, bladder, prostate, and gallbladder [2,11].

Chu et al. reported paraneoplastic acanthosis nigricans appearing on the oral mucosa in a 59-year-old patient with endometrial carcinoma. This patient experienced papillomatic lesions that appeared in several parts of the body, especially on the lips, oral mucosa, and axilla. A skin biopsy examination of the lesions from the oral mucosa and axilla showed similar features [12].

It should be raised suspicion if the AN occur in sudden onset, in nonobese-patients and involved more widespread/ atypical area (interdigital, soles, palm, eyelids, perioral, or mucosal surfaces) [13]. Microscopically, skin biopsy would have feature of hyperkeratosis, papillomatosis, acanthosis, elongated dermal projections, or epidermal atrophy, and absence of inflammatory infiltrate (Figure 2).

It is important to note that AN is not specific to cancer and can occur in a variety of contexts. The presence

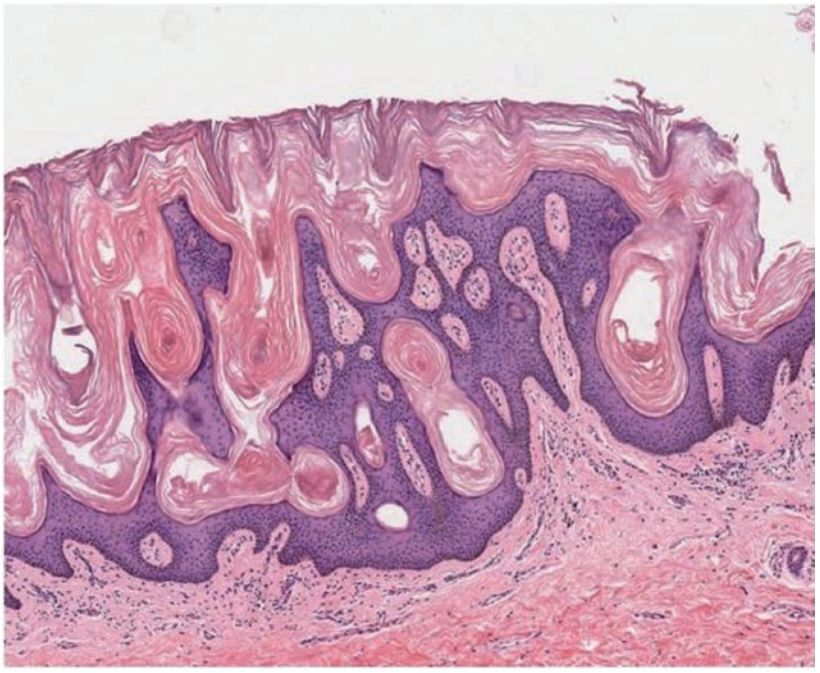

FIGURE 2. *Histopathology feature of AN. A skin biopsy showing hyperkeratosis, papillomatosis, acanthosis, and increased dermal pigmentation in epidermis (HE, 200x) [12]*

of AN may prompt further investigation to rule out underlying malignancy, especially if it presents suddenly, is extensive, or is associated with other signs that suggest a paraneoplastic syndrome.

Paraneoplastic Pemphigus (PNP)

An autoimmune condition known as pemphigus causes a spectrum of blistering diseases called acantholysis, in which immunoglobulins attack keratinocyte cells and cause the epidermal cells to separate from one another. Although pemphigus vulgaris is the most common variety, malignancies may occasionally coexist with pemphigus. Among the scope of paraneoplastic syndromes, this condition is known as paraneoplastic pemphigus [14].

While PNP and pemphigus vulgaris typically affect the elderly, it has been discovered that PNP can also affect young people. PNP is most frequently linked to hematolymphoid cancers, including Castleman disease, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. PNP in thymomas is likewise uncommon, but it does occur occasionally [14-15]. Castleman disease is typically the cause of PNP in children and adolescents [16].

Both pemphigus vulgaris and paraneoplastic pemphigus affect the skin and mucosa generally. The clinical symptoms of both vary but usually begin with lesions on the mucosa, (e.g oral mucosa, lips, conjunctiva, gastrointestinal and respiratory tract). Skin manifestation appears later and varies, from blistering to lichenoid lesion. Joy et al. reported a case of PNP in a 13-year-old teenager with erosion of the oral mucosa for 18 months without any lesions on the skin or other mucosa. The patient was diagnosed with pemphigus vulgaris but did not respond to therapy and even worsened. Symptoms of stomatitis in PNP are generally more severe than in pemphigus vulgaris and do not respond to therapy. After a thorough examination, it was discovered that Castleman disease was present in the abdomen [17].

Before making a PNP diagnosis, Steven Johnson syndrome (SJS) and Toxic Epidermal Necrosis (TEN), must be ruled out. Despite having numerous similar features, SJS/TEN and PNP need to be distinguished from one another due to their very distinct management and prognosis. The treatment of PNP involves treating the main tumor, while in SJS/TEN requires discontinuing the causing drugs and giving steroids [15]. PNP has a mortality rate of up to 90% and a significantly less favorable outlook than SJS/TEN. Sepsis, gastrointestinal hemorrhage, and bronchitis obliterans are the complications that led to death [10,15].

It's yet unclear what causes PNP pathogenesis. Didona et al. state both humoral and cellular immunity has been shown to be involved in PNP. Cellular immunity is represented by T cells and Natural Killer Cells in the dermo-epidermal junction, and humoral immunity is represented by antibodies against adhesion molecules on the surface epithelium, such as plakin, plakophilin, and desmoglein [10].

Immunofluorescence, immunoprecipitation, and histological analysis are used to confirm the diagnosis of PNP. Histopathologically, PNP shows inflammatory cell infiltration and suprabasal acantholysis, which may be associated with epidermal necrosis (Figure 3A); in

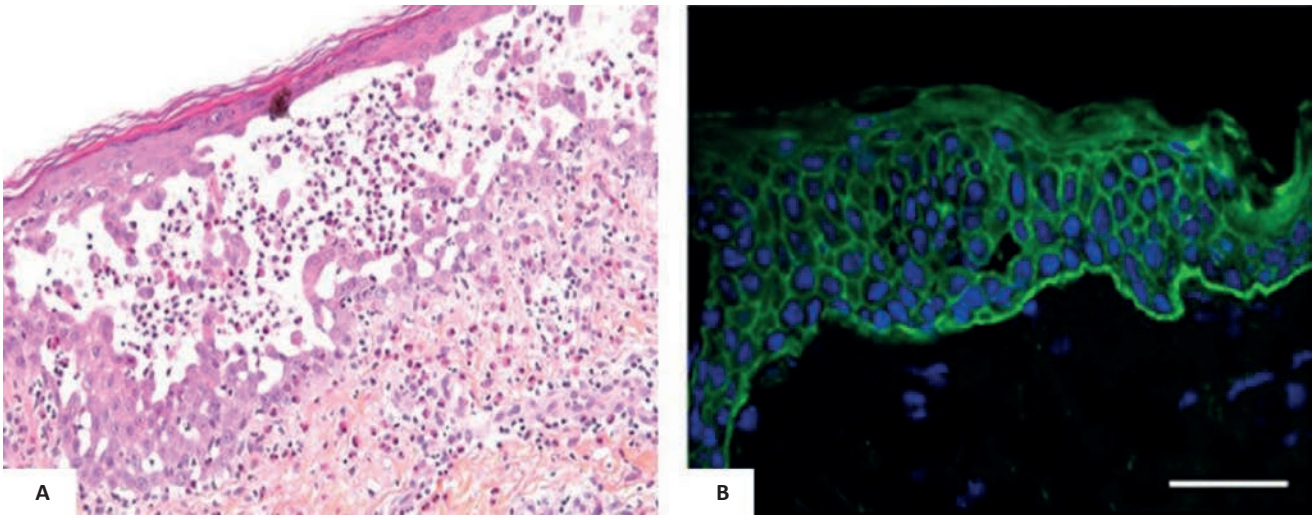

FIGURE 3. *Histopathology and immunofluorescence feature of PNP. (A) Suprabasal acantholysis and intraepidermal blister formation with eosinophil and lymphocyte infiltrate (HE, 100x) [18]; (B) Direct immunofluorescence showed IgG deposit at intercellular spaces and dermoepidermal junction (IgG Immunofluorescence, 100x) [16]*

contrast, SJS/TEN shows epidermal necrosis along with a normal stratum corneum. IgG deposits can be detected in the basement membrane and epidermal intercellular space by immunofluorescence analysis of PNP (Figure 3B). Finding protein complexes (plakin) in immunoprecipitation examination is the gold standard for diagnosing PNP [10,15,16,18].

Paraneoplastic Dermatomyositis (DM)

Paraneoplastic DM is a rare autoimmune disease and is usually considered a diagnosis of exclusion. DM is an autoimmune inflammatory myopathy characterized by muscle weakness and skin rash. To be able to diagnose DM, the clinician needs to exclude other diseases such as psoriasis, lichen planus [19], seborrhoeic dermatitis, SLE, and drug eruption [20]. While it can occur on its own, it is considered a paraneoplastic syndrome when it is associated with an underlying malignancy. Patients with DM have an increased risk of developing certain types of cancer compared to the general population. In many cases, DM precedes the diagnosis of cancer, which suggests that it can be a paraneoplastic syndrome associated with an underlying malignancy. Some of the malignancies reported to be associated with DM are ovarian, lung, gastrointestinal, nasopharyngeal, breast, prostate, kidney, non-Hodgkin lymphoma, and even some cases of sarcoma [21]. For this reason, it is necessary to carry out a thorough history regarding the presence of additional symptoms, history of previous illnesses, medication history, family history, as well as factors that trigger and relieve the symptoms. In addition, physical and other supporting procedures, for example, muscle enzyme examination, electromyography, serological examination of anti ds-DNA, ANA, and skin and muscle biopsy [20].

Like other autoimmune diseases, DM is more common in women. Symptoms of DM generally begin with varying skin symptoms and last for several months to years before muscle involvement occurs. Clinician should suspect of DM if specific signs are found, especially Gottron's sign and Gottron's papule. Gottron's sign is the presence of erythematous macules on the extremities, especially on the dorsal and lateral areas of the fingers, knees, and elbows. Gottron papules are red-purple papules on prominent body surfaces, for example, the MCP area, interphalanges, and distal interphalangeal joints. These lesions can extend to the nail border [10,19].

This feature needs to be differentiated from lichen planus and psoriasis. Ricceri et al. reported a case of a 30-year-old woman with lesions in the form of reddish papules in the MCP area and interphalangeal joints. There was no increase in muscle enzymes or changes in electromyography, so the patient was diagnosed with psoriasis, but it did not improve with topical treatment [19].

Aside from periungual telangiectasis with dystrophic cuticles and local hemorrhagic infarction (Keining's sign), other skin symptoms associated with DM include symmetrical erythema in the face accompanied by edema (heliotrope rash), erythematous rash in the thoracic and back areas (shawl and V-sign), vasculitis, and calcinosis cutis. It is necessary to distinguish these symptoms from seborrheic dermatitis and SLE [10].

In addition to cutaneous complaints, DM also causes weakness in the muscles. Dysphagia, which may be accompanied by diaphragmatic weakness, and gradual symmetrical weakness in the proximal extremities are among the symptoms 22. The outcomes of the follow-up examination, which revealed variations in the waves on the electromyography examination and an

increase in muscle enzyme levels (e.g CKMB, CPK, and LDH) are likely to confirm the presence of this weakness 10 It was discovered that several autoantibodies against TIF1-Y and anti-NXP-229 were implicated in DM, and the presence of these antibodies further raised the risk of malignancy [23].

Merry et al. reported a case of DM in a 43-year-old female patient with metastatic leiomyosarcoma accompanied by symptoms of DM. The patient complained of a maculopapular rash on the face and chest area that extended to the extremities, accompanied by periorbital edema and weakness in both legs. Laboratory results showed a slight increase in leukocyte count, C-reactive protein, creatine kinase, alanine transaminase, and ANA test levels. The myositis antibody panel only showed positive results for TIF1-Y. A muscle biopsy was not performed to minimize the risk of metastasis [21].

Histopathological images from skin biopsies in patients with DM show thinning of the epidermis, hydropic degeneration of basal cells, edema in the papillary dermis accompanied by mononuclear inflammatory cell infiltrates, and mucin deposition in the dermis and DEJ layers (Figure 4) [24]. Skin biopsy examination with hematoxylin eosin makes it difficult to differentiate between DM and SLE. Histopathological examination of a muscle biopsy shows segmental necrosis of muscle fibers accompanied by loss of capillary blood vessels and infiltration of lymphocyte, histiocytes and plasma cells [10,20].

Sweet syndrome (SS)

Sweet syndrome also known as acute febrile neutrophilic dermatosis, is a rare skin condition characterized by fever, painful skin lesions, and neutrophilic infiltration of the skin. While Sweet syndrome can be associated with malignancies, including deep organ malignancies, it is more commonly associated with various other conditions, such as infections, inflammatory diseases, medications, and autoimmune disorders [25]. When Sweet syndrome occurs in association with malignancy, it is termed “paraneoplastic Sweet syndrome.” The malignancies most commonly associated with paraneoplastic Sweet syndrome include hematologic malignancies (such as acute myeloid leukemia, myelodysplastic syndromes, and Hodgkin lymphoma as well as solid tumors like gastrointestinal, genitourinary, and respiratory tract cancers [2,26]. Gormley et al. reported Sweet syndrome in melanoma patient treated with ipilimumab [27].

Sweet syndrome can be associated with deep organ malignancies, but it is important to recognize that it can also occur in association with various other conditions. Further evaluation is necessary to determine the underlying cause in each individual case. There is a recognized association between Sweet syndrome and myeloproliferative disorders (MPDs). MPDs are a group of hematologic malignancies characterized by the abnormal proliferation of blood cells in the bone marrow. Examples of MPDs include polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Sweet

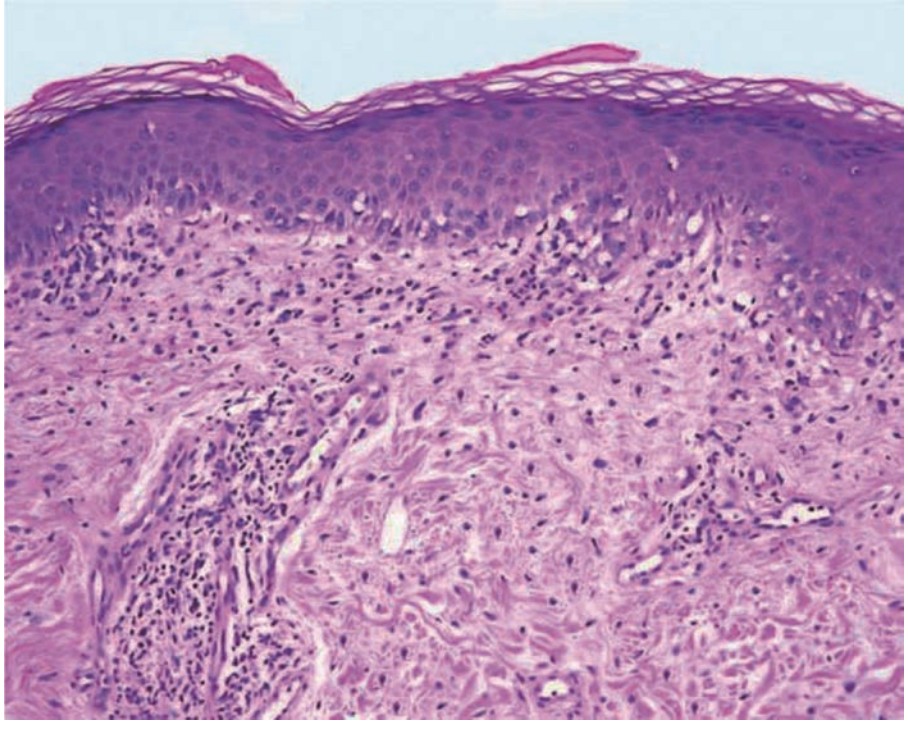

FIGURE 4. *Histopathology feature of paraneoplastic DM. A skin biopsy from dermatomyositis patients showed thinning of the epidermis, hydropic degeneration of basal cells, edema in the papillary dermis accompanied by lymphocytes, histiocytes, plasma cells, and mucin deposition in the dermis (HE, 200x) [24]*

syndrome can occur in individuals with myeloproliferative disorders, particularly in cases where there is an underlying inflammatory or immune dysregulation. In fact, Sweet syndrome is considered one of the dermatologic manifestations of myeloproliferative disorders. The exact mechanisms underlying the association between Sweet syndrome and myeloproliferative disorders are not fully understood, but it is believed to involve the release of pro-inflammatory cytokines and other inflammatory mediators from dysregulated immune cells and leukocytes in the bone marrow [26]. Heath and Ortega-Loayza showed that neutrophils in patients with Sweet syndrome had a lower apoptotic rate and higher survival ability, resulting in high G-CSF levels in these patients. This situation is exacerbated by tumor cells, which can also produce G-CSF [28].

When Sweet syndrome occurs in association with a myeloproliferative disorder, it is important for healthcare providers to evaluate and manage both conditions simultaneously. Treatment may involve addressing the underlying MPD as well as providing symptomatic relief for Sweet syndrome skin lesions, often with corticosteroids or other immunosuppressive agents [29].

There is a recognized association between Sweet syndrome and lymphoproliferative disorders (LPDs). Lymphoproliferative disorders are a group of conditions characterized by the abnormal proliferation of lymphocytes, which are a type of white blood cell involved in the body's immune response. Examples of lymphoproliferative disorders include Hodgkin lymphoma, non-Hodgkin lymphoma, and lymphocytic leukemia [29].

If a histological study reveals neutrophil infiltrates in the skin lesion, SS can be diagnosed. These skin lesions can occur anywhere on the body, from the head to the toes, and can vary in size from painful plaques to pustules. Aside from that, peripheral leukocytosis, arthralgia, and fever also accompany the onset of these disorders. It can be challenging to distinguish this disease from necrotizing fasciitis in severe situations. In a case series of 54 patients, Sanchez et al. found that 51 percent of them had necrotizing fasciitis and were therefore not treated appropriately [30].

When Sweet syndrome is evaluated histopathologically, extensive neutrophil infiltrates can be observed in the reticular dermis along with blood vessel dilation and papillary dermal edema. The epidermis appears normal with mild spongiosis [27].

Pyoderma gangrenosum (PG)

Pyoderma gangrenosum is a rare and progressive skin disease. Clinically, PG manifests as pustules - painful reddish vesicles that can coalesce quickly and cause ulceration and necrosis. PG is a chronic skin disease, and initially thought to be the result of an infectious process. However, debridement and antibiotics did not seem to cure PG; on the contrary, they seemed to worsen the disease [10,31]. Therapy with steroids and immunosuppressant drugs actually gives better results; therefore, PG is considered to be more related to the process of autoimmunity, and neutrophils are thought to play an important role in the pathogenesis of this disease [31,32].

Until now, the pathogenesis of PG has been unclear. According to Gameiro et al., PG is most likely caused by an imbalance in neutrophil homeostasis. In PG and several other neutrophilic diseases (e.g., Sweet syndrome), there are increased levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-Y), and G-CSF) in the blood and various organs, especially the skin. The presence of proinflammatory cytokines and various chemokines such as IL-8/CXCL8 and CXCL 1,2,3 will cause active recruitment and infiltration of T cells and neutrophils into the skin. Apart from that, Matrix metalloproteinase (MMP) expression was also found, which destroys the extracellular matrix and plays a role in producing neutrophilic chemokines. The increase in Elafin, a neutrophil elastase inhibitor expressed by damaged keratinocytes, plays a role in enhancing the process of tissue damage and apoptosis. This process contributes to ulcer formation, impaired remodeling, and the wound healing process in PG [31].

PG is generally a manifestation of several diseases, both neoplastic and non-neoplastic. While PG is frequently linked to rheumatoid arthritis, autoinflammatory disorders, and IBD, it can also occasionally be a sign of solid organ and hematological malignancy. Multiple reports in the literature have found an association between PG and solid organ tumors [33]. Hematolymphoid malignancies are more frequently associated with PG and usually take the form of AML.

In research by Shah et al., it was found that the solid organ malignancy most commonly associated with PG was breast cancer (31.6%), followed by carcinoma of the gastrointestinal tract (colorectal, gastric, ileum), respiratory tract (lung, hypopharynx), and renal carcinoma [32].

Histopathological examination of PG does not provide a specific picture. Microscopically, polymorphonuclear (PMN) infiltrates were only found in the dermis. In late-stage cases, it can be accompanied by mononuclear inflammatory cell infiltrates and fibrosis, as well as leukoclastic and lymphocyte-mediated vasculitis [10].

Because it is a rare case, to be able to diagnose PG as paraneoplastic dermatoses, other diseases and PG associated with other autoimmune diseases must be excluded. According to You et al. (2018), a PG is considered to be a paraneoplastic dermatosis if the lesion does not respond to immunosuppressive agents commonly used as PG therapy; the lesion disappears with-

out recurrence within 3 years after complete removal of the primary tumor [34].

CONCLUSION

Several inflammatory dermatoses have been identified as paraneoplastic dermatoses. These dermatoses are an inflammatory condition that does not have any atypia nor malignant features; however, they can be a sign to other deep organ malignancy. There were no differences between paraneoplastic dermatoses compare to non-paraneoplastic counterpart. Therefore, an abrupt onset of these conditions condition should raise a suspicious of paraneoplastic syndrome and a search must be done thoroughly to find whether there was any malignancy of other deep organs in the body.

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