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Parapsoriasis – A Diagnosis with an Identity Crisis: A Narrative Review

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ABSTRACT

Parapsoriasis is an uncommon inflammatory skin disease which is characterized by chronic patches that may be resistant to therapy. It was primarily introduced and classified 120 years ago, and the original classification incorporated parapsoriasis and pityriasis lichenoides under the same umbrella of parapsoriasis group. After a major change in classification, parapsoriasis now exclusively refers to small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP). However, debates still frequently occur regarding various nomenclatures and classifications used by different authors. Moreover, parapsoriasis may progress to overt cutaneous lymphoma, most commonly mycosis fungoides (MF), and it is very difficult to distinguish these two conditions despite modern histologic and molecular testing techniques.

As parapsoriasis is a rare disease; there is a lack of studies and clinical guidelines to assist physicians in clinical practice. In our comprehensive review, we review several aspects of parapsoriasis, from the history of nomenclature and classification, clinical characteristics, immunohistopathology, and advanced molecular techniques for the diagnosis of this condition, to the most current treatments. We also propose a scheme for distinguishing parapsoriasis from early-stage MF in this review.

Keywords: Parapsoriasis; Small plaque parapsoriasis; Large plaque parapsoriasis; Digitate dermatosis; Poikiloderma vasculare atrophicans; Mycosis fungoides; Premycotic dermatosis

Key summary points

- Parapsoriasis is a group of rare, chronic, recalcitrant asymptomatic inflammatory skin diseases. In the current classification. It is divided into small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP).

- The diagnosis of parapsoriasis is predominantly based on clinical grounds. SPP presents with oval patches, less than 5 cm, and LPP presents with patches, larger than 5 cm. The immunohistopathologic findings are nonspecific and it can mimic various inflammatory skin diseases and mycosis fungoides.

- SPP rarely progresses, but LPP has a substantial risk to evolve to MF. LPP and patch stage MF share many common features, both clinically and histologically, so may be difficult to differentiate between the two. TCR gene rearrangement studies cannot make a distinction among SPP, LPP, and patch stage MF. The prognosis of both LPP and patch stage MF is excellent.

- Most patients with SPP and LPP are asymptomatic, but they respond to treatment poorly. Observation or topical therapy, such as emollients, topical corticosteroids, and phototherapy are commonly prescribed.

INTRODUCTION

Parapsoriasis is an uncommon inflammatory skin disease. Originally, the conditions grouped under the umbrella of parapsoriasis were different from the current classification that most dermatologists recognize nowadays. The confusion occurred due to the diverse nomenclatures and definitions associated with parapsoriasis in the past, as well as the different interpretations when translating from different languages. Moreover, parapsoriasis is a misnomer because it is entirely unconnected to psoriasis. The risk of these conditions progressing to cutaneous lymphoma is a major concern, and it has been investigated extensively.

In this review, we intend to update the classification of parapsoriasis, including its evolution and clarify the confusing and overlapping terminologies used in the past. We also provide the most recent knowledge about clinical characteristics, histopathology and immunophenotypes, treatment, and the association to lymphomas among the members of the parapsoriasis group according to the current or modern classification.

The term parapsoriasis was first introduced by Brocq in 1902, referring to a group of rare inflammatory skin diseases, which were idiopathic, chronic, often asymptomatic, and resistant to therapy [1].

At that time, parapsoriasis encompassed various separate diseases, which had been described previously by different authors, including parakeratosis variegata or retiform parapsoriasis, first described in 1890 by Unna et al [2], and pityriasis lichenoides described in 1894 by Neisser and Jadassohn [3, 4], erythrodermies pityriasques en plaques disseminees, which is clinically equivalent to small and large plaque parapsoriasis, established by Brocq in 1897 [5], and pityriasis lichenoides chronica (PLC), described by Juliusberg [6], in 1899.

Subsequently, there were a number of emerging terms identified as distinct subtypes of parapsoriasis proposed by several authors. For example, acute pityriasis lichenoides was named in 1916, and pityriasis lichenoides et varioliformis acuta (PLEVA) was named in 1925, by Mucha [7] and Habermann [8] respectively. Currently, Mucha- Habermann disease is an alternative term of PLEVA [9, 10].

Historically, the classification of parapsoriasis originally constituted two major diseases, parapsoriasis or parapsoriasis en plaques and pityriasis lichenoides. Parapsoriasis en plaques was divided into two subtypes: small plaque parapsoriasis (SPP) and large plaque parapsoriasis (LPP). Likewise, pityriasis lichenoides was divided into two main subtypes: PLEVA and PLC [9, 10] (Table 1).

Later, in 1926, Wile removed pityriasis lichenoides from the parapsoriasis group, which was was widely accepted. Most physicians agreed to reclassify parapsoriasis as a separate entity, which was documented in the literature [9].

After decades, the original classification of parapsoriasis became less popular and most dermatologists, nowadays, generally consider parapsoriasis as a single disease with two subtypes: SPP and LPP (Table 1). However, confusion with the nomenclature of these diseases still frequently occurs, not only with the ambiguity or variety of names but also with the language translation. For example, “parapsoriasis en plaques” was originally established by a French physician, and the word “plaque” in French means “patch” in English. Consequently, some physicians might have misinterpreted clinical appearance. Furthermore, the term “parapsoriasis en plaques” was interchangeably used for different conditions either SPP or LPP in prior studies. Another confusion is the overlapping terminologies between parapsoriasis and mycosis fungoides (MF), such as parapsoriasis lichenoides, retiform parapsoriasis, and parapsoriasis variegata. Some of these terms were used by experts to identify MF and continued to be used by some experts in the present day [9, 11, 12].

This review contains the names that were used to call parapsoriasis, LPP, and SPP in the past in order to facilitate clear communication in dermatology globally without generation gaps or languages barriers.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. All patients provided written consent for their pictures to be published.

CLINICAL CHARACTERISTICS

Parapsoriasis (parapsoriasis en plaques)

Parapsoriasis is an uncommon, chronic papulosquamous dermatosis of unknown etiology. It occurs worldwide and most commonly affects middle-aged or older adults with a male preponderance [13]. Most patients are asymptomatic or mildly pruritic, but usually respond poorly to treatments.

SPP

Former names: *Chronic superficial dermatitis, Parapsoriasis guttata, benign type, Leopard-spot parapsoriasis, Parapsoriasis en plaques, small plaque type/ simple discrete type/ benign type*

SPP typically appears with round to oval erythematous, yellow or brown macules and patches with fine scales. Most lesions are less than 5 cm in diameter, and commonly involve the trunk and proximal extremities. SPP rarely progresses.

"Digitate dermatosis" is a distinctive variant of SPP originally reported by Hu and Winkelmann in 1973 [14], presented with elongated, fingerlike patches located on the flanks in a parallel pattern (Figure 1). The long axis of skin lesions may be larger than 5 cm. The term “Xanthoerythrodermia perstans” has been used to identified patients with yellowish skin lesions [9].

LPP

Former names: *Atrophic parapsoriasis, Poikilodermatous parapsoriasis, Parapsoriasis en plaques, large plaque type /atrophic type, Parapsoriasis en grandes plaques simples, Parapsoriasis en grandes plaques poikilodermiques, Lichenoid stage of mycosis fungoides, Poikilodermic mycosis fungoides, Prereticulotic dermatitis, Prereticulotic poikiloderma, Parapsoriasis en plaques, Poikiloderma vasculare atrophicans, Parapsoriasis lichenoides*

LPP is characterized by ill-defined, erythematous to brown patches or thin plaques with fine scales. Wrinkling skin surface may be evident. Most lesions are irregular in shape and greater than 5 cm in diameter. The predilection sites are the trunk, flexural areas, thighs, buttocks, and breasts (Figure 2). Skin atrophy, telangiectasia, and mottled hyperpigmentation are occasionally appreciated. The skin lesions composed of this triad are called poikiloderma or poikiloderma vasculare atrophicans (Figure 3). Retiform parapsoriasis (parapsoriasis variegata, parapsoriasis lichenoides) is a very rare LPP variant characterized by widespread reticulated skin lesions with frequent atrophic and scaly macules [9, 10]. Some experts considered this variant as poikilodermatous MF [15, 16].

HISTOPATHOLOGY

The histopathologic findings of both subtypes of parapsoriasis are non-diagnostic and can mimic various skin diseases, ranging from inflammatory dermatoses to cutaneous T- cell lymphoma (CTCL).

SPP shows mild acanthosis with parakeratosis, spongiosis, and sparse superficial perivascular lymphohistiocytic infiltrate. A confluent linear parakeratosis with plasma collection over a basket weave keratin is a characteristic finding (Figure 4A).

Histologically, LPP may be identical to SPP. In addition, LPP may show more epidermal atrophy, patchy lichenoid lymphohistiocytic infiltrate, and basal vacuolization with melanin incontinence. Atypical lymphocytes or haloed lymphocytes may occasionally appear singly or in a small group of few cells in the epidermis, but Pautrier's microabscesses are uncommon. It is very difficult to differentiate LPP from early patch-stage MF with subtle or nonspecific histopathologic findings (Figure 4B).

The immunohistochemical staining reveals CD4+ T-cells in most infiltrating lymphocytes with a minor population of CD8+ T-cells. The CD4:CD8 ratio is usually normal or mildly elevated. The reactive T-cells express CD2, CD3, and CD5. Loss of CD7 expression may be observed [17, 18].

ASSOCIATION WITH LYMPHOMA

"The risk of progression to lymphoma is minimal in SPP, but it is dramatically higher in LPP". This may be a fundamental concept regarding parapsoriasis in medical dermatology practice. Much attention has been drawn to its malignant potential that may cause serious complications. There are many investigations focusing on the risk of malignant transformation in parapsoriasis patients.

LPP is a well-known premycotic dermatosis. Prior studies demonstrated a progression to CTCL or MF in approximately 10-35% of LPP cases. Retiform parapsoriasis variant may have the highest risk among the LPP group. while most dermatologists consider LPP as a premycotic dermatosis, some authorities hypothesize that LPP is exactly MF from the beginning. Controversy persists because LPP and MF are considerably overlapped both clinically and histopathologically [9, 13]. However, current evidence that strongly supports the hypothesis that "LPP is MF" is still not enough. Moreover, in patients who have a definitive diagnosis of MF, most of them do not have a history of preceding parapsoriasis.

The relationship between SPP and cutaneous lymphoma is more controversial. SPP was defined as a benign disease with no or minimal risk of malignant transformation. Some studies even

documented SPP never developed MF or other lymphoma. Conversely, there are few studies reported the cases of SPP transforming to overt lymphoma. A retrospective study of 105 parapsoriasis patients from Finland reported 10% of SPP patients developed MF during a median of 10 years. Additionally, there are case reports and a systematic review that support the malignant potential of SPP [13, 19, 20].

As a rule, it is crucial to discriminate benign from malignant conditions. Dermatologists and dermatopathologists suggest some clues to differentiate parapsoriasis from MF. Clinically, parapsoriasis manifests as chronic, asymptomatic, recalcitrant patches or thin plaques, similar to early-stage MF. The clinical of thick plaques or tumors as well as symptoms such as moderate to severe itch indicate the diagnosis of MF, but not parapsoriasis. Histopathologically, epidermotropism and lymphocytic atypia can be seen in both diseases, but they are less pronounced and not very common in parapsoriasis, compared to MF. Pautrier's microabscesses are much more specific to MF. Immunohistochemistry (IHC) may be helpful in confirming a diagnosis of MF. The elevated CD4:CD8 ratio (>6) and the loss of common T-cell markers, most commonly CD7 have been widely used to support the diagnosis of MF [21]. However, an increased CD4:CD8 ratio is more evident in advanced-stage MF, but it may be inconspicuous in early patch-stage MF lesions, and the loss of CD7 expression can also be observed in various inflammatory dermatoses, including parapsoriasis. A substantial loss of CD7 expression (CD7+ < 10% of infiltrating lymphocytes) is more specific to MF with 41–80% sensitivity and 93–100% specificity, according to a previous report [22]. For these reasons, physicians may not be able to distinguish parapsoriasis from early-stage MF based only on the clinicopathological and immunohistochemical grounds. Given a major concern about the risk of malignant transformation of parapsoriasis, some research focusing on the diagnostic and prognostic markers by using modern molecular genetic techniques have been performed.

In reviewing the literature, T cell receptor gene (TCR) rearrangements analysis has been utilized to support the diagnosis of early-stage MF for at least 15 years. The monoclonality can be detected not only in malignancy, but also in inflammatory skin diseases. In reverse, it may be negative in MF or other cutaneous lymphomas as well. Hence, the results should be interpreted with caution. Detection of identical clones from two different skin sites is highly suggestive of MF [23].

Regarding parapsoriasis, T cell receptor gene (TCR) rearrangements can be identified both in the blood and the skin lesions from patients with SPP and LPP, but no correlation between the presence of T-cell clonality with the clinical features, histopathology, or immunophenotypes were emphasized [24-

26]. Another study by Klemke et al. displayed the TCR clonality detected in the blood in 12.5% of early-stage MF and 26.7% of LPP, and in the skin lesions in 66% of early MF and 19.2% of LPP [27]. Generally, a higher incidence of monoclonality was found in MF than in parapsoriasis. As a matter of fact, the detection of T cell monoclonality may not provide either diagnostic or prognostic significance for parapsoriasis, according to these authors. In an attempt to differentiate MF from inflammatory skin diseases, in 2005, the International Society for Cutaneous Lymphoma proposed an algorithm for diagnosing early-stage MF using a 4-point scoring system. It comprised clinical, histologic, immunophenotypic, and molecular criteria [22, 28]. Later, several studies evaluating the validity and reliability of the algorithm showed that it was very sensitive but not very specific for diagnosis MF (87.5-100% sensitivity, 60% specificity) [22].

The advances in molecular laboratory techniques dramatically improved in MF, and they may be beneficial for parapsoriasis as well. Previously, monoclonality detected by TCR-Y assay was demonstrated in 52% to 75% of patients with patch stage of MF. From recent research, TCR-β clonality assay was more sensitive than TCR- Y in early MF lesions (83% vs 43%; P = .002), and the specify was 100% in both essays (using BIOMED-2 primers). However, parapsoriasis was not included in the negative control group [23]. High- throughput sequencing (HTS) of the T-cell receptor beta gene (TRB) maybe useful for diagnosis early-stage MF with high sensitivity and specificity, but more studies still are required. To date, the use of T-cell receptor HTS in distinguishing parapsoriasis vs MF has not been published [29].

Because it is very important to assess risks for developing cancer as well as detect early-stage cancers, investigators attempt to discover and develop biomarkers that can distinguish malignant and benign conditions that would never cause serious symptoms to reduce overtreatment. Recently, there was an experiment using molecular techniques to identify the genetic alteration and changes of gene expression, compared between LPP and MF.

To date, available laboratory tools, immunohistopathology, and clonality testing can provide only little or no diagnostic and prognostic values for parapsoriasis. It is challenging to give a definitive diagnosis with confidence, especially in borderline cases with mixed features of parapsoriasis and MF. This is clearly confirmed in a recent publication in certain pathologists avoid giving the definitive diagnosis as “parapsoriasis” in their pathology reports, some even suggested excluding the term “parapsoriasis” from medical vocabulary [30].

Interestingly, Ackerman [31] and Cerroni [15] considered both subtypes of parapsoriasis as early-stage MF, so it is unnecessary to distinguish between these two entities. In contrast, many physicians prefer to use the term parapsoriasis in borderline cases, because the words “cancer” or “lymphoma” can cause a tremendous negative psychological impact to some patients, and premature diagnosis of MF may result in unexpected overtreatment and impact on obtaining medical/disability/life insurance in some countries. The diagnostic dilemma remains controversial until the present day. Nevertheless, both conditions have excellent prognosis and similar treatment plans. The survival rate and life expectancy are comparable to normal healthy populations [32]. We propose a flowchart summarizing the approach to differentiate parapsoriasis and MF in Figure 5.

In the authors’ opinion, watchful follow-up and rebiopsy of suspicious skin lesions (ideally 2 weeks off any active therapy such as topical steroids) is an appropriate strategy when the clinical and laboratory findings of the patients are probable but not diagnostic for MF. Meanwhile, parapsoriasis can be used as a working diagnosis.

TREATMENT

Parapsoriasis is a chronic, indolent disease that may persist for many years. Most patients are asymptomatic and generally in good health. Most cases respond poorly to treatment.

To date, there are no randomized controlled trials for the treatment of this condition. We summarized the current treatment for parapsoriasis in Table 2.

Watchful observation and emollients are considered in mild cases or SPP. In LPP patients with progressive disease, skin biopsies should be performed periodically. The treatment regimens for early-stage MF can be used in severe, recalcitrant LPP cases.

The cohort studies from Denmark substantiated an increased risk of venous thromboembolism, acute myocardial infarction or stroke, subsequent cancers, and increased mortality in patients with parapsoriasis and MF. Subsequent cancer associated with parapsoriasis included non-Hodgkin lymphoma (MF excluded) [33-35].

Regular long-term follow-up is recommended regarding the risk of progression to MF. Most experts recommend examining patients regularly every 3 to 6 months and subsequently every year [10].

CONCLUSIONS

Parapsoriasis is a poorly defined chronic skin disease without specific clinical and immunohistopathological features. Many confusions and debates persist regarding the classification and terminology as well as the overlapping of SPP, LPP, and early-stage MF. Regardless of the higher usability of modern molecular biology technologies, it is still difficult to differentiate these complex conditions. Consequently, many dermatologists and dermatopathologists nowadays seldom use the term “parapsoriasis” as a definitive diagnosis in their reports. However, because of its malignant potential, parapsoriasis may be used as a working diagnosis in cases with clinically suspected MF but inconclusive histopathologic results. While the risk of progression to MF in LPP is significant, it is minimal in SPP. Even though parapsoriasis tends to persist, its prognosis is excellent. The conservative treatment with skin-directed therapy and regular follow-up are appropriate, even in borderline LPP/MF patients.

In this review, we describe all clinical forms of parapsoriasis, an approach to diagnosis, and the current treatment regimens. Additional studies focusing on parapsoriasis are needed, with an emphasis on the molecular and immunologic basis of disease, and identification of diagnostic and prognostic factors. They may finally be able to provide an answer to a longstanding question “Should parapsoriasis still be regarded as a distinct disease entity?”

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450 **Table 1** The original and current classifications of parapsoriasis

Parapsoriasis	**Original Classification**			
Entities	**Parapsoriasis** (Parapsoriasis en plaques)		**Pityriasis lichenoides**	
Subtypes	Large plaque parapsoriasis (LPP)	Small plaque parapsoriasis (SPP)	Pityriasis lichenoides et varioliformis acuta (PLEVA)	Pityriasis lichenoides chronica (PLC)
Variants	Poikilodermatous, retiform	Digitate dermatosis		
Parapsoriasis	**Current Classification**			

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453 **Table 2** Treatments for parapsoriasis

Medication	Level of evidence[a]	Mechanism of action
Topical Therapy		
Corticosteroids [9, 10]	2	Anti-inflammation, inhibition of cell proliferation
Bexarotene [36]	2	Inhibition of cell proliferation
Nitrogen mustard [37])mechlorethamine or mustine(	2	Inhibition of cell proliferation
Carmustine)BCNU([38]	2	Inhibition of cell proliferation
Hydrogen-water bathing [39]	2	Anti-oxidation
Imiquimod [10, 40]	3	Immunomodulatory
Coal tar[10]	3	Anti-inflammation, inhibition of cell proliferation, antibacterial, and antipruritic effects
Laser and light-based therapy		
BB or NB-UVB [41-44]	2	Immunomodulatory, immunosuppression, apoptosis of T cells
UVA1 [45, 46]	2	
PUVA [44, 47]	2	
Bath PUVA [48]	3	
Topical PUVA[49]	3	
Excimer- laser)308 nm([50]	3	
Balneophototherapy [51]	3	
Sunlight/heliotherapy [10]	3	

[a]Level of Evidence: 1, indicates randomized controlled trial; 2, uncontrolled trial; and 3, case report, case series (Adapted from the Canadian Task Force on Periodic Health Examination). BCNU, 1,3-bis(2-chloroethyl)-N-nitrosourea; BB, broadband; NB, narrowband; UVA/B, ultraviolet A/B; PUVA, psoralen and ultraviolet A.

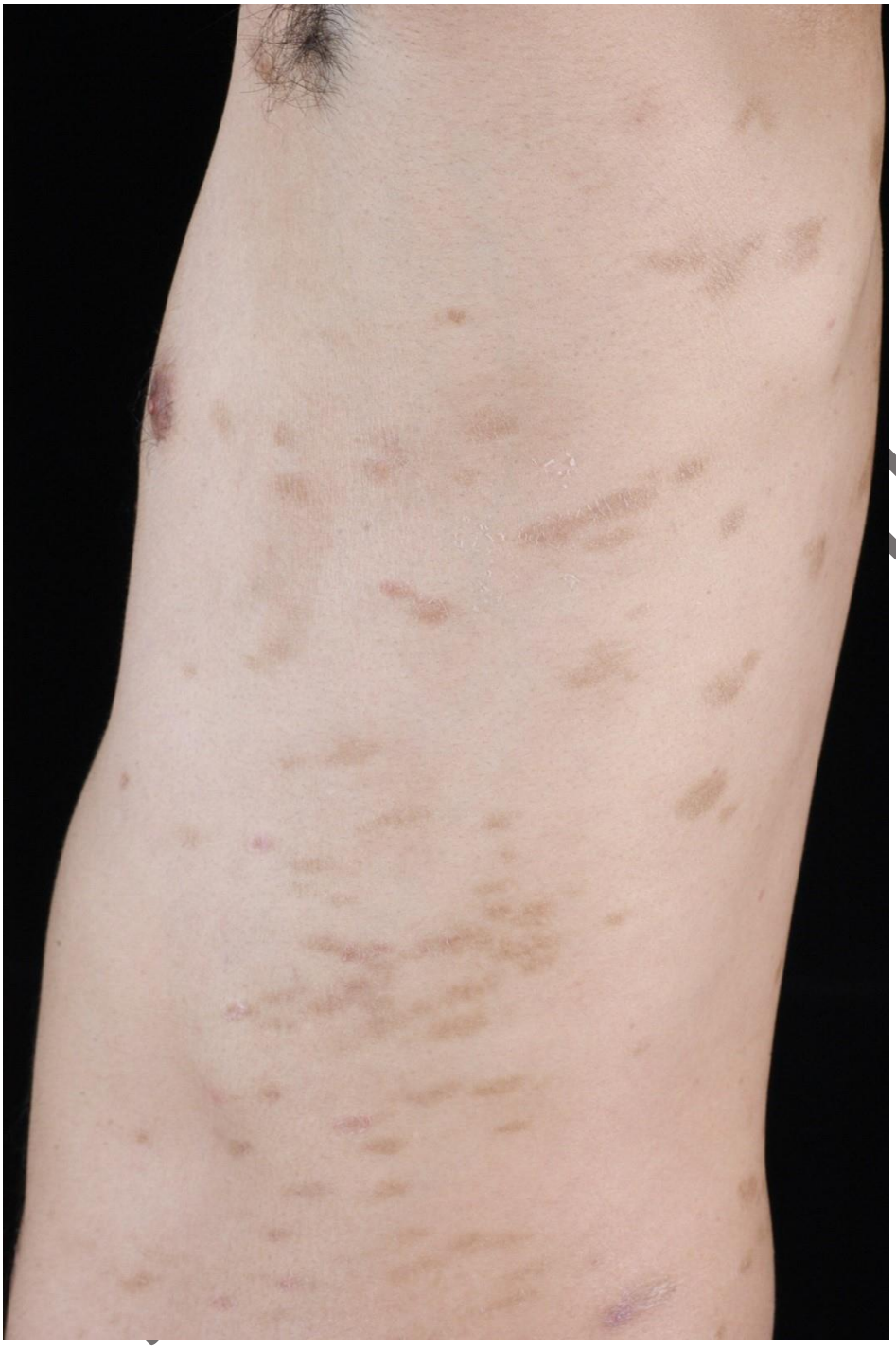


Figure 1 Digitate dermatosis. Multiple brownish elongated, finger-like patches, distributed on the flanks.

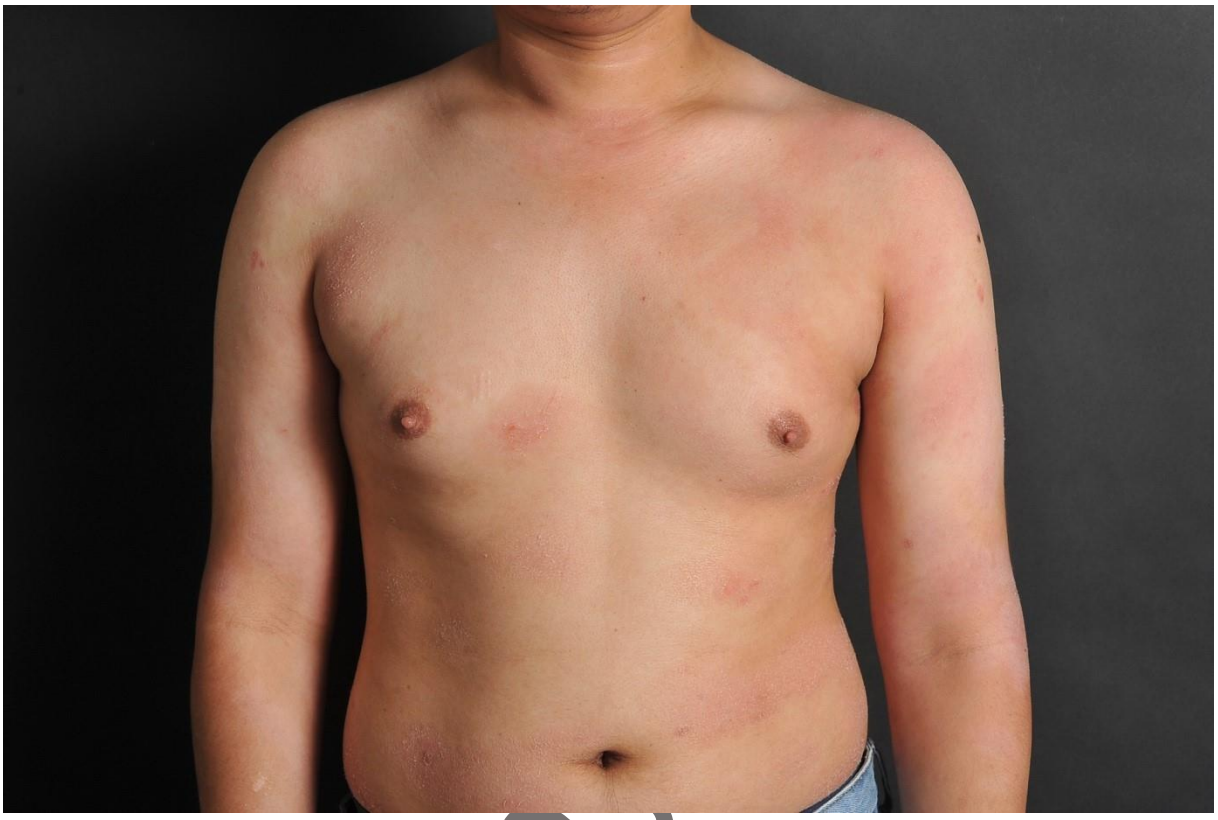


Figure 2 Large plaque parapsoriasis. Slightly scaly erythematous patches of variable size and shape on the torso and both arms.

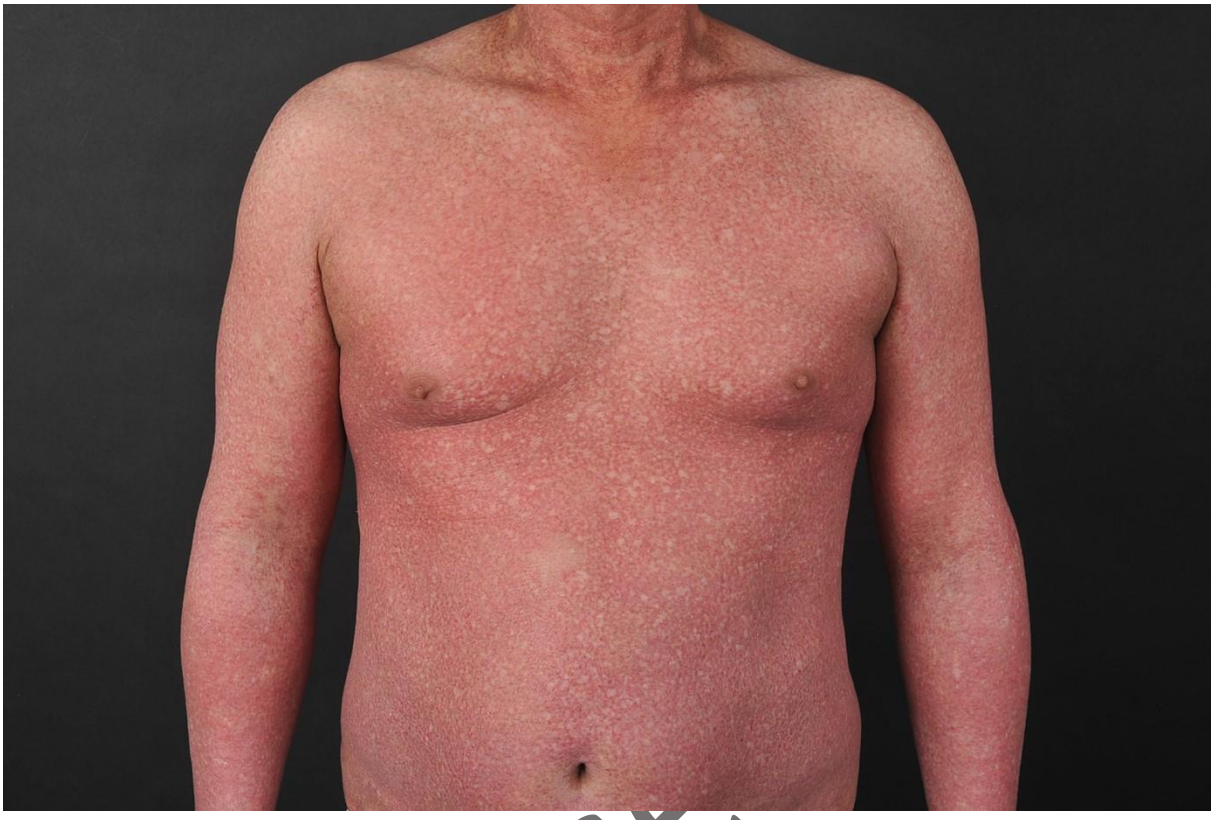


Figure 3 Poikiloderma vasculare atrophicans. Erythematous confluent scaly maculopapules with atrophy and prominent telangiectasias in a reticulated or net-like pattern on the trunk, abdomen and upper extremities.

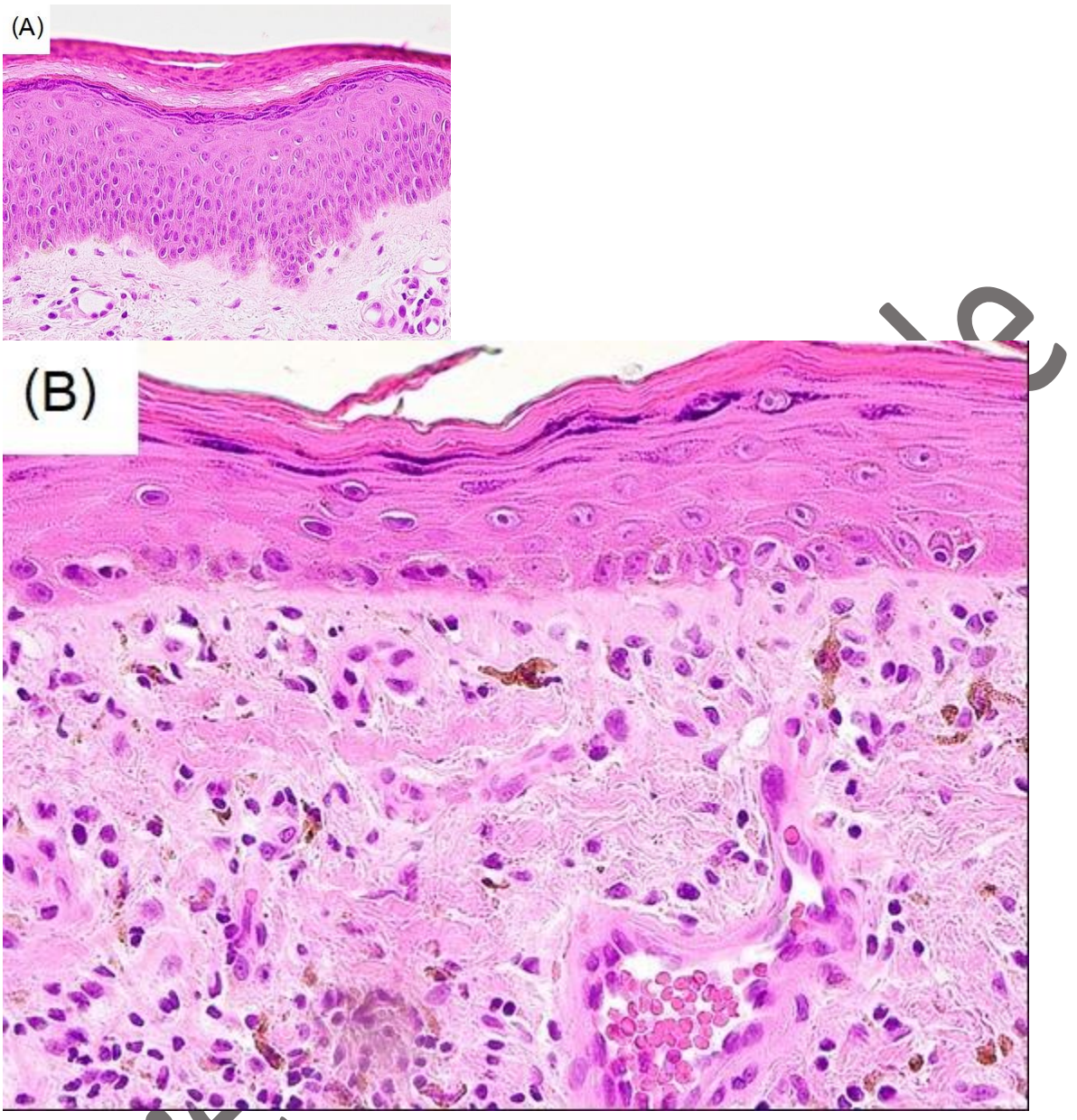
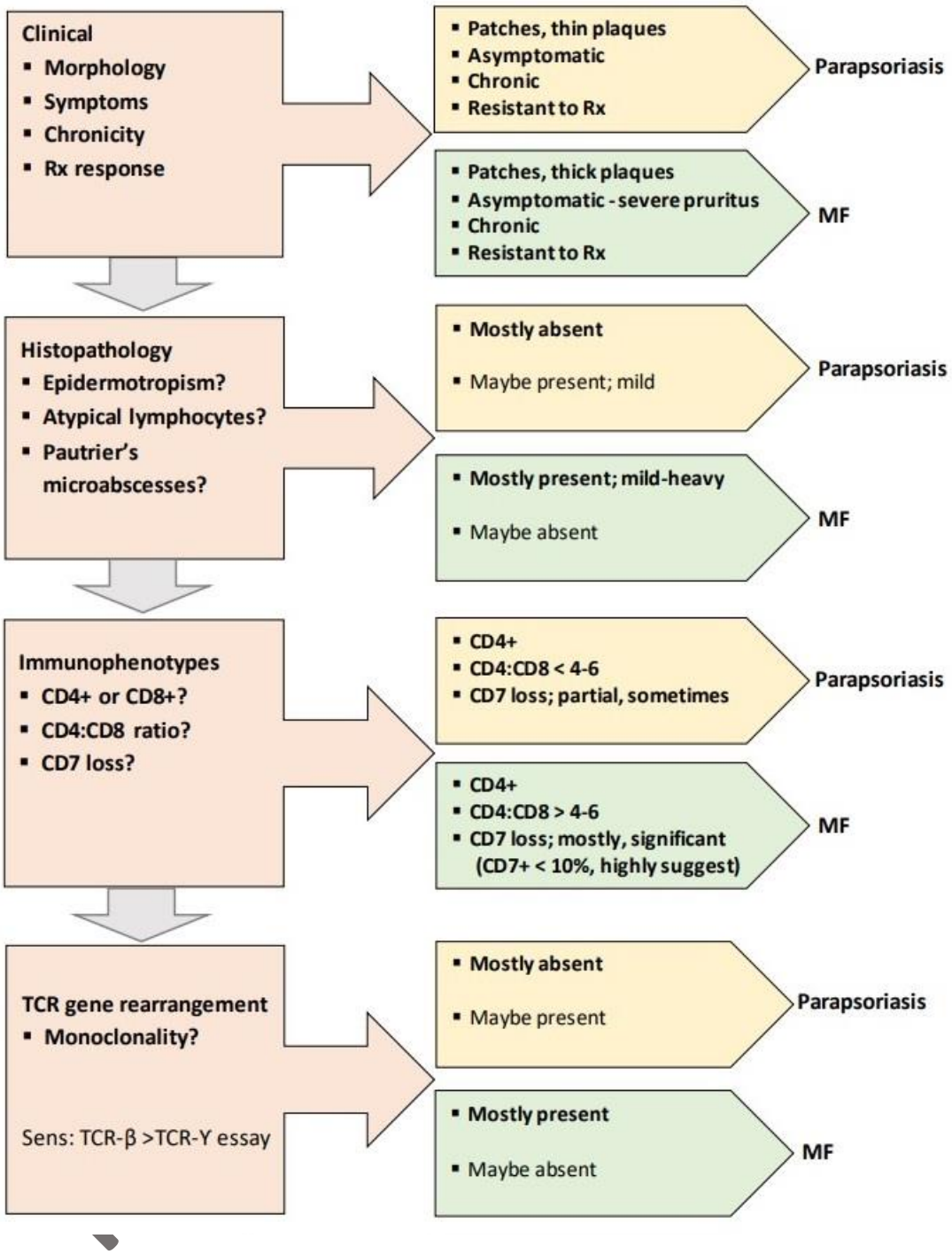


Figure 4 (A) Histopathologic findings demonstrate a characteristic finding of SPP: confluent linear parakeratosis with plasma collection over a basket weave keratin, mild acanthosis and sparse superficial perivascular lymphohistiocytic infiltration (H&E stain; original magnification, 20X). (B) A biopsy specimen shows typical histological features of poikiloderma vasculare atrophicans: compact hyperkeratosis, thinned epidermis, effacement of the rete ridges and perivascular infiltrate of mostly lymphocytes, melanin incontinence, with dilated capillaries in the upper dermis (H&E stain; original magnification, 20X).



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490 **Figure 5** Flow chart summarizing the approach to differentiate parapsoriasis and MF.