

# When mycosis fungoides seems not to be within the spectrum of clinical and histopathological differential diagnoses

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## Abstract

The most prevalent primary cutaneous T-cell lymphoma, mycosis fungoides (MF), is characterized by the development of plaques and nodules after an erythematous patchy phase that is non-specific. An infiltrate of atypical small- to medium-sized cerebriform lymphocytes in the superficial dermis, with variable epidermotropism, is the histopathological hallmark of the disease. In more advanced stages of the illness, large-cell transformation may be seen. Early diagnosis of MF can be very challenging based only on histopathologic or clinical findings, so it is critical to have a clinical-pathological correlation. Many atypical variants of MF that deviate from the classic Alibert-Bazin presentation of the disease have been described over the past 30 years, sometimes with different prognostic and therapeutic implications. Clinically or histopathologically, they can mimic a wide range of benign inflammatory skin disorders. To make a conclusive diagnosis in these cases, it is recommended to take multiple biopsies from various lesions and to carefully correlate the clinical and pathological

findings. We have outlined the various facets of the illness in this review, positioning MF as a “great imitator”, with an emphasis on the more recently identified variations, differential diagnosis, and its benign mimics.

## Introduction

Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma. The clinical course of the disease is typically characterized by the progression from a nonspecific phase of erythematous patches to the appearance of plaques and ultimately, in some patients, nodules and tumors.<sup>1</sup> Microscopically, the hallmark of the disease is an infiltrate of atypical small- to medium-sized cerebriform lymphocytes in the superficial dermis with variable epidermotropism, from sparse cells to large collections, namely Pautrier/Darier’s pseudoabscesses. Notably, the epidermotropism may be totally absent in advanced lesions. Large-cell transformation is generally observed in advanced stages of the disease when the probability of having nodal and visceral involvement is higher.<sup>2</sup> It is defined by the presence of >25% large cells, forming microscopic nodules and expressing CD30.<sup>3</sup> These cases have to be distinguished from lymphomatoid papulosis and cutaneous anaplastic large-cell lymphoma.<sup>3</sup>

MF may be an extremely difficult diagnosis on histopathologic grounds alone, especially in its early phase, when lesions mimic the tissue reaction patterns observed in inflammatory disorders. In these cases, there are some useful diagnostic clues as alignment of atypical lymphocytes along the epidermal basal layer (“basilar epidermotropism”), the presence of many neoplastic lymphocytes in the epidermis in association with minimal spongiosis (“disproportionate epidermotropism”), fibrosis of the papillary dermis with characteristic wire bundles of collagen.<sup>4</sup> Eosinophils are uncommon but may be present, especially in small numbers.

The lymphocytic infiltrate of MF is constituted by  $\alpha/\beta$  T helper memory cells CD45Ro<sup>+</sup>, CD3<sup>+</sup>, CD5<sup>+</sup>, CD20<sup>-</sup>, CD4<sup>+</sup>, CD8, TIA1<sup>-</sup>, granzyme B<sup>-</sup>, perforin<sup>-</sup>,  $\beta$ F1<sup>+</sup>, TCR $\gamma/\delta$ <sup>-</sup>. Rarely, it may exhibit cytotoxic or  $\gamma/\delta$  phenotype, without prognostic implications.<sup>5</sup> In advanced stages, a defective T-cell phenotype may be shown, with variable loss of CD3, CD2, and CD5, or aberrant double positivity/negativity for CD4 and CD8. Moreover, in this phase, a prominent amount of reactive CD20<sup>+</sup>, CD79 $\alpha$ <sup>+</sup>, PAX5<sup>+</sup> B-cells may be present. The role of CD7 in differential diagnosis between MF and benign cutaneous T-cells infiltrates is controversial, as also inflammatory conditions may show a loss of CD7 expression in some cases.

Despite the well-known histopathological features of MF and the large use of immunohistochemistry, the diagnosis of MF may be difficult, especially in the early stage. When also the clinical-pathological correlation does not definitely address the diagnosis, molecular analysis is a further ancillary tool. Detection of the

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same T-cell receptor (TCR) rearrangement in lesions from different skin sites is more characteristic for MF when compared with benign inflammatory infiltrates, even though not completely specific.<sup>6</sup> In fact, inflammatory disorders sometimes may harbor TCR monoclonality.<sup>7</sup>

Over the past 30 years, numerous atypical types of MF, which deviate from the classic Alibert-Bazin presentation of the disease, have been described, sometimes with different therapeutic and prognostic implications.<sup>8</sup> These variants can mimic a wide variety of benign inflammatory skin disorders either clinically or histopathologically. In these cases, taking multiple biopsies from different lesions is advisable and careful clinical-pathological correlation is crucial to reach a definitive diagnosis. We have summarized the many faces of the disease, which set MF as a “great imitator,” with a special focus on the more recently described variants, differential diagnosis, and its benign mimickers.

## Mycosis fungoides variants mimicking other conditions

### Folliculotropic mycosis fungoides

Folliculotropic MF represents one of the most common clinical-pathological variants, accounting approximately for 10% of all cases. Clinically, it is characterized by indurated erythematous plaques associated with acneiform lesions (follicular papules, comedones and cysts), frequently associated with alopecia (Figure 1A).<sup>9</sup> The disease is more apparent in the head-neck region, due to a larger amount of hair follicles, but any district may be involved. It is accompanied by severe itching, commonly resistant to standard treatments. Microscopically, the lymphocytic infiltrate is predominantly folliculotropic and is associated with variable follicular mucinosis (Figure 1B and C). Epidermotropism is uncommon.<sup>10</sup> Mucin deposition may be so impressive to disrupt the hair follicle, inducing a prominent granulomatous reaction masking the folliculotropic lymphocytic infiltrate. The advanced form of folliculotropic MF, with thicker plaques of alopecia and deep dense lymphocytic infiltrate, and/or erythroderma, and/or extracutaneous disease, has an aggressive course and needs to be treated more intensively, whereas the early phase presenting with follicular papules, acneiform lesions, and alopecic patches run an indolent course, as the classic form of MF which has a different prognosis depending on the stage.<sup>11</sup> The recent observations on early follicular MF challenged the concept of folliculotropic MF as a distinct entity, with an intrinsically worse prognosis compared with conventional MF,<sup>12-19</sup> suggesting that the classification of follicular MF into early and advanced stages may be prognostically relevant.<sup>11,20-23</sup> Indeed, before 2010, studies on “classic folliculotropic MF” and its aggressive course included mainly patients with an advanced clinical disease stage at diagnosis (IIA, IIB), where follicle-based infiltrated plaques and tumors appeared variably mixed with more superficial lesions.<sup>23</sup>

Patients with early follicular MF are usually younger than those with conventional MF without a difference in gender. According to Hodak *et al.*, this variant is prevalent in children and adolescents.<sup>21</sup>

Two subvariants of early folliculotropic MF are particularly interesting both clinically and histopathologically, pointing out problems of differential diagnosis: the spiky variant and the one with eruptive infundibular cysts.

Spiky follicular MF is typically located on the trunk and extremities.<sup>11,20-23</sup> It is characterized by tiny hyperkeratotic spines

protruding from the follicular ostia, strikingly reminiscent of lichen spinulosus (Figure 2A). Biopsy of these lesions shows parakeratotic columns protruding from dilated follicular openings and atypical lymphoid infiltrate composed of small and medium-sized cerebriform lymphocytes surrounding and infiltrating the infundibulum and the sebaceous gland with minimal, if any, follicular mucinosis (Figure 2B-D).<sup>22-24</sup>

The clinical and histopathologic differential diagnoses include keratosis pilaris, lichen spinulosus, multiple minute digitate hyperkeratosis, hyperkeratotic spicules, filiform hyperkeratosis, trichodysplasia spinulosa, and lichen planopilaris. The different clinical settings and/or histopathologic and immunohistochemical and molecular features allow for a clear-cut differentiation.<sup>25</sup>

MF with eruptive infundibular cysts may present as localized or generalized eruption of comedones and infundibular cysts, that may be confluent due to the marked hair follicles involvement, giving the clinical impression of milia en plaque (Figure 1A). It may be associated with irregular areas of alopecia, while mucin deposition is not invariably present. Histopathology shows epidermoid cystic structures in the superficial dermis surrounded and infiltrated by atypical T-cells (Figure 1B, C).<sup>26</sup> Although multiple cutaneous lesions are commonly recognized as the classical clinical presentation of MF, patients may rarely present with single lesions occupying <5% of the cutaneous surface.

Alopecia occurring in the course of folliculotropic MF, known as alopecia mucinosa, is a common phenomenon. The pattern of distribution can be either generalized or localized and is characterized by the presence of pink-to-yellow-white, follicular papules and plaques with hair loss in hair-bearing areas. These may resemble other forms of alopecia including alopecia areata, androgenetic alopecia and frontal fibrosing alopecia (Figure 3).<sup>27</sup> In alopecia areata, hair loss patches are usually irregular in size and shape, and broken hairs are observed. Biopsy can be helpful especially when alopecia is the only presentation.

Follicular MF presenting as an acneiform eruption had been described in few case reports and small case series. This unusual MF variant clinically presents as asymptomatic or pruritic skin-colored to erythematous papules on the cheeks, forehead, neck, and arms of young patients, usually women (Figure 4).<sup>28</sup> The typical patient describes a chronic rash with periodic flare-ups despite multiple treatments for acne, acne rosacea, or folliculitis. The course is indolent with no progression to advanced stages.

### Syringotropic mycosis fungoides

Syringotropic MF is an uncommon variant of the disease showing eccrine coils involvement, which may be in combination with follicular infiltration. Clinically, it is characterized by erythematous lesions of variable broadness and thickness, in which the follicular plugging gives an agminated arrangement, accompanied generally by alopecia and anhidrosis (Figure 5A). Palms and soles are commonly involved, but classic MF lesions may be present in other body districts at the same time. In the majority of cases, a band-like infiltrate is evident in the papillary dermis, but the histopathological hallmark is represented by a dense lymphoid infiltrate located around hyperplastic eccrine glands and coils, which present variable degrees of syringometaplasia (Figure 5B, C). The exclusive involvement of the acral district (MF palmaris et plantaris) was rarely reported in literature, with spreading to the dorsal aspect of the extremities and sometimes to the nails. The clinical course is indolent, even though the diagnosis is generally delayed as it mimics clinically eczematous/dyshidrotic conditions of the palms and soles.<sup>29</sup> The microscopic aspects are similar to those observed in classic MF.

## Dyshidrotic mycosis fungoides

It is an extremely rare clinical and histopathological variant of MF presenting with vesiculobullous lesions on the acral sites, with pompholyx-like appearance at the microscopic ground.<sup>30</sup> The differential diagnosis is with chronic dyshidrosiform dermatoses of the palms and/or soles, which are characterized clinically by pruritic and recurring vesicles at varying intervals and histopathologically by chronic spongiotic dermatitis, with variable degrees of spongiotic vesiculation. Pathologic sections reveal conventional MF epidermotropic infiltrate, which is disproportionate with respect to the associated spongiosis, that may hesitate in intraepidermal vesiculation. Dyshidrotic MF may also be associated with lesions of conventional MF on other body sites, in these cases addressing the correct diagnosis is easier.

There are many hypotheses to explain vesicles formation. In some cases, a preexistent dyshidrotic dermatitis may be colonized by the neoplastic process. Otherwise, Authors suggested that the vesicles may be induced by the confluence of the intraepidermal lymphocytic collections.<sup>31</sup> In other cases, the detachment of the epidermis may be explained by the cytotoxic effect of the infiltrate.

The experience with these cases is limited as they are rarely reported in literature. However, the course tends to be indolent, even when extension to limbs and trunk occurs.<sup>32</sup>

## Localized pagetoid reticulosis (Woringer-Kolopp disease)

Pagetoid reticulosis is a variant of MF with an excellent prognosis. It is characterized by a solitary, slowly growing psoriasiform, hyperkeratotic lesion often located on acral sites (Figure 6A). Disease progression or extracutaneous involvement are referred to as disseminated pagetoid reticulosis (Ketrion-Goodman disease) and are considered expression of an aggressive cytotoxic lymphoma, with epidermotropism, more than a variant of MF.<sup>33</sup> From a histopathological point of view, there is a prominent pagetoid lymphocytic infiltrate in the context of a marked hyperplastic epidermis. The neoplastic cells are medium-sized and pleomorphic, with a pale halo surrounding large hyperchromatic nuclei, showing a cytotoxic phenotype by immunohistochemistry (CD8<sup>+</sup>, CD4<sup>-</sup>) with CD30 expression in most cases (Figure 6B). The differential diagnosis with type D lymphomatoid papulosis is possible only by clinical-pathological correlation, as the latter is characterized by waxing and waning lesions, usually sparing acral sites.

## Granulomatous mycosis fungoides

Granulomatous MF is an infrequent histopathological variant of the disease which must be diagnosed on skin biopsy, as the clinical presentation is similar to classic MF, with patches, plaques and nodules depending on the stage. Lymph nodes may be affected in some cases. The granulomatous aspects are evident by the histopathology, which is characterized by histiocytes and multinucleated giant cells interspersed in the atypical neoplastic lymphocytic infiltrate in association with perivascular sarcoidal granulomas. Epidermotropism is a helpful clue when present, but in granulomatous MF is generally minimal or even missing. Prognosis seems to be worse than conventional MF, due to the poor response to therapies.<sup>34</sup>

A subvariant of granulomatous MF is granulomatous slack skin (GSS), which can be easily distinguished from the former clinically and presents typically erythematous, lax and pendulous skin folds at the flexural areas of elderly patients (Figure 7A, B).<sup>35</sup> Although the clinical-pathological correlation is necessary to

achieve the correct diagnosis in cases of GSS, actually, some helpful criteria on histopathological grounds are more in the direction of this variant. In fact, in the literature, a higher number of multinucleated giant cells and the presence of elastolysis and elastophagocytosis are reported in higher proportion in the context of GSS, where the infiltrate is generally deeper and involves also the subcutis (Figure 7C-F). Contrary to granulomatous MF, GSS follows an indolent course, but tend to recur after surgical excision.

## Erythrodermic mycosis fungoides

During the course of a conventional MF, patients may develop erythroderma (Figure 8). This change does not mean an evolution to Sézary syndrome, as the diagnostic criteria are not met (pruritic erythroderma, generalized lymphadenopathy, and circulating malignant T lymphocytes), which remain the main differential diagnosis. It is still unclear the relationship between MF and Sézary syndrome. Several studies strongly support their independence based on phenotypic and genetic analyses,<sup>36,37</sup> while others show similarities in blood biomarkers between the two entities, probably suggesting the existence of a spectrum.<sup>38</sup>

As in the cases of conventional MF, differential diagnosis with Sézary syndrome on histopathological grounds alone is almost impossible and correlation with clinical-serological data is mandatory to correctly address the diagnosis.

## Hypopigmented mycosis fungoides

It is an uncommon clinical variant characterized by hypopigmented patches and plaques, without atrophy, misinterpreted as vitiligo, pityriasis versicolor, or pityriasis alba. Dark-skinned individuals and children are more frequently affected. In lesions successfully treated, gradual repigmentation occurs and can be considered a marker of therapy effectiveness. The histopathological features are those of conventional MF, but by immunohistochemistry the infiltrate is composed of CD8<sup>+</sup> cytotoxic lymphocytes, possibly highlighting some pathogenetic similarities with the inflammatory phase of vitiligo.<sup>39</sup> The differential diagnosis between hypopigmented MF, on the one hand, and atopic dermatitis and inflammatory stage of vitiligo, on the other hand, may be extremely difficult and clinical-pathological correlation is mandatory to correctly address the diagnosis. A potential diagnostic clue stays in the evaluation of the number of melanocytes, which are completely absent in vitiligo, while diminished in MF,<sup>40</sup> as demonstrated by the repigmentation occurring after the successful treatment of a lesion of hypopigmented MF.

## Hyperpigmented mycosis fungoides

Hyperpigmented MF is an infrequent clinical variant of the disease that can be characterized by hyperpigmented lesions only.<sup>41</sup> They are due to pigment incontinence and melanophages accumulation in the papillary dermis, in association with the histopathological aspects of otherwise conventional MF (Figure 9). As in the hypopigmented variant, the infiltrate expresses generally a cytotoxic phenotype. The most important differential diagnosis is with Sézary syndrome, as it may present clinically with diffuse hyperpigmented lesions covering the entire body surface – namely melanoerythroderma – closely mimicking the presentation of hyperpigmented MF. Clinical-pathological correlation helps to address the correct diagnosis.

Hyperpigmented MF has an excellent prognosis, following an indolent clinical course.<sup>41</sup>

## Papular mycosis fungoides

It is a clinical variant of MF characterized, since the onset, by small erythematous, partly scaly, papules, unrelated to the follicular ostia, in the absence of patches on the trunk and extremities (Figure 10A-C). The histopathological features are common to conventional MF, but the infiltrate is delimited in tiny papules without follicular or eccrine structures involvement (Figure 10D).<sup>42</sup> It was first described as an indolent variant of the disease, with favorable long-term prognosis, but anecdotal reports of erythrodermal evolution and progression to tumor stage have been more recently reported.<sup>43</sup>

Given the atypical clinical presentation, diagnosis is generally challenging, and some entities have to be considered in the differential diagnosis, as lymphomatoid papulosis and pityriasis lichenoides. The spontaneous regression of the lesions seen typically in lymphomatoid papulosis is absent in the papular MF, which, on the contrary, is relatively stable. Moreover, CD30 is negative or positive only in isolated scattered medium-sized cells in papular MF. In contrast to pityriasis lichenoides, which is a CD8<sup>+</sup> disease, papular MF does not present with ulcerative lesions nor residue varioliform scars.

## Psoriasiform mycosis fungoides

Patients present clinically with multiple well-delimited erythematous plaques covered by thick scales all-over the body surface (Figure 11A).<sup>44-46</sup> Nails are generally spared, unless in advanced stages.<sup>47</sup>

This clinical variant is particularly rare and frequently misdiagnosed for long time, as classical lesions of MF are generally absent and topical steroids administered are effective both on psoriasis and MF.<sup>48</sup> During the course of the disease, the lesions stop responding to the treatment leading to perform a skin biopsy to confirm the diagnosis.

From a histopathological point of view, the lesions are characterized by marked psoriasiform hyperplasia of the epidermis, the result of the long-lasting untreated disease, with scant spongiosis and prominent atypical lymphocytes infiltrate in the dermis with variable epidermotropism (Figure 11B, C). The infiltrate is poor of neutrophils, which are the expected inflammatory cells in the course of psoriasis.

The immunohistochemical staining may show both complete or defective T-cell phenotype, and CD30 positive large cell transformation may or may not be present.

Given the high prevalence of psoriasis in general population, psoriasiform MF may actually represents a collision of the two diseases instead of a distinct clinical variant of MF. Moreover, psoriatic patients present a higher risk of developing malignancies, especially cutaneous T-cell lymphomas.<sup>49</sup> It is still unclear whether the chronic immune stimulation of psoriasis, or the effect of the treatments employed, or patients' comorbidities and lifestyle play a role in the onset of MF in preexistent psoriasis. Regardless of this, the importance of differentiating MF from psoriasis/recognizing MF underlying psoriasis is crucial as commonly used therapies effective on psoriasis may worsen MF,<sup>50</sup> until aggressive T-cell lymphoma development and fatal outcome.<sup>51</sup> Skin biopsies are highly suggested in putative cases of progressive psoriasis which are refractory to conventional treatments, particularly before starting immunosuppressive agents. For those patients in which also the histopathological evaluation may not conclude for one of the two entities, combination treatments targeting both MF and psoriasis have been experienced, leading to acceptable results.<sup>49</sup>

## Symmetric mycosis fungoides

Lesions of MF, independently from the patch, plaque or tumor stage, can be generalized or localized, but also in the last case they are distributed randomly on a district of the body surface. Real symmetric presentation has been reported in literature only few times.<sup>52,53</sup>

In one of the cases reported, lesions were described as symmetric and recurrent red scaling annular patches on trunk and extremities mimicking erythema annulare centrifugum, with temporary improvement under corticosteroids. At the histopathological examination, an atypical lymphocytic infiltrate with superficial perivascular and lichenoid distribution was observed. A partial defective T-cell phenotype was demonstrated by immunohistochemistry, with loss of CD7 expression in about 40% of the infiltrate. Moreover, molecular studies revealed an oligoclonal T-cell receptor gene rearrangement.<sup>53</sup>

In the other case, the patient had history of treated MF and presented later four symmetric, rupoid lesions growing on his forehead and cheeks. The histopathological examination of the skin biopsy performed on one of the lesions revealed findings consistent with MF and microbiologic cultures highlighted *Pseudomonas aeruginosa* involvement. The administration of antibiotics and subsequent radiation therapy resolved the condition.<sup>52</sup>

These cases raise the concern that even though MF does not present generally with symmetric lesions, this particular distribution may not exclude *a priori* this diagnosis and a skin biopsy should be performed to evaluate the histopathological features (Figure 12), with eventual additional immunohistochemical and molecular tests.

## Nail involvement by mycosis fungoides

Nail involvement in primary cutaneous T-cell lymphoma, and MF in particular, has been rarely reported in literature.<sup>54</sup> It is probably underestimated, as in a recent study 30% of the patients demonstrated at least minimal nail changes,<sup>55</sup> and generally represents a feature of the advanced stages of the disease, when the patients have multiple lesions all over the body surface.<sup>56</sup> Non-specific onychodystrophic changes may be observed in one or more nails, going from slight yellowish discoloration to markedly thickened nail plate, with subungueal hyperkeratosis and consequent onycholysis.<sup>57</sup> The histopathological evaluation of specimen from the nail matrix and bed shows an atypical lymphocytic infiltrate in the superficial dermis, with epidermotropism. If the sampling does not include nail matrix and bed, but only the tissues around the nail apparatus, the findings may be so subtle that, in the absence of clinical-pathological correlation, a final diagnosis of nail involvement by MF may not be established.<sup>55</sup> Fungal infections should always be excluded with histochemical stains or microbiological cultures. Treatment of this district is particularly difficult as in any other skin disease involving the nails, but topical mechlorethamine provided some effects.<sup>58</sup>

## Mycosis fungoides in children and adolescents

Any age group may be affected by MF, even the youngsters. Several clinical presentations are more typical of this age group, such as the hypopigmented or the localized pagetoid reticulosis. The diagnoses in these cases are frequently delayed due to two principal motivations: the general reluctance to perform biopsies in young patients and the deceiving clinical presentation, which mimics diseases more frequently encountered in younger age groups, such as atopic/eczematous dermatitis or warts. The immunohistochemical analyses reveal more frequently a cytotoxic phenotype.

Pityriasis lichenoides-like MF is a variant that causes troubles in terms of differential diagnosis in children. It has been originally described just in children,<sup>59</sup> but subsequently, this presentation has been recognized also in adults.<sup>60</sup> Two distinct entities are considered in this variant, one mimicking pityriasis lichenoides clinically and the other one histopathologically. In the first case, the clinical presentation reminds the scaly eruption of pityriasis lichenoides, but the biopsy then reveals histopathological features of conventional MF. On the other hand, patients have a classic cutaneous involvement by MF, but the microscopic and immunohistochemical aspects are similar to those observed in pityriasis lichenoides, as vacuolar alterations and necrosis of basal keratinocytes, “busy” stratum corneum, and frequent cytotoxic phenotype (Figure 13).

Annular lichenoid dermatitis of youth is a condition almost exclusively reported in children and adolescents and constitutes a MF simulator in this age group.<sup>61</sup> The clinical presentation is characterized by annular macules that evolve in patches with erythematous elevated borders and depigmented center, localized on the trunk (Figure 14A). The histopathological examination reveals a band-like lymphocytic infiltrate, with cytotoxic phenotype, associated with vacuolar changes at the dermo-epidermal junction and necrotic keratinocytes at the tips of the rete ridges, which assumes a “squared off” aspect (Figure 14B-D).

### Inflammatory conditions histopathologically mimicking mycosis fungoides

In exceptional cases, cutaneous lymphomas, including MF, may be simulated histopathologically by several benign inflammatory conditions, which are generically designated as pseudolymphomas of the skin. Some of those entities have been already mentioned in this contribution when the corresponding MF variant was considered. Benign follicular mucinosis and annular lichenoid dermatitis of youth are well-recognized entities that have to be considered in the differential diagnosis with MF, as they have different treatments and prognoses. The same goes for pityriasis lichenoides and the inflammatory stage of vitiligo, which may mimic MF due to their prominent band-like infiltrate with epidermotropic features.

In these cases, the evaluation of the rearrangement of TCR genes researching monoclonality may be helpful in the differential diagnosis. Remarkably, parapsoriasis/early phase MF lacks monoclonal rearrangement, while inflammatory conditions with heavy lymphocytic infiltrate, which may include, among the others and in addition to those already mentioned, lichen sclerosus et atrophicus, pigmented purpuric dermatoses, a superficial variant of lupus erythematosus, lymphomatoid drug eruption and contact dermatitis, may harbor TCR clonality. Up to 60% of cases of pityriasis lichenoides show monoclonal rearrangement, as it is observed also in 6% and 13% of cases of lichen planus and lichen sclerosus et atrophicus, respectively.<sup>62,63</sup> Clinical-pathological correlation is, therefore, essential to avoid diagnostic misinterpretations. For example, lymphomatoid contact dermatitis presents clinically with pruritic and eczematous lesions localized in areas exposed to allergens. Moreover, it shows histopathologically a superficial band-like lymphocytic infiltrate, with epidermotropism, associated with variable degrees of epidermal spongiosis and eosinophilic component.<sup>64</sup> The same goes for lymphomatoid drug eruption, which commonly presents with macules and papules abruptly arising in response to the administration of any kind of therapy (topical, oral, or injected), characterized by symmetry, involvement also of sun-exposed areas, and less than 6 months of length in duration.<sup>65</sup> Even infection-related inflammatory infiltrate may

simulate MF. *Borrelia* may induce, besides the well-known B-cell pseudolymphoma, a superficial dermal-epidermal T-cell-rich infiltration mimicking MF, which presents clinically with lichenoid patches and plaques or with the classical acrodermatitis chronica atrophicans features. Detection of the microorganism genetic material by polymerase chain reaction (PCR) in the skin infiltrate confirms the diagnosis.<sup>66</sup> Cutaneous leishmaniasis may present with an amastigote-negative lymphocytic-rich variant, simulating MF. Also in these cases, PCR is helpful to identify the causal agent and it is recommended in all the presumptive cases of idiopathic pseudolymphoma in endemic countries.<sup>67</sup> Finally, acquired immunodeficiency may be accompanied by cutaneous eruption mimicking MF.<sup>68</sup> It has been reported in the literature in HIV patients with severe immunosuppression and high viral load, but also in solid organ transplant recipients. The clinical presentation is protean, including infiltrated erythematous plaques, erythroderma, palmoplantar hyperkeratosis, associated or not with generalized lymphadenopathy. From a histopathological point of view, the principal observation is an epidermotropic CD8<sup>+</sup> cytotoxic lymphocytic band-like infiltrate, without significant cytological atypia. Polyclonality is generally found in molecular biology.

Clinical information is essential in all the cases mentioned above to reach the correct diagnosis, in fact, by histopathologic grounds alone, the diagnosis of cutaneous pseudolymphoma may be completely missed. Therefore, clinical-pathological correlation, which is useful and helpful in dermatopathology, should be mandatory when managing with these conditions.

### Conclusions

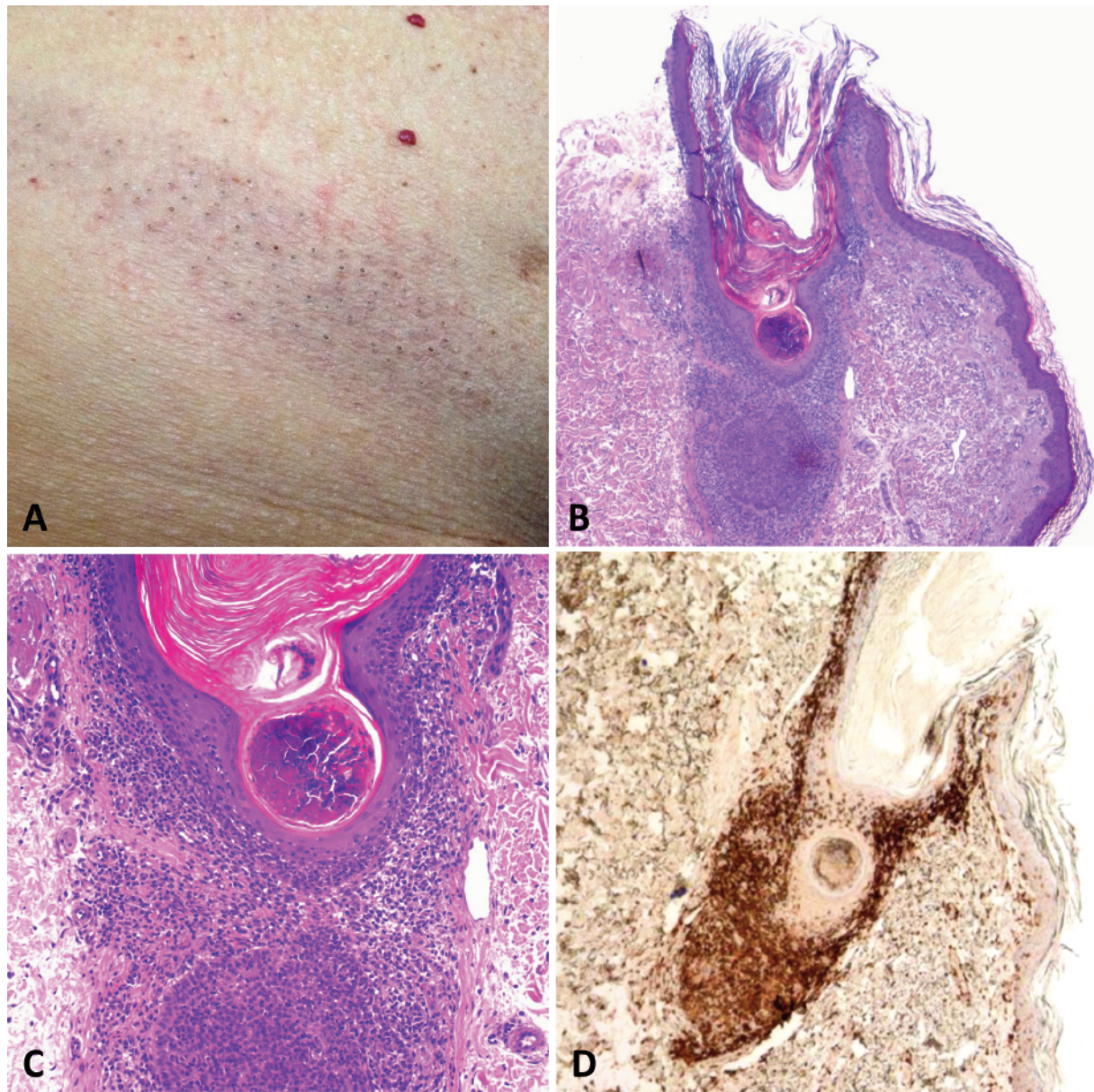
This contribution has been conceived to summarize the most common variants of MF which, at first glance, seem not to be within the spectrum of the differential diagnoses for some clinical or histopathological presenting features diverging from conventional MF. Moreover, the large spectrum of cutaneous pseudolymphoma has been also briefly taken into account to approach the topic from the opposite direction. In fact, anything hinders a patient with vitiligo or extra-genital lichen sclerosus et atrophicus from also developing MF, making it extremely complex to recognize the lymphoproliferative disease and to distinguish it from the inflammatory disorder. In all these cases, taking multiple biopsies from different lesions is advisable and careful clinical-pathological correlation is crucial not to misinterpret the diagnosis, as each of these conditions has specific therapeutic and prognostic implications.

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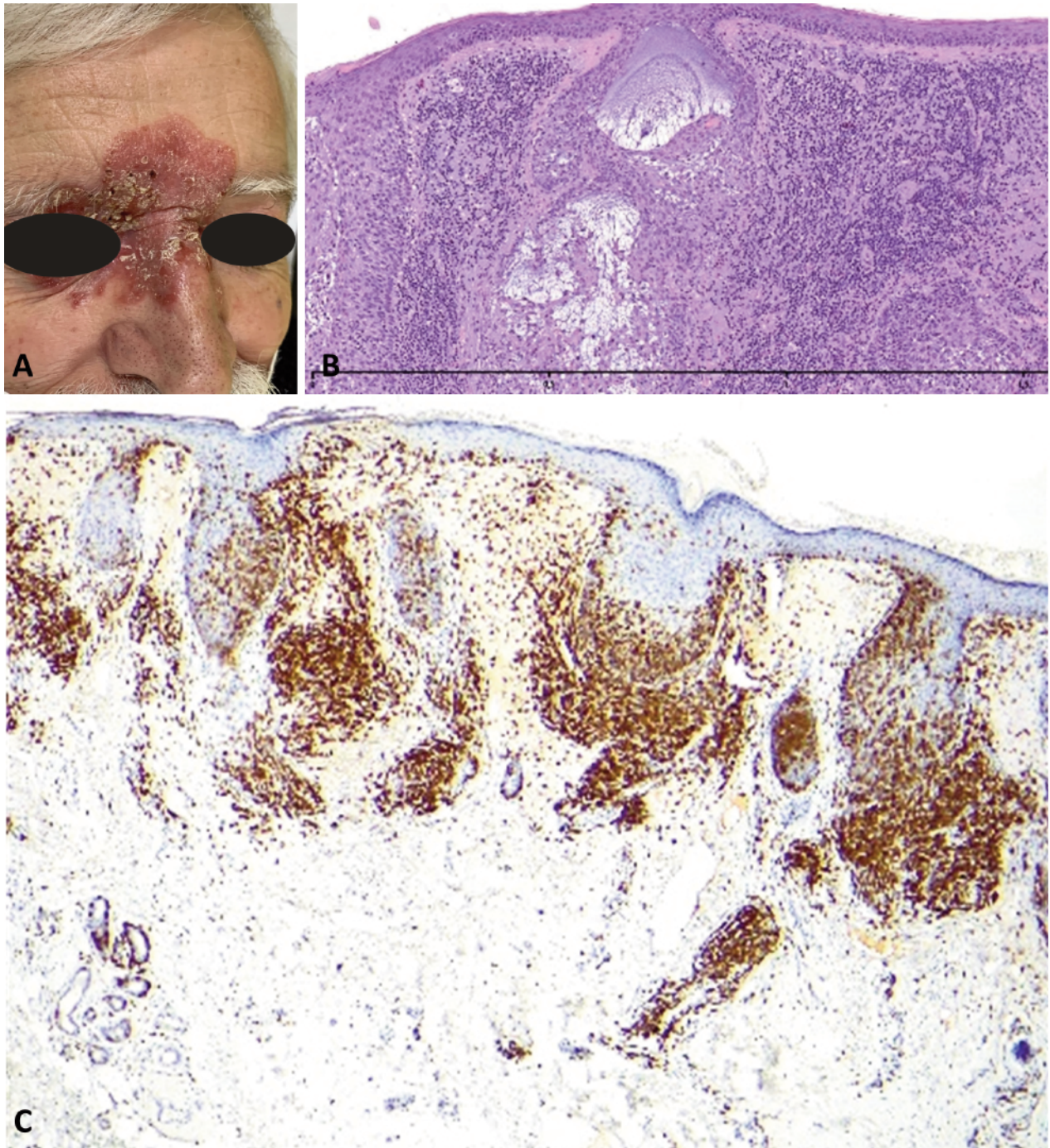
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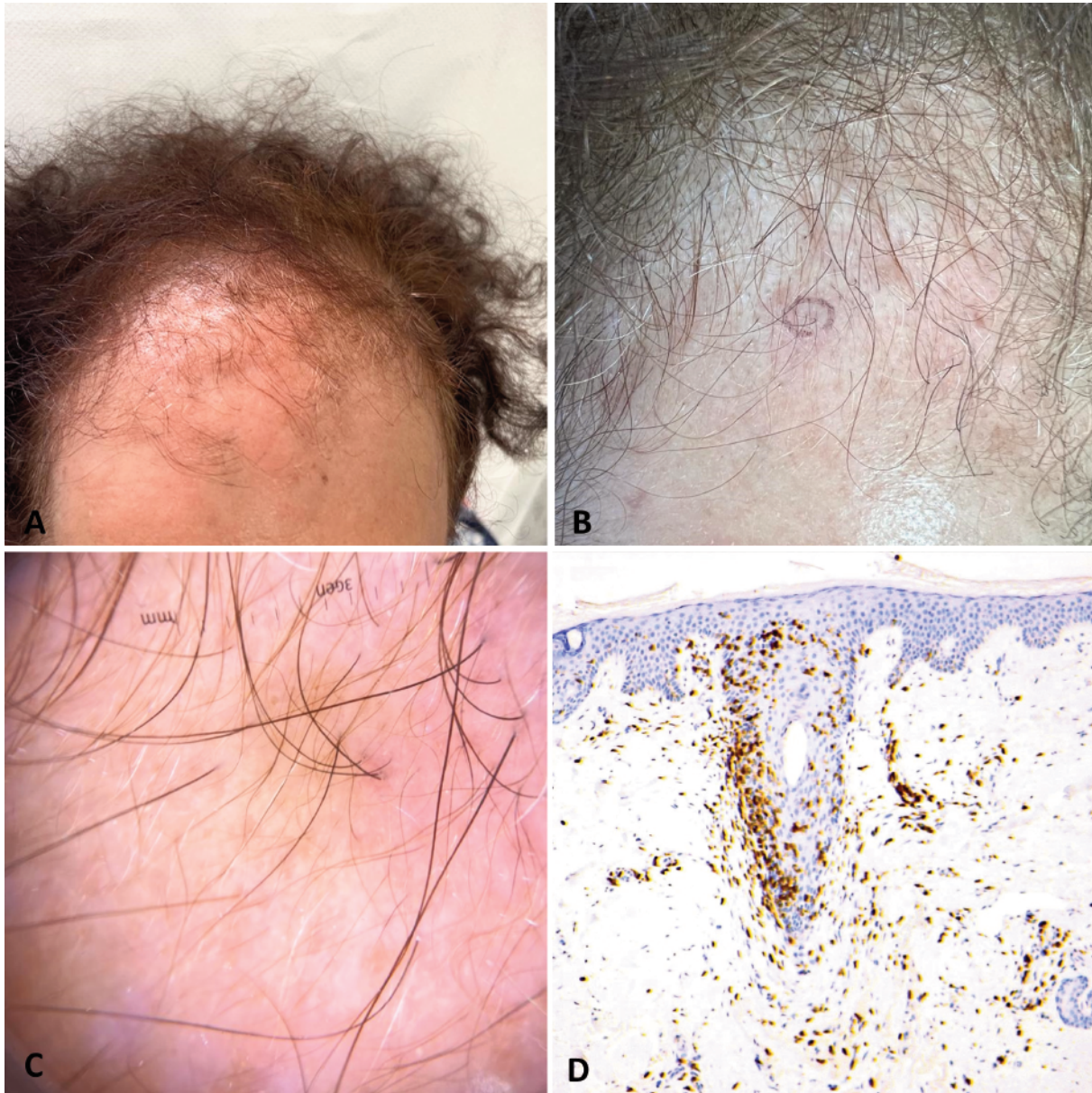


**Figure 1.** A) Oval patch with comedo-like papules on the flank; B) involvement of the infundibulum by lymphocytes with almost no epidermotropism; C) at the base of the infundibulum, a folliculotropic lymphocytic infiltrate is seen; D) immunohistochemical labeling with CD4 shows infiltration of the follicular epithelium by lymphocytes.

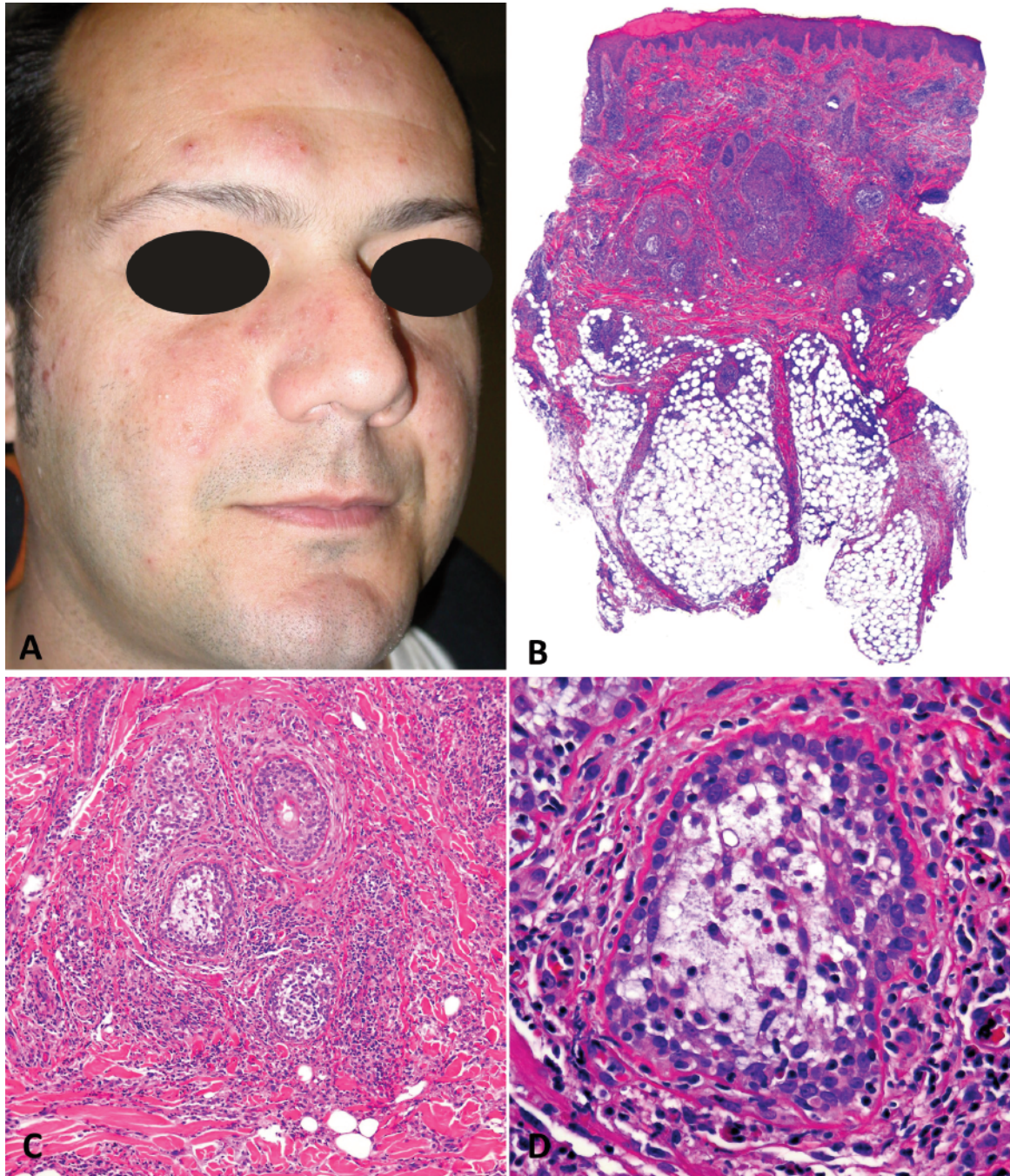




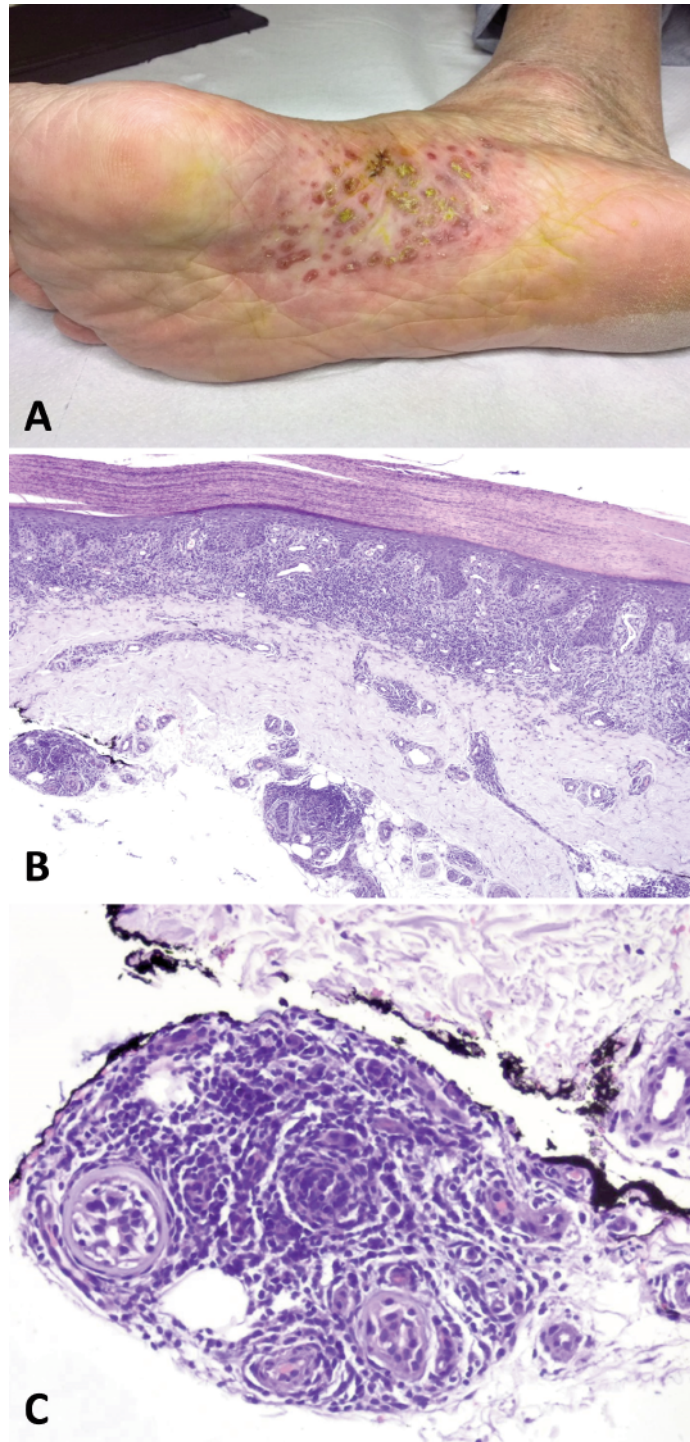
**Figure 2.** A) Erythematous plaque involving the forehead and eyebrows with alopecia of the medial brow; B) massive infiltration of the hair follicle with atypical T-cells and follicular mucinosis; C) immunohistochemical labeling with CD3 highlights the lymphocytic infiltration.



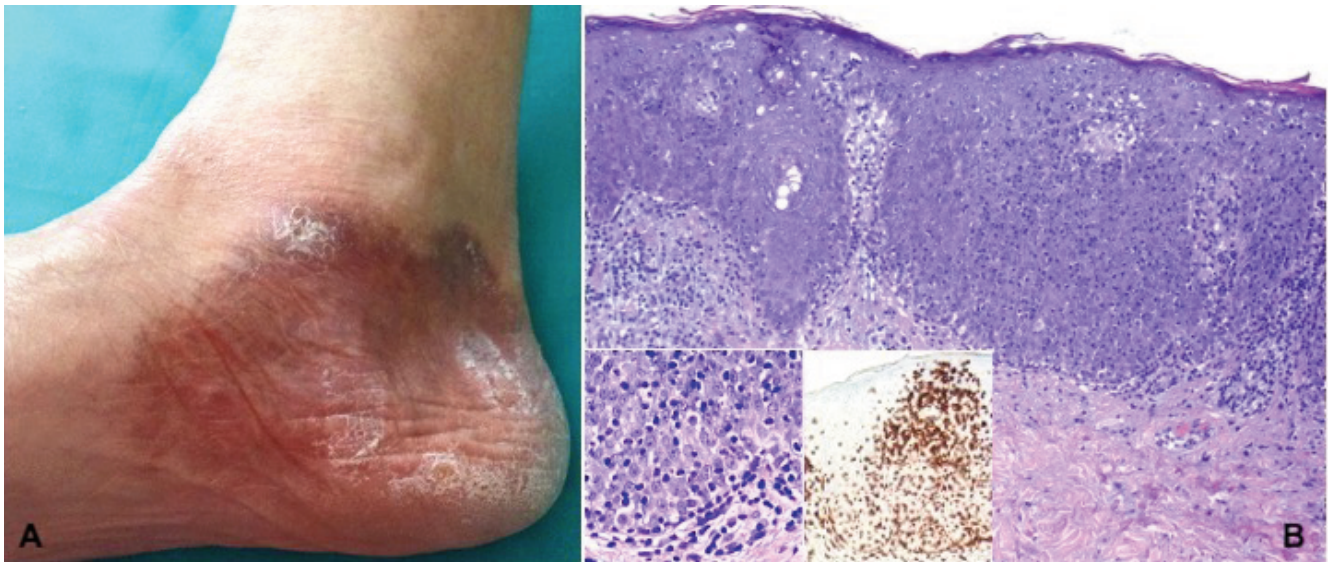
**Figure 3.** A) Solitary, minimally infiltrated plaque on the scalp; B, C) the clinical and dermoscopic hair loss pattern mimic androgenetic alopecia; D) Immunohistochemical labeling with CD4 shows infiltration of the follicular epithelium with lymphocytes.



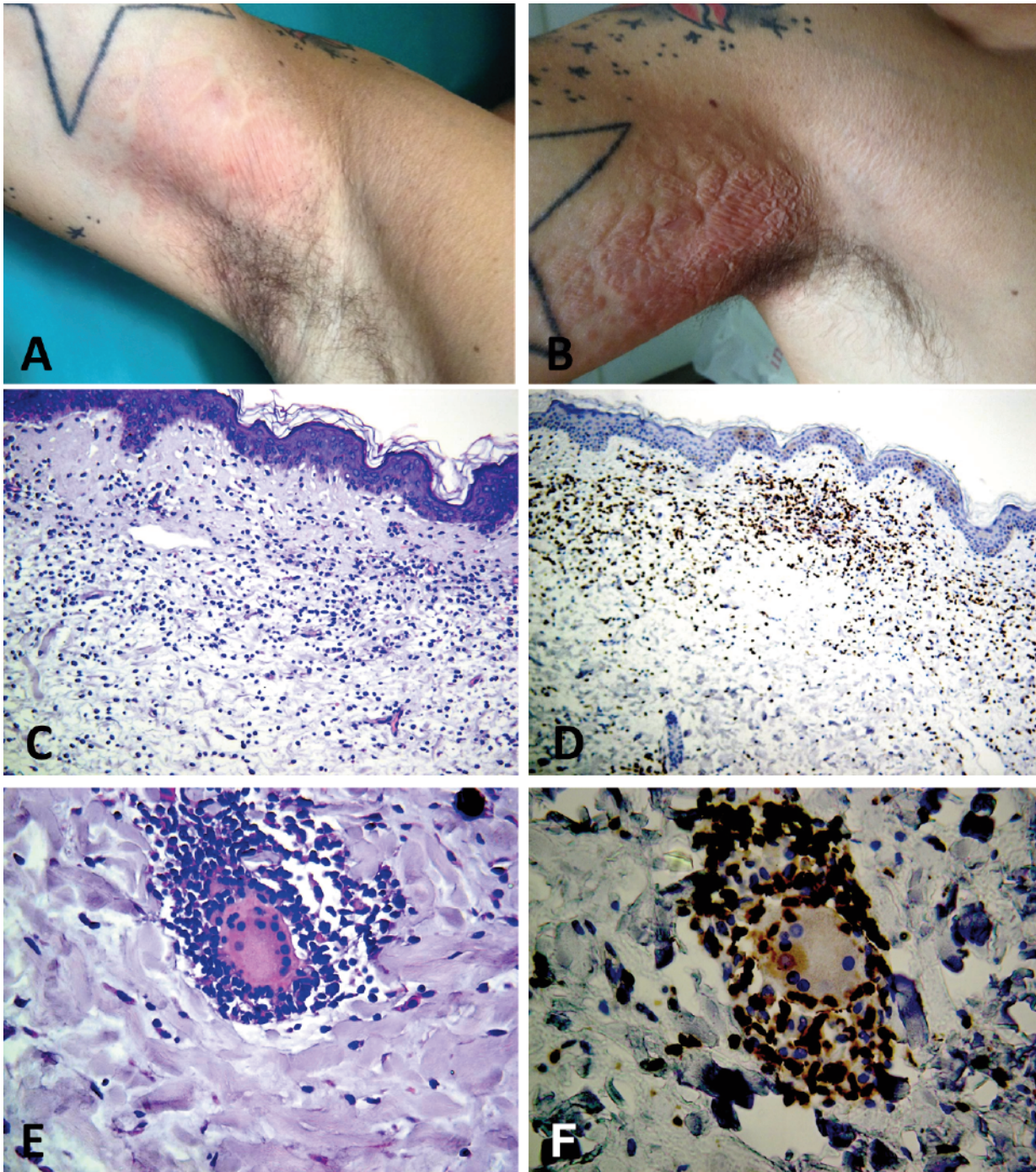
**Figure 4.** A) Multiple skin-colored papules and plaques on the cheeks and forehead; no comedones visible; B-D) mucin within the folliculosebaceous units with a mild perifollicular and intraepithelial lymphocytic infiltrate.



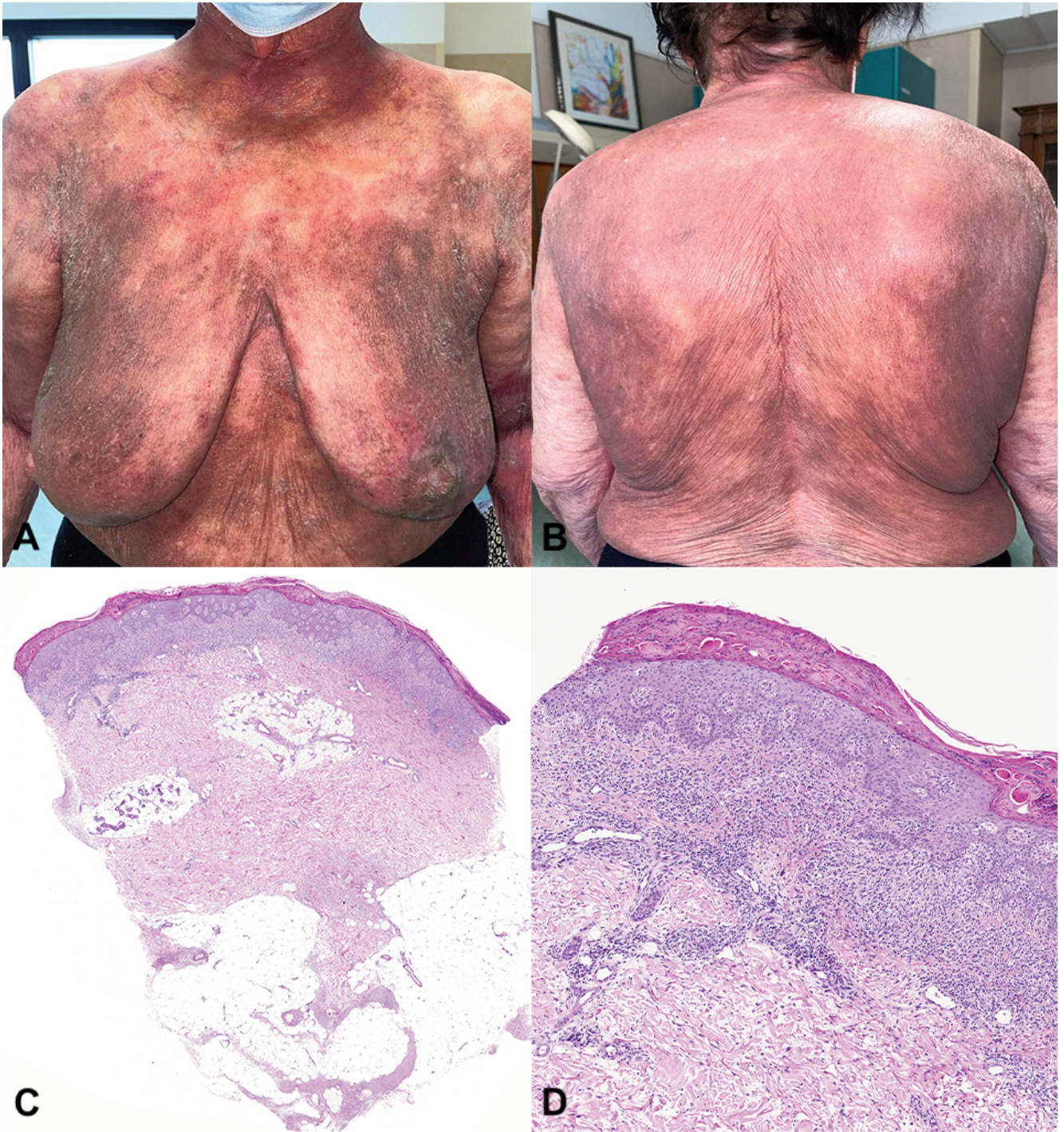
**Figure 5.** A) Erythematous, scaly, distinct papules on the medial sole; B) band-like infiltrate of lymphocytes in the superficial dermis; C) dense mononuclear infiltration around deep dermal eccrine ducts and syringometaplasia.



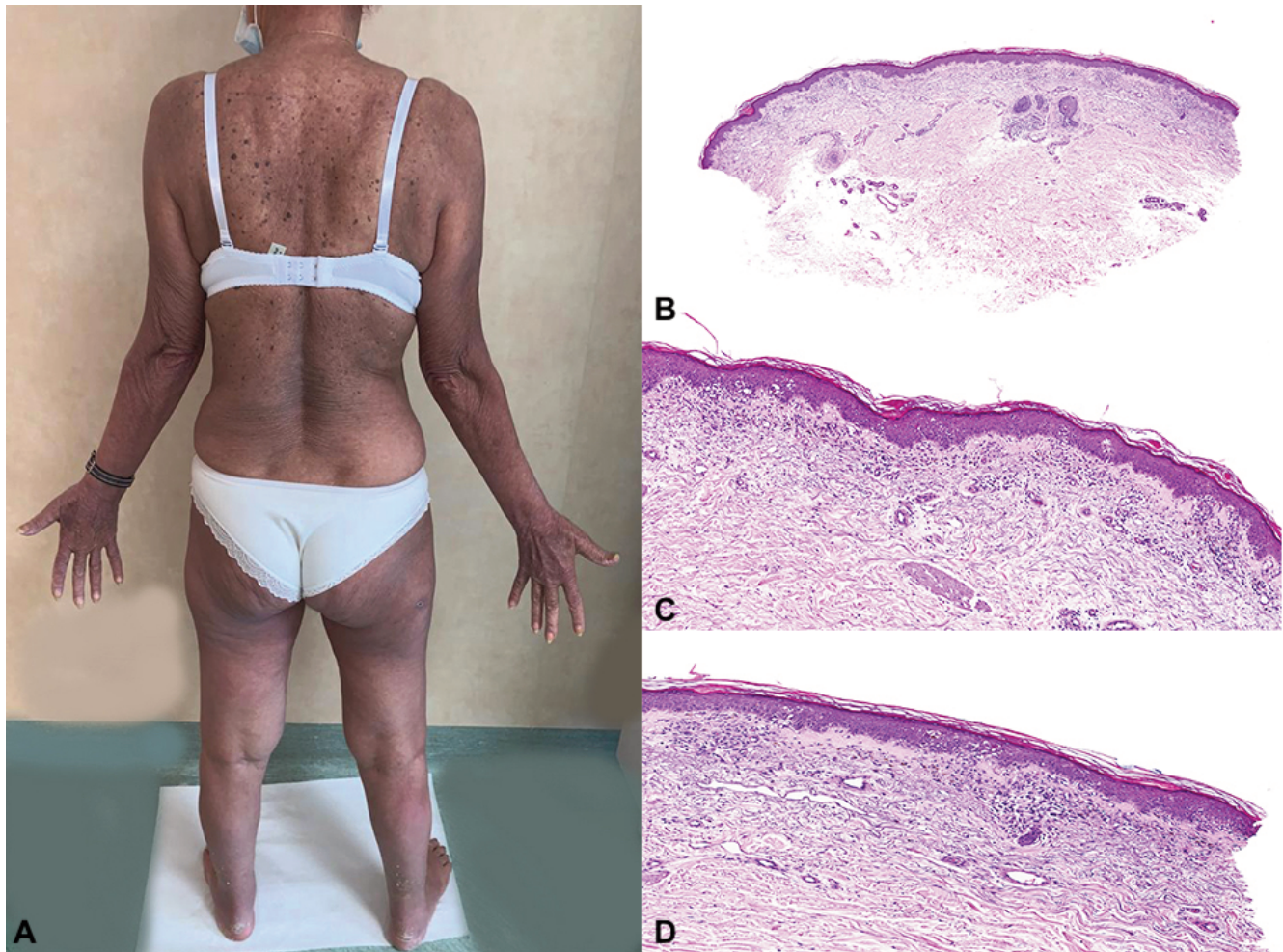
**Figure 6.** **A)** Large, scaly, erythematous patch on the medial aspect of the heel; **B)** psoriasiform hyperplasia of the epidermis with overlying parakeratosis and dense intraepidermal lymphocytic infiltrate, characterized by a disproportion between the density of lymphocytes within the epidermis and that in the upper dermis, with only few perivascular cells in the dermis. In the inset, at higher power, the epidermotropic lymphocytes are medium to large with hyperchromatic and irregular nuclei, variably prominent nucleoli and minimal-to-abundant pale-staining or eosinophilic cytoplasm. In the other inset, immunohistochemical labeling with CD8 shows epidermotropic medium-sized lymphocytes infiltrate.



**Figure 7.** **A, B)** Atrophic lax skin in the right axillary area; **C, D)** diffuse granulomatous dermal infiltrates composed of atypical lymphocytes, histiocytes and giant cells; **E)** multinucleated giant cell and adjacent atypical T lymphocytes; **F)** immunohistochemical labeling with CD4 highlights the atypical T-cells surrounding a multinucleated giant cell.

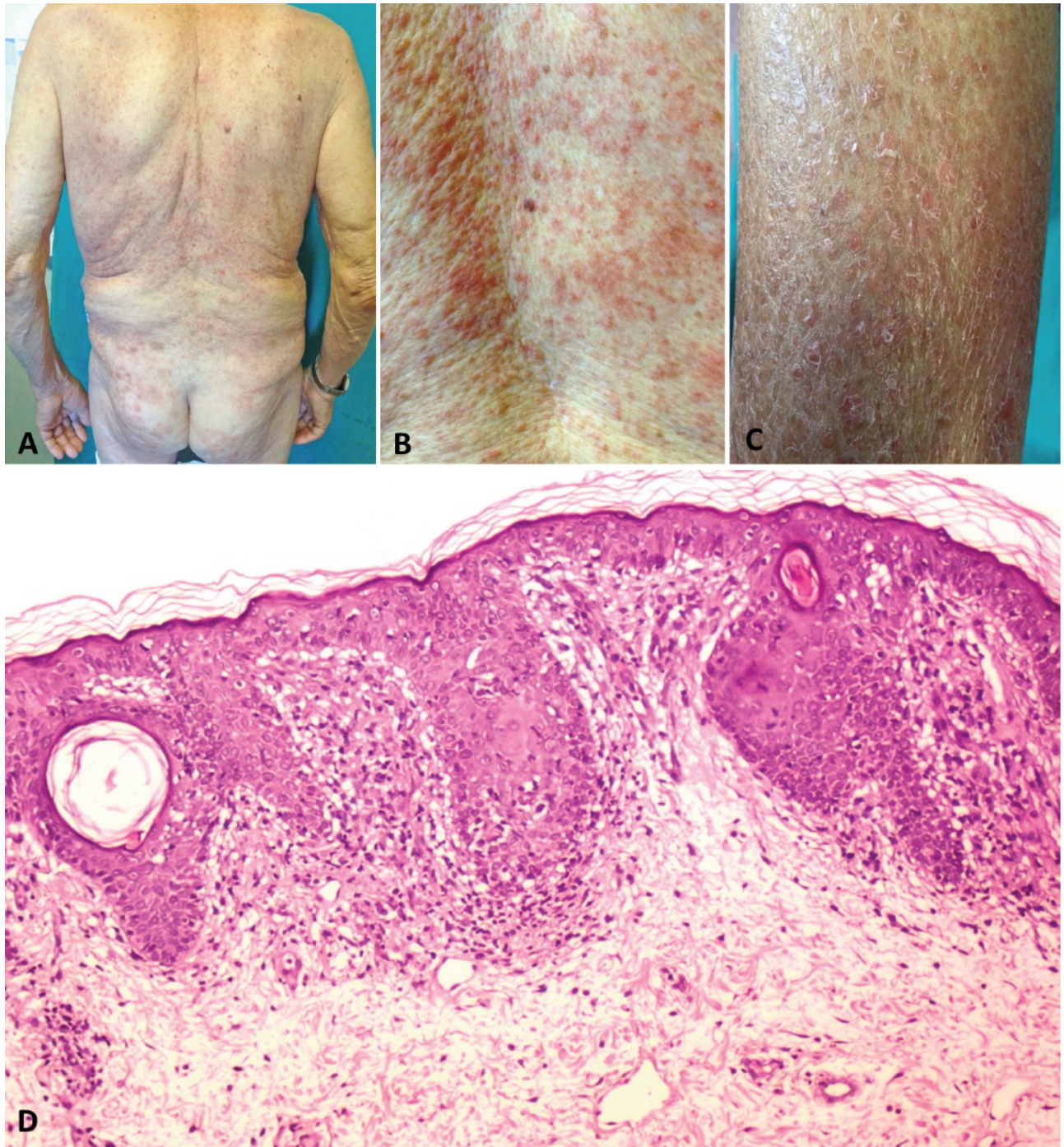


**Figure 8.** A, B) Diffuse erythematous, dusky discoloration involving the trunk, the limbs, and the neck; C, D) band-like lymphocytic infiltration of the papillary dermis with evident epidermotropism and a serum crust on the top.

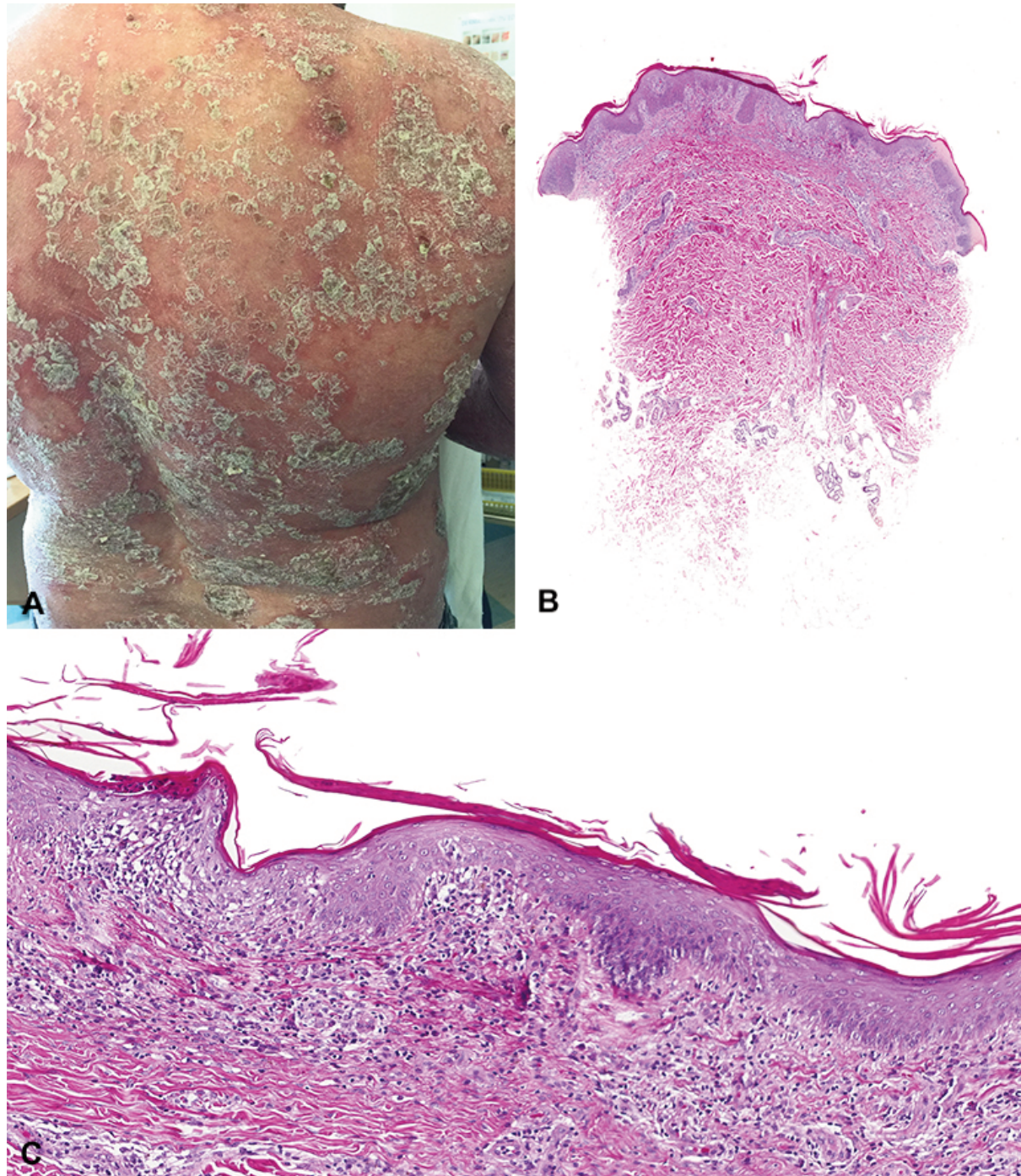


**Figure 9.** A) Diffuse brownish discoloration of the skin; B-D) epidermotropic lymphocytic infiltrate, with scattered melanophages in the papillary dermis.

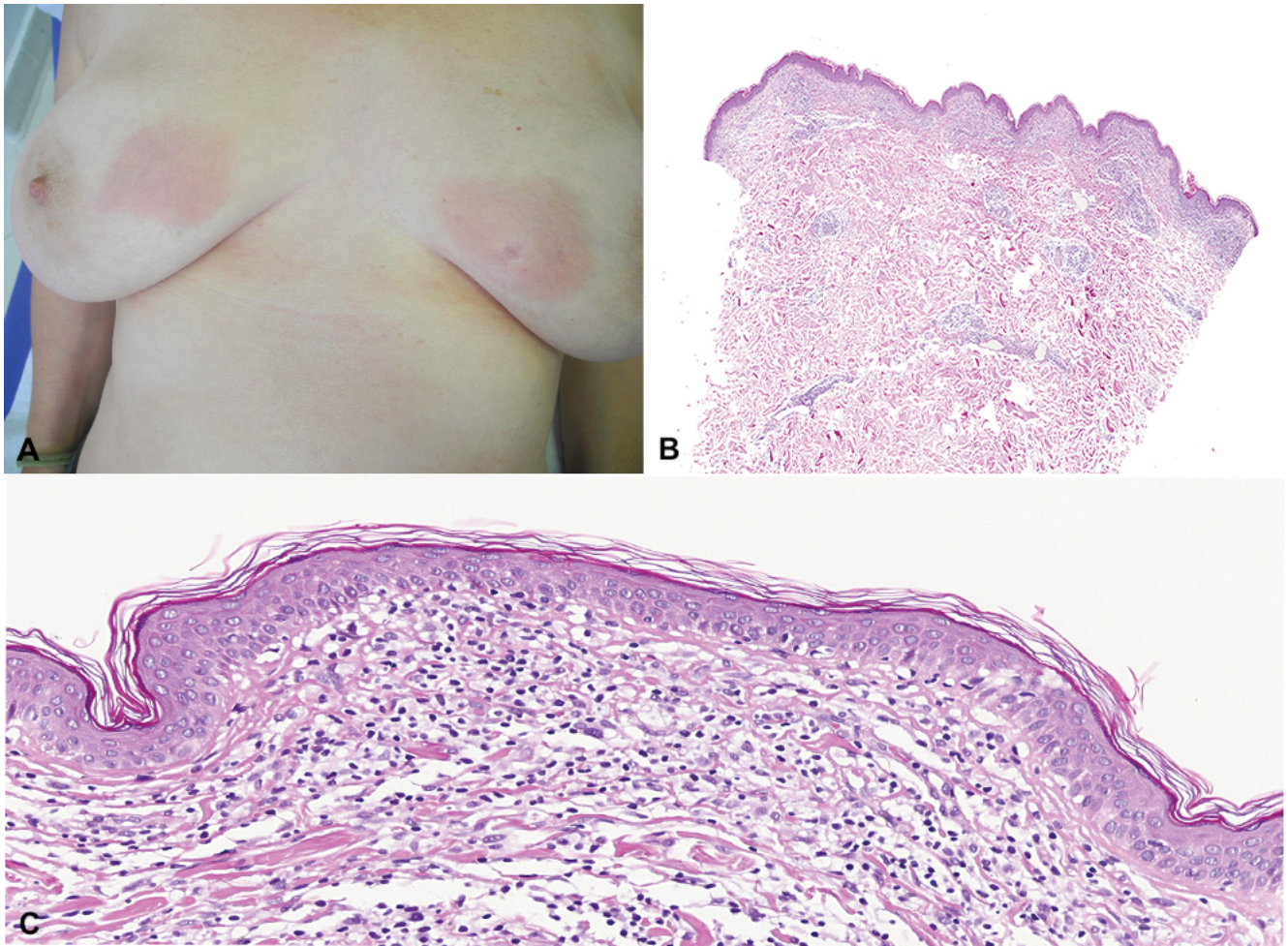




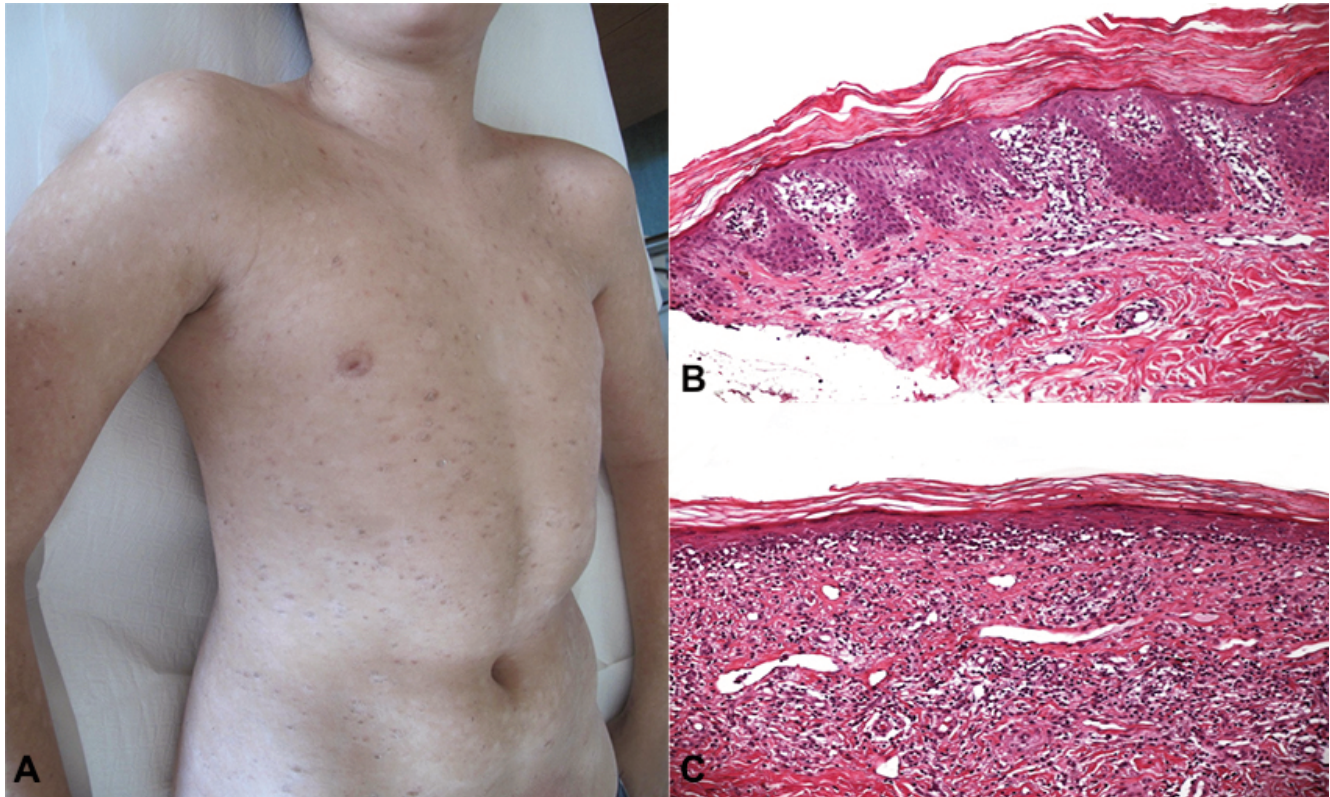
**Figure 10.** A-C) Diffuse erythematous papules on the trunk and arms; D) lymphocytic infiltrates in papillary dermis and small intraepidermal collection of lymphocytes.



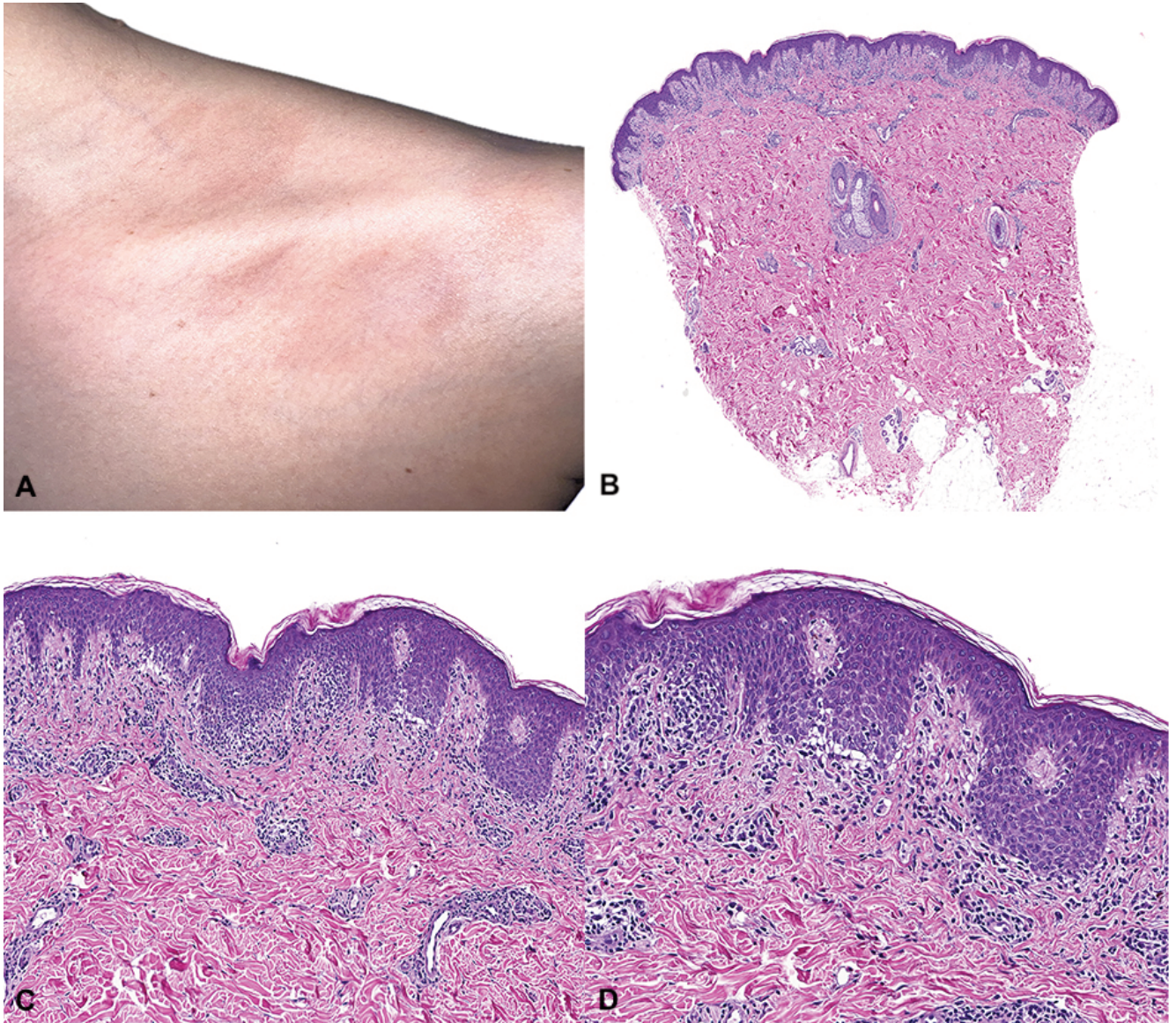
**Figure 11.** A) Diffuse erythematous and scaly plaques on the back, mimicking psoriasis; B, C) psoriasiform epidermal hyperplasia in association with a dermal lymphocytic infiltrate, displaying epidermotropism.



**Figure 12.** A) Two, symmetric, erythematous patches on the medial aspect of the breast; B, C) band-like lymphocytic infiltration in the papillary dermis, with mild epidermotropism.



**Figure 13.** A) Diffuse maculo-papular scaly eruption on the trunk and extremities, including also hypopigmented lesions; B) in one biopsy, there is a lichenoid lymphocytic infiltrate in the papillary dermis, associated with a thick stratum corneum, alternating ortho- and parakeratosis; C) in another biopsy, the lichenoid infiltrate is more epidermotropic, with prominent vacuolar changes at the dermo-epidermal junction. Necrotic keratinocytes are absent and the lymphocytes are large and atypical, with hyperchromatic nuclei and clear perinuclear halo.



**Figure 14.** **A)** Erythematous, annular patches on the clavicular area; **B)** lichenoid lymphocytic infiltrate in the papillary dermis; **C, D)** the lymphocytes show moderate epidermotropism, associated with prominent vacuolar changes at the dermo-epidermal junction and necrotic keratinocytes at the tips of the rete ridges, which assumes a “squared off” aspect.