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None.

Lymphomatoid papulosis

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Summary

Lymphomatoid papulosis (LyP) is characterized by a varied clinical presentation that includes erythema, papules, pustules, vesicles, plaques, nodules and ulcerations. While its biological course is typically marked by spontaneous regression, the histopathological findings of LyP are consistent with cutaneous T-cell lymphoma. Provided patients do no develop a secondary lymphoma, they exhibit unusually high 10-year survival rates (> 90 %), which is a typical feature of LyP. To date, the etiology and pathogenesis of LyP have not been elucidated. One particular subtype of LyP is known to be associated with chromosome 6p25.3 rearrangement (DUSP22-IRF4 translocation).

Treatment is guided by the clinical presentation. In addition to a wait-and-see approach, recommended options include topical corticosteroids and PUVA therapy.

Epidemiology

Lymphomatoid papulosis (LyP) is a rare disease, with an estimated incidence of 1.2–1.9/1,000,000 [1]. In two retrospective studies of 118 and 180 patients, respectively, men were slightly more commonly affected than women (69.49 % vs. 56.7 %) [2, 3]. While LyP may occur at any age, even in childhood [4], its peak incidence is in the 4th and 5th decade [1, 3].

Clinical features

LyP is characterized by a varied clinical morphology. Early lesions appear as small red or reddish-brown papules that measure a few millimeters in diameter (Figure 1a); they may be solitary, grouped or generalized. As the lesions grow, they may develop into larger nodules and plaques, usually with a maximum diameter of no more than 1–2 cm [3]. While complete regression may occur within a few weeks, the papules may also develop into sterile pustules or they may become necrotic, followed by hemorrhagic crusts and varioliform scars [2, 4, 5–7]. In patients with intermittent flares of LyP, the lesions may coexist in different developmental stages, resulting in a varied, polymorphic clinical picture (Figure 2a). Lymphomatoid papulosis primarily occurs on the extremities and trunk, less often on the face [7]. There have been only few reports of oral or genital involvement [4, 5]. Apart from the classical form described above, there are less common morphological LyP variants that include vesicular, plaque-type eczematoid (Figure 3a) and ulcerative (Figure 4a) manifestations (Table 1). Irrespective of the morphology, the capability for spontaneous regression is characteristic and an important diagnostic criterion of LyP [3, 5]. Roughly 40–55 % of patients report pruritus [3, 4]. The clinical features of LyP do not include palpable lymph nodes or hepatosplenomegaly [5, 7]. Lymphomatoid papulosis runs a chronic recurrent course over months and even decades, with 5-year and 10-year survival rates of 100 % and 92 %, respectively [8]. Provided patients develop no secondary lymphoma, the prognosis of LyP is not affected by any etiological, clinical or histopathological factors [8].

Histopathology

Based on histopathological criteria – including infiltration pattern, tumor cell morphology and phenotype – the 2016 WHO classification of cutaneous lymphomas distinguishes LyP types A through E. In addition, a 6th type has been defined that is associated with rearrangement of chromosome

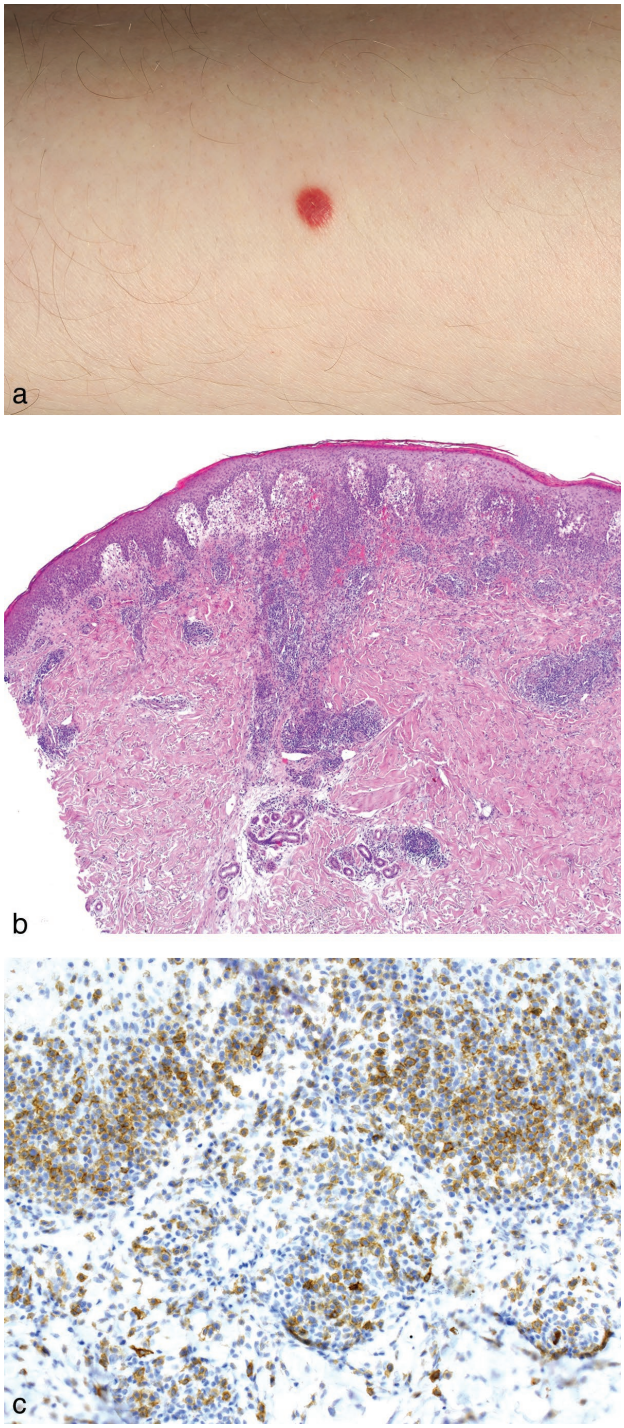

Figure 1 38-year-old male patient. Six-month history of solitary erythematous papules (5–6 mm in diameter) on the trunk and extremities. Spontaneous regression with subtle scar formation after 2–3 weeks (a). Wedge-shaped lymphocytic infiltrate with erythrocyte extravasation and papillary edema (type A) (b). A large percentage of atypical lymphocytes in the epidermis and dermis express CD30 (c).

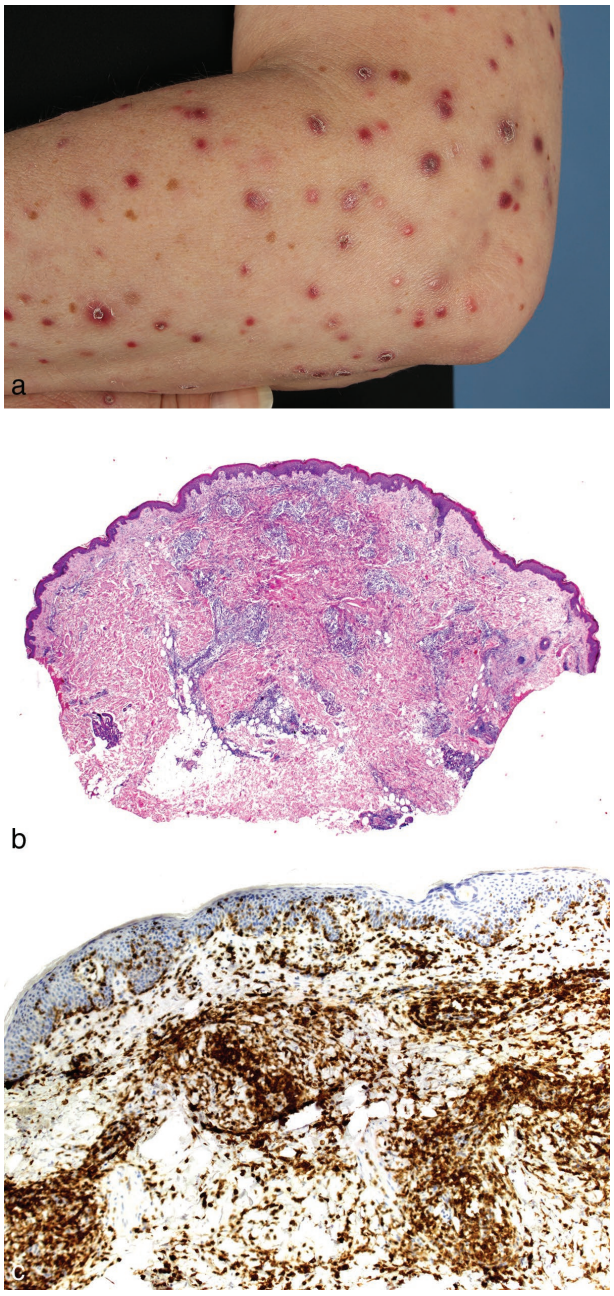

Figure 2 50-year-old female patient. Ten-month history of continuously developing pruritic lesions on the trunk and extremities. Status post four cycles of chemotherapy (CHOEP-14), mobilization chemotherapy with DHAP and autologous stem cell transplantation, with no effect on the skin lesions. Generalized erythematous papules (5–10 mm in diameter) predominantly affecting the extremities. The figure shows the left forearm. Significant yet not complete regression following oral PUVA therapy (a). Sheets of large pleomorphic atypical lymphocytes. Wedge-shaped epidermotropic lymphocytic infiltrate (type D) (b). All lymphocytes express CD8 (c).

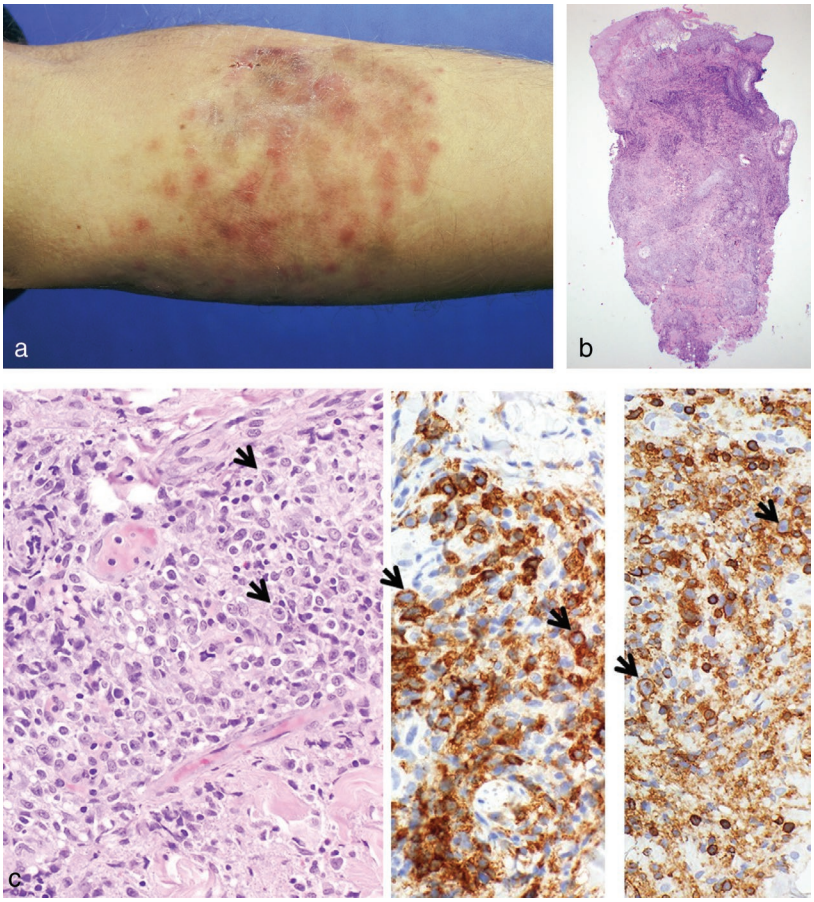

Figure 3 43-year-old female patient. Three-year history of persistent lesions on the left elbow, marked by variable severity. Palm-sized area with solitary and confluent, ill-defined, infiltrated erythematous scaly patches with circumscribed lichenification; in addition, there is postinflammatory hyperpigmentation (plaque-type eczematoid LyP) (a). Ulcerated epithelium. Predominantly lymphocytic infiltrate (b). Mixed infiltrate consisting of lymphocytes, histiocytes, few eosinophils and blasts (blasts are marked by arrows). Blasts express CD30 and CD3 (c).

6p25.3 [9]. Type A is the most common form and accounts for approximately 50 % of cases. It is characterized by a mixed dermal infiltrate consisting of large pleomorphic and anaplastic CD30⁺ lymphomatoid cells intermingled with neutrophils, eosinophils and histiocytes (Figures 1b, c, 3b, c). Type B is significantly less common than type C and shows a bandlike epidermotropic infiltrate of small and medium-sized atypical lymphocytes with cerebriform nuclei. There is little or no CD30 expression. Type C is characterized by clusters or sheets of large CD30⁺ tumor cells with relatively few inflammatory cells (Figure 4b, c). Type D accounts for approximately 8 % of cases and is characterized by atypical, epidermotropic small to medium-sized CD8⁺ and CD30⁺ lymphocytes with or without perivascular arrangement in the deep dermis (Figure 2b, c). Type E accounts for less than 1 % of cases and presents with angiocentric infiltration and vascular destruction [3, 9].

In 2013, Kempf et al. were the first to describe another LyP variant that is supposed to account for up to 10 % of all LyP cases. Unlike the aforementioned LyP types, this variant shows perifollicular infiltration [10].

Recently, a publication in JDDG proposed a simplified terminology for LyP that also included special variants [11].

Associated lymphomas

Patients with LyP may develop other lymphatic neoplasms, which may precede, be associated with or follow the disease. Reports indicate that between 19.4 % and 52 % of patients are affected, with some individuals developing more than one lymphoma [2, 3]. The mean interval between diagnosis of lymphomatoid papulosis and the occurrence of a secondary lymphoma is approximately 3–4 years. Given that 26 % of patients develop secondary lymphomas only after LyP has resolved, this underscores the necessity for continued follow-up, even if patients no longer exhibit clinical signs of LyP [3]. Risk factors for developing secondary lymphomas include male gender (men: female ratio > 2: 1), childhood-onset LyP and histopathological types B and C [3, 12]. The most common secondary lymphoma associated with LyP is mycosis fungoides (MF) [2, 3]. In a cohort of 93 patients with associated lymphomas, MF accounted for 61 % of cases, followed by primary cutaneous anaplastic large cell lymphoma (cALCL) at 26 % [3]. It should be noted, though, that the most common secondary lymphomas associated with LyP are also differential diagnoses thereof. This may lead to overestimating the prevalence of secondary neoplasms

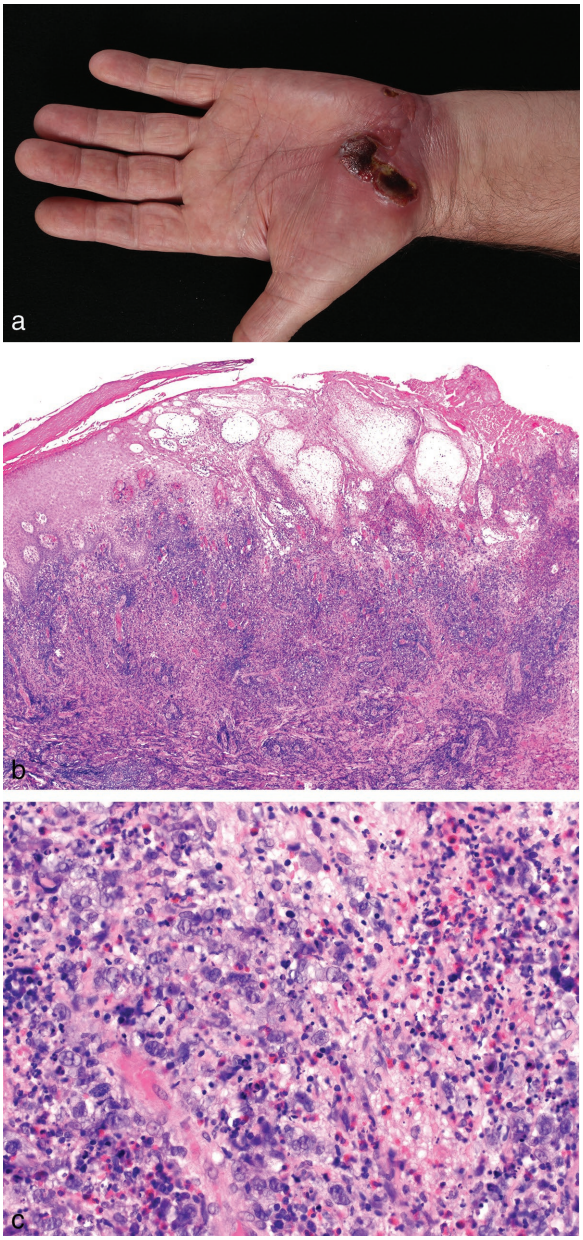

Figure 4 62-year-old male patient with acute onset of a painful ulceration on the right thenar. Two coin-sized, confluent ulcerations covered with an adherent hemorrhagic crust. Spontaneous healing after three months, prior to initiation of scheduled radiation therapy (a). Dense lymphocytic infiltrate with central epidermal necrosis (type C) (b). Close-up: sheets of large pleomorphic atypical lymphocytes (c).

(see "Differential diagnoses"). As both primary cALCL and LyP are included in the group of CD30-positive cutaneous lymphoproliferative disorders and as the various subtypes within this group are frequently difficult to distinguish, the former is primarily a differential diagnosis and not so much

Table 1 Rare clinical LyP variants [5, 24].

- vesicular/papulovesicular LyP
- follicular LyP
- plaque-type eczematoid LyP
- ulcerative LyP
- LyP with white halo
- localized LyP
- special form: agminated LyP

a genuine secondary neoplasm. Other secondary lymphomas reported to be associated with LyP comprise Hodgkin lymphoma, chronic and acute leukemias, cutaneous NK/T-cell lymphoma and Waldenström's macroglobulinemia [3, 5, 8]. It remains subject to controversial debate whether evidence of clonal rearrangement in LyP is associated with an increased risk of developing a secondary lymphoma [13].

Etiopathogenesis

The etiology and pathogenesis of LyP have not been elucidated. For lymphomas, it has generally been postulated that tumorigenesis involves continuous stimulation of a single lymphocyte or lymphocyte clone by a persistent antigen (e.g., of viral origin), which in some cases results in accumulation of mutations and subsequently in uncontrolled proliferation, and thus a neoplasm [14, 15]. Studies investigating the spontaneous regression of LyP examined the interaction between CD30 and its ligand and found that healing lesions were characterized by a significant increase in ligand expression compared to non-healing lesions [16].

In their study of eleven LyP patients, Karai et al. described a new molecular genetic subtype characterized by rearrangement of the DUSP22-IRF4 locus on chromosome 6p25.3. As a result of this translocation, they observed – at least for this subtype – downregulation of DUSP22, which might act as a tumor suppressor gene through a specific phosphatase [17].

Differential diagnoses

The diagnosis of LyP poses a clinical challenge, and the condition frequently goes undetected for long periods of time [5]. The average interval between the onset of lesions and the definitive diagnosis is 45–75 months [3]. The diagnosis usually requires clinicopathological correlation, and the spontaneous regression of LyP lesions plays a pivotal role in this context. Typical differential diagnoses of LyP presenting with papular lesions include arthropod bite reactions, persistent scabies nodules and (in case of facial lesions) eosinophilic granuloma. Papulonecrotic lesions, on the other

hand, may frequently be confused with pityriasis lichenoides et varioliformis acuta as well as atypical mycobacteriosis, sporotrichosis, and furunculosis [4, 5]. The differential diagnosis of plaque-type eczematoid LyP includes various forms of localized dermatitis [18], whereas ulcerative LyP, as in one of our cases, may make one think of pyoderma gangrenosum (Figure 4a). Other differential diagnoses in such cases are herpesvirus infections, chancre and various other necrotizing tumors [19]. The histopathological differential diagnoses depend on the LyP type. Mycosis fungoides is one of the most important differential diagnoses of types A and B. Tumor-stage mycosis fungoides may particularly resemble LyP with abundant CD30-positive blasts. Patients with a history of mycosis fungoides or mycosis fungoides-like lesions in other sites should therefore be diagnosed with LyP only if the clinical presentation and disease course are characteristic [20]. Otherwise, the diagnosis should be tumor-stage mycosis fungoides with CD30 expression. Hodgkin's lymphomas very rarely infiltrate the skin. If the condition in question is a primary cutaneous disorder, we believe the relevance of this differential diagnosis to be overrated. It is important to note that CD30-positive cells in patients with LyP may spread to draining lymph nodes where they may mimic Hodgkin's lymphoma [21]. However, there is no relevant spread beyond the draining lymph nodes in LyP.

Given its clinical presentation, type C LyP must be distinguished from primary cALCL in particular, whereas type D requires differentiation from cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. Differential diagnoses of type E include NK/T-cell lymphoma and γ/δ T-cell lymphoma [10]. The clinical presentation with spontaneous regression is the essential criterion in the differential diagnosis of any rare LyP variant (types C, D, E), as the histological findings may not offer any significant clues.

Treatment

Treatment of LyP is guided by the number, size, morphology and distribution of the lesions as well as the disease course. Depending on the constellation of clinical findings, and irrespective of the histopathological LyP type, options comprise a wait-and-see approach as well as local and systemic treatments. Considering the benign biological behavior and high spontaneous remission rates of LyP, it is advised not to employ any aggressive treatments, especially as there is no evidence that chemotherapy is effective in patients with LyP. Given the high percentage of recurrences following chemotherapy, this treatment option is not recommended. In patients with associated lymphomas, it was shown that only the lymphomas responded to chemotherapy, whereas the LyP lesions showed no improvement [22]. The patient shown in Figure 1b had previously undergone polychemotherapy followed by autologous stem cell transplantation, which had had no effect on her LyP. Although topical corticosteroids have repeatedly been reported to be a treatment option, studies have failed to provide evidence for a high level of effectiveness.

Table 2 lists the various treatment options based on the distribution pattern of the lesions. In addition to what has

Table 2 Treatment options.

Clinical morphology	Solitary/grouped lesions	Generalized lesions
Papulonodular LyP	Class 3–4 topical corticosteroids	PUVA – systemic – bath PUVA
Plaque-type eczematoid LyP	Class 3–4 topical corticosteroids Cream PUVA	UVA_1 [5] Methotrexate [25] Alpha-interferon [26] – with etretinate [27]
LyP with large nodules	Excision Radiation therapy	Bexarotene [3] Brentuximab [3, 28, 29, 30] Extracorporeal photopheresis [22]
Ulcerative LyP	Excision Radiation therapy Cream PUVA [31] Triamcinolone suspension [32]	

In generalized disease, the choice of treatment is independent of clinical morphology; however, LyP with large nodules and ulcerative LyP usually do not present with generalized lesions.
Review articles on treatment options [2, 3, 5, 22]. Regarding the value of individual treatments, the reader is referred to Kempf et al. [23].

been addressed in the present review, the reader is referred to the 2011 consensus recommendations (developed by three lymphoma societies) in which the value of individual treatment options is discussed [23].

Outlook

There is no medical need associated with CD30-positive lymphoproliferative disorders that would urgently warrant the necessity for research to be conducted. This circumstance has adverse effects both on molecular research into these disorders as well as on investigations into other relatively benign lymphoproliferative skin diseases. However, given that these disorders are considered to be models of disseminated T-cell lymphomas, their molecular characterization may significantly contribute to our understanding of other lymphoma entities and may possibly help identify additional LyP subtypes.

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