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REVIEW ARTICLE

Lymphomatoid papulosis: an update and review

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Abstract

Lymphomatoid papulosis (LyP) is a benign chronic often relapsing skin condition that belongs to the CD30-positive cutaneous lymphoproliferative disorders. LyP typically presents as crops of lesions with a tendency to self-resolve, and morphology can range from solitary to agminated or diffuse papules and plaques to nodules or tumours. The clinical–histological spectrum can range from borderline cases to overlap with primary cutaneous anaplastic cell lymphoma (pcALCL). Histology and immunophenotype commonly show overlap with other CD30-positive disorders and sometimes may be identical to pcALCL, making its diagnosis more difficult. Patients with LyP have an increased risk of developing a second neoplasm such as mycosis fungoides, pcALCL and/or Hodgkin lymphoma. Clinical correlation allows its proper classification and diagnosis, which is fundamental for treatment and prognosis. This review focuses on the clinical appearance, histopathological features, diagnosis, differential diagnosis and management of LyP.

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Conflict of interest

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Introduction

Lymphomatoid papulosis (LyP), first described by Macaulay in 1968,[1] is a recurrent chronic papulonodular dermatitis. This disease characteristically follows a benign course, even though it belongs to the CD30-positive cutaneous lymphoproliferative disorders and malignancies, and has malignant histopathologic features with large atypical CD30 lymphoid cells[2,3] (Table 1). This disease is classified in the division of cutaneous T-cell and NK-cell lymphomas in the 2018 update of the WHO-European Organization for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas with primary cutaneous manifestations[4,5] and in the division of Mature T and NK neoplasms in the 2016 WHO classification of mature lymphoid, histiocytic and dendritic neoplasms.[3] In 1982, Willemze *et al.*[6] classified LyP into two histological subtypes: A and B, but it was not until years later that these were identified as CD30+ lymphoproliferative disorders.[7,8] CD30, previously known as Ki-1, has been associated with Hodgkin's disease.[9] This molecule is a 120-kDa type I transmembrane glycoprotein of the tumour necrosis factor (TNF) receptor superfamily. It is a cell surface cytokine receptor expressed on activated T and B cells that interact with CD30 ligand (CD30L, CD153, TNFSF8), a 40-kDa type II membrane associated glycoprotein belonging to the TNF family.[10] The function of the CD30/CD30L system is to regulate cellular survival vs. apoptosis.[10] CD30 can be upregulated on lymphoid cells of both B- and T-cell lineages in benign conditions including blastic transformation induced by antigen, mitogen, certain lymphotropic viruses and proliferative processes induced by viral infections and arthropod bites 8.[11] It is expressed in 10–20% of B-cell malignancies, 30% of T-cell malignancies and all CD30+ lymphoid proliferations and malignancies.[12–14] The CD30 molecule has also been described in carcinomas and mesenchymal neoplasms.[15,16]

Materials and methods

A review of LyP cases reported in the literature was carried out by searching PubMed–MEDLINE and EMBASE between 1988 and July 2018. Search MeSH terms were 'Lymphomatoid papulosis,' including the subheadings of epidemiology, aetiology, pathology, physiopathology, diagnosis, therapy,

Table 1 CD30-positive cutaneous lymphoproliferative disorders and malignancies

Primary CD30-positive cutaneous lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Cutaneous T-cell lymphoma with expression of CD30+
Mycoses fungoides with large cell transformation
Pagetoid reticulosis
Sézary syndrome with large cell transformation
Extranodal NK/T-cell lymphoma, nasal type
Peripheral T-cell lymphoma, not otherwise specified
Mature T and NK neoplasms
Angioimmunoblastic T-cell lymphoma
Systemic anaplastic large cell lymphoma

Adapted from Swerdlow, *et al.* and WHO-European Organization for Research and Treatment of Cancer Classification 2018.[3,5]

drug therapy, surgery and mortality. Publications were limited to the English language. Metanalysis, systematic reviews, clinical trials, original articles and case reports were included.

Etiopathogenesis

The incidence of LyP is 1.2–1.9 cases per 1 000 000 people and is more predominant in males. It may occur at any age, although it is unusual in childhood.[17,18] The inciting event resulting in lymphoproliferation is not known, but various authors have proposed associated viral aetiologies including HTLV-1, herpesvirus and endogenous retroviruses.[19,20] However, detailed studies have not been able to confirm this association.[21–25] Growth of lesions may be associated with genetic mutations of the growth inhibitory effect of transforming growth factor-β type I receptor in the CD30-positive tumour cells.[26] Other proliferation signals implicated include external factors such as radiation and drugs such as fingolimod, infliximab, adalimumab and efalizumab.[27–33] A co-occurrence between LyP and myeloproliferative hypereosinophilic syndrome has been reported in the literature,[34–37] but it is unknown which mechanisms are implied. Some authors suggest a tyrosine–kinase-mediated mechanism might be playing a role considering that imatinib has been effective as a therapeutic treatment in these patients.[34,38] Eosinophilia can be observed, and the release of eosinophil-stimulating cytokines (interleukin 3, interleukin 5, and granulocyte macrophage – colony-stimulating factor) secreted by abnormal T lymphocytes has been documented in some cases.[39] To explain the characteristic self-resolving nature of the disease, it was suggested that CD30/CD30 ligand interaction within the lesions may induce this phenomenon by triggering apoptosis. This interaction was found to be higher in the regressing lesions of LyP than in the evolving lesions.[40]

Clinical presentation

Most commonly, LyP presents as recurrent crops of disseminated pruritic pink papules of variable size, between 0.5 and 1 cm in diameter. This papulonodular eruption may range from a single to a few to hundreds of lesions over the trunk and/or limbs, becoming postinflammatory hyperpigmented macules and eventually atrophic varioliform scars in the process of spontaneous resolution (Fig. 1).[41,42] Common morphological variants include solitary papules, diffuse, agminate and plaque-like.[43–45] Rare cases can have a segmental or localized presentation including acral and facial involvement.[42,46–52] Uncommon morphologic variants include mucosal, follicular, bullous and pustular.[53–59] Although LyP is a self-healing condition, patients require surveillance as between 10% and 40% of patients will develop a second lymphoproliferative disorder such as a CD30-positive anaplastic large cell lymphoma (ALCL), Hodgkin lymphoma or mycosis fungoides.[18,60] Several studies have revealed clonal similarities between the cells of LyP and the cells of mycosis fungoides and ALCL in patients that develop both diseases, suggesting a common origin.[61]

Dermoscopy

Moura *et al.*[62] reported dermoscopy at four different stages of LyP in eight cases: at the initial stage, inflammatory papules have a vascular pattern of tortuous irregular vessels radiating from the centre to the periphery of the lesion with white structureless areas around the vessels; at the second stage, more mature lesions such as hyperkeratotic papules, a whitish structureless area at the centre of the lesion surrounded by vessels can be identified; at the third stage, ulcerated lesions, brown-grey structureless areas with peripheral vessel patterns predominate; and at the cicatricial stage, brown-grey structureless areas without vessel patterns are seen. Another study reported the coexistence of all four stages demonstrated by dermoscopy in the same patient at the same time.[63] To our knowledge, there are not published studies regarding specificity and sensitivity of these dermoscopy findings; however, none of the four stages have been seen in other cutaneous lymphomas or pseudolymphomas.[64,65]

Differential diagnosis

The differential diagnosis varies based on the morphology and histopathology of the lesion[66] (Table 2). Histopathologically, LyP should be differentiated from benign conditions that might express CD30-positive lymphoid cells such as atopic dermatitis, viral infections, scabies, mycobacterial infection, drug reactions (Fig. 4) and from malignant disorders including mycosis fungoides.

Studies comparing benign inflammatory conditions with CD30 expression from LyP have not identified histopathologic findings that can distinguish between these two. A literature review reported that CD30 expression in reactive inflammatory disorders is not as high as typically seen in LyP. Furthermore,

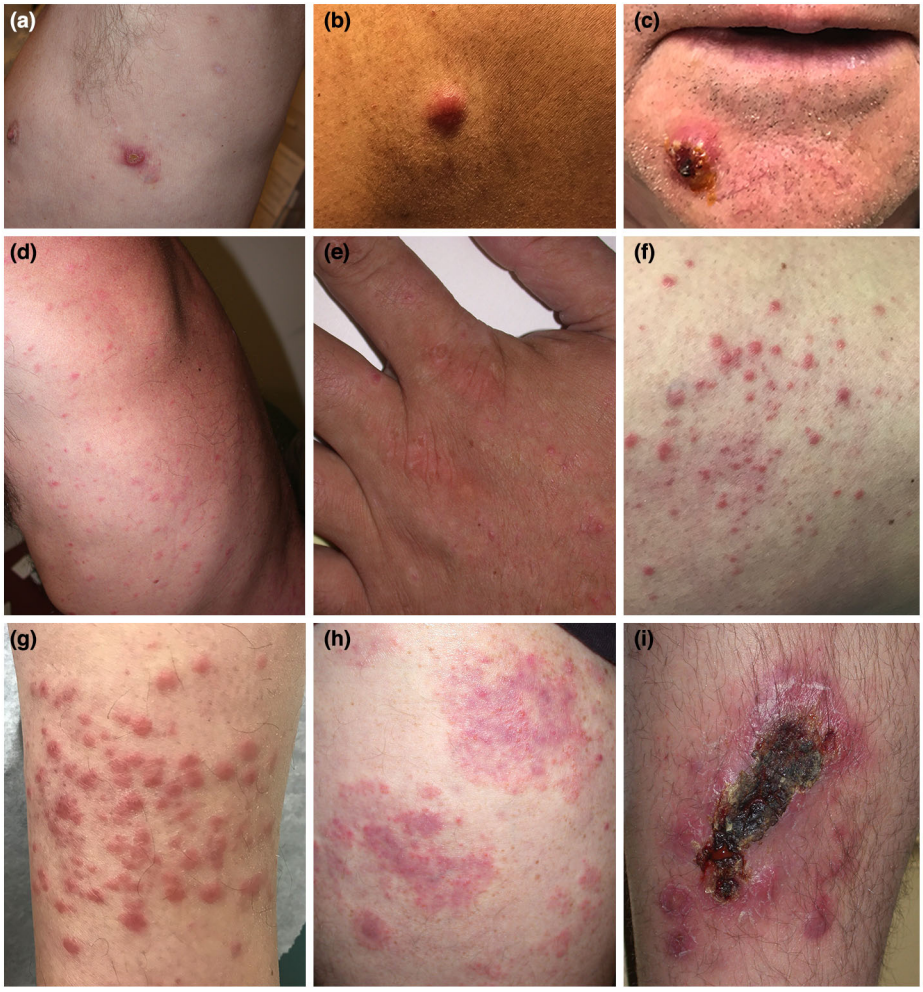

Figure 1 Morphology. Solitary lymphomatoid papulosis (LyP) (a); papulonodular LyP (b); ulcerating papulonodular LyP (c); diffuse papular type (d); varioliform scars (e); agminate LyP (f, g); plaque-like (h); and a borderline lesion of LyP (i).

with inflammatory disorders, CD30 expression is present in small- or medium-sized lymphoid cells unlike LyP, in which CD30 is expressed by large anaplastic or pleomorphic lymphoid cells.[67] However, there are exceptions to this, as viral infections can show dense lymphoid infiltrates expressing CD30 in large lymphocytes.[11] Moreover, careful clinicopathologic correlation is necessary, particularly in arthropod bite reactions that share not only histopathologic features but also an identical morphology with LyP.

One of the most difficult differential diagnosis to elucidate is the papular variant of mycosis fungoides (PMF) from LyP-B.[68,69] This variant was described for the first time in 2005.[68] Since then, several case reports supporting this diagnosis have appeared in the literature[69–77]; however, other authors do not recognize it as a single entity, believing that PMF and LyP-B are the same disorder.[78,79] Considering PMF exists, it needs cautious clinicopathological correlation and a closer follow-up to differentiate it from LyP.

Papular variant of mycosis fungoides is described as an early stage of MF that manifests with multiple small (≤1 cm) red to brown papules that commonly present with symmetrical distribution anywhere on the body without any evidence of pre-existing MF skin lesions.[68,80] Clinically, PMF does not show a waxing and waning presentation, and its morphology is more uniform and monomorphous in contrast to what is seen in LyP; however, it is expected that papules of PMF reappear in the future.[80] On evolution, a PMF patient might develop the typical patches, plaques or tumours that characterize a MF.[74] Histologically, PMF shows features of early MF such as epidermotropism of small to medium atypical lymphocytes, vacuolar interface changes and a band-like lichenoid infiltration of lymphocytes in the upper dermis. However, it is characterized by an absence of tropism for

Table 2 Differential diagnosis of morphological and histological variants of LyP

Morphology variants	Differential diagnosis
Solitary	Basal cell carcinoma, ALCL, keratoacanthoma, nodular hidradenoma, eccrine poroma, leiomyomas, pilomatrixoma, nodular amyloidosis, dermatofibroma, amelanotic melanoma, impetigo, nodular scabies, insect bite reaction and pseudolymphoma
Agminate	Insect bite reaction, pseudolymphoma, leiomyomas, segmental neurofibromatosis, sarcoidosis and ALCL
Plaque-like	Pseudolymphoma, B-cell lymphoma, mycosis fungoides and ALCL
Diffuse papular	Pityriasis lichenoides varioliformis et acuta, papular MF, langerhans cell histiocytosis, folliculitis, prurigo nodular, scabies, multifocal pcALCL and secondary skin involvement by systemic ALCL
Borderline†	Pseudolymphoma, B-cell lymphoma, mycosis fungoides and ALCL
Histopathology variant	Differential
A	Hodgkin lymphoma, papular MF and CD30-positive transformed MF
B	Plaque stage of MF, papular MF and cutaneous gamma/delta lymphoma
C	pcALCL/sALCL, adult T-cell lymphoma/leukaemia, peripheral T-cell lymphoma and transformed MF
D	Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, cutaneous gamma/delta lymphoma and pagetoid reticulosis
E	Extranodal NK/T-cell lymphoma nasal type, cutaneous gamma/delta lymphoma and pcALCL/sALCL
F	Follicular mycosis fungoides, CD30-positive transformed MF, concurrent of MF and LyP

†Borderline lesion is defined as a growing nodule without a definite distinction between LyP and pcALCL at clinicopathologic correlation.
ALCL, anaplastic large cell lymphoma; LyP, lymphomatoid papulosis; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma; sALCL, systemic anaplastic large cell lymphoma.

hair follicles and eccrine glands.[69] PMF has the same immunohistochemical criteria as MF, being CD30 negative.[72] At histopathology, LyP-B mimics MF. The presence of Pautrier collections does not provide any diagnostic aid since they have been reported in both conditions.[79] A similar situation exists with CD30 expression, which is negative in PMF, but its expression is variable in LyP.

Because LyP-B is commonly seen simultaneously with other LyP subtypes, some authors suggest that the absence of this coexisting with LyP A-C supports a PMF diagnosis.[69,72,78,79,81] However, the co-occurrence of LyP and MF is not uncommon.[82] Thus, in many cases, LyP may be histologically impossible to distinguish from PMF, in which the clinical evolution will determine the diagnosis.

The recognition of coexistence of LyP and MF has been reported in several studies, and evidence suggests these conditions are closely related.[82,83] A common clonal origin from LyP and MF was initially observed in a few cases.[61,84] A study, which included 15 cases, found the same T-cell clone in both skin lesions from LyP and MF in three of the cases.[85] Another study observed an identical clone in LyP and MF in seven patients.[82] A year later, another case series, including 12 patients, identified the same T-cell receptor (TCR) rearrangements in skin lesions of MF and LyP in each of six patients, suggesting that LyP and MF may represent a different clinical manifestation of a unique T-cell lymphoproliferative clonal expansion.[86] Another study demonstrated an identical pattern of monoclonal TCR gene rearrangement in both LyP and MF in 10 of 11 patients.[87] These case series have suggested that patients with the association of LyP and MF seem to have a favourable prognosis; however, prospective cohort studies are still lacking. Basarab *et al.*[85] reported no death at 15 years of follow-up from the onset of the first lesion, and Zackheim *et al.*[82] reported all patients alive at 6 years of follow-up (median; range of 0.5–21 years). Gallardo *et al.*[86] found an indolent evolution in 10 years of follow-up (median; range: 4–40 years) except for one death in the eldest patient who died of advanced CTCL.

When LyP is histologically and clinically divergent, the term 'borderline lesion' is recommended as a working diagnosis with close monitoring. In cases of overlapping clinical features of both LyP and ALCL, the term 'overlap' is recommended.

Histopathology

Lymphomatoid papulosis has five classically recognized histopathologic subtypes: A, B, C, D and E,[3,81,88,89] which vary based on the predominant cell type and tropism (Figs 2 and 3; Table 3). The most common is type A, which includes 75% of all cases,[90] and has been associated with early relapse of disease.[90] Commonly, more than one subtype may be seen in a single histopathology section or in different biopsies from the same patient, suggesting that these are overlapping entities. Other rare histological LyP patterns include perifollicular infiltrates and folliculotropism (F subtype, which is not officially recognized in the WHO classification),[91,92] follicular mucinosis, syringotropic, non-caseating granulomas, pseudoepitheliomatous hyperplasia, spindle cell, angioinvasive and an intralymphatic variant.[49,53,81,93–99] A new genetic variant LyP with chromosome 6p25 rearrangement has also been recognized by the WHO classification 2016.[3,93]

There is no solid clinical pathological correlation between LyP subtypes, with a few exceptions. LyP subtype E is characterized by eschar-like necrosis, ulceration and larger papules as a

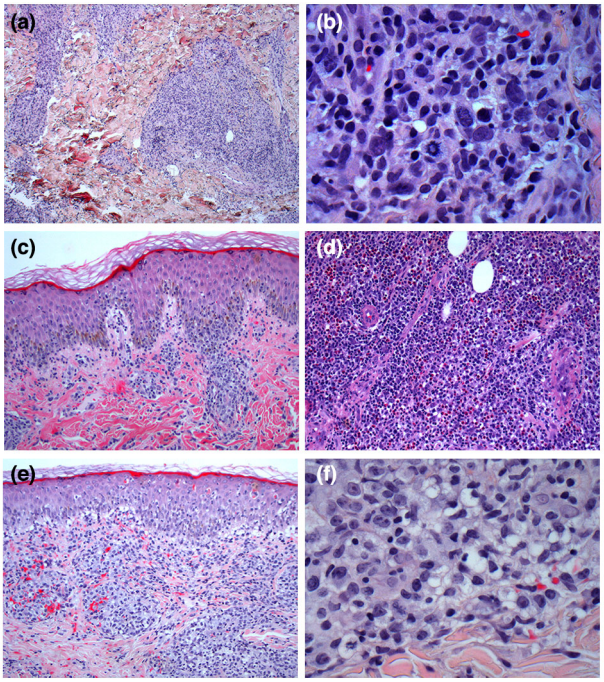

Figure 2 Histopathology. (a) Lymphomatoid papulosis (LyP) A high power. The wedge-shaped dermal cellular infiltrate. (b) LyP A medium power. Clusters of a mixture of large anaplastic pleomorphic cells, plasma cells, lymphocytes and histiocytes. Note the anaplastic cells have a vesicular nucleus containing prominent nucleoli and abundant cytoplasm, resembling Reed–Sternberg cells. (c) LyP-B medium power. Note epidermotropism and a lymphocytic infiltrate in a band-like distribution in the upper dermis, simulating mycosis fungoides. The type B cells are small- to medium-sized lymphocytes with enlarged, irregular hyperchromatic nuclei and scanty cytoplasm. (d) LyP-C medium power. Note a dense dermal infiltrate with cohesive sheets of type A cells with relatively few inflammatory cells. (e) LyP-D medium power. Note the epidermotropism with atypical small- to medium-sized CD8 T cells. (f) LyP-D high power. Note atypical small- to medium-sized CD8 T cells.

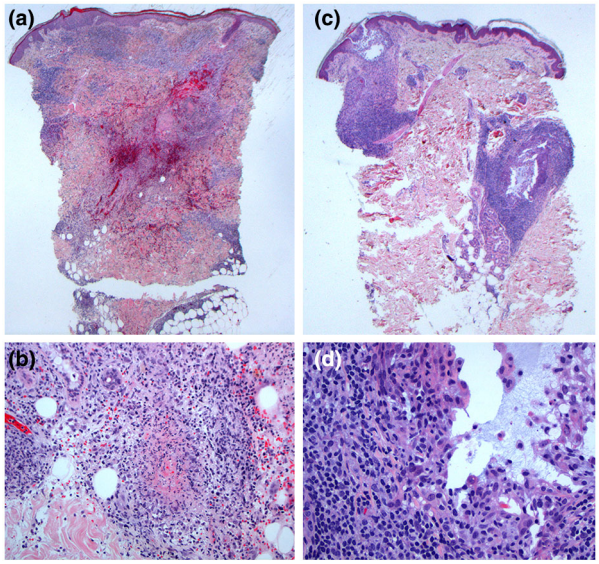

Figure 3 Histopathology. (a) Lymphomatoid papulosis (LyP)-E. The angiocentric and angiodestructive infiltrates of lymphocytes, and haemorrhage with extensive necrosis. (b) LyP-E. Note the medium-sized atypical lymphocytes, with some eosinophils and vascular occlusion. (c) LyP-F low power. Note the perifollicular atypical lymphocytic infiltrate. (d) LyP-F high power. Note the infiltration of large atypical lymphocytes in the hair follicle.

consequence of the infiltration and destruction of dermal and subcutaneous vessels.[88] Follicular LyP subtype (F) that has CD30+ atypical lymphocytic infiltration of the follicular epithelium clinically gives rise to a papular and/or pustular phenotype as neutrophils and eosinophils are attracted to the infiltrate.[53,54] In few cases, the association of folliculotropism and follicular mucinosis in LyP has been documented.[53,81,100]

As mentioned, the histological findings are variable and one lesion may show overlapping features.[101] The immunophenotype of the proliferating cells in LyP is typically CD3+, CD4+, CD25+, CD30+, (Ki-1), CD45RO+ and express HLA-DR.[102–104] CD30-negative entities are type B LyP with a variable expression of CD30 (77% of the cases) and some cases of type D LyP.[105–107] LyP subtypes D and E are unique for expressing CD8+.[88,108,109] This marker is also seen in many cases of LyP in children.[110] There is a variable expression of pan-T-cell antigens, although CD2, CD3, CD5 and CD7 are commonly absent.[104] Other positive markers that can be seen include cytotoxic molecules such as T-cell intracellular antigen 1 (TIA-1), granzyme B and perforin.[111–113] Cells are CD56 positive in 10% of LyP biopsies; CD15 positive in 18%[114,115]; and usually negative for epithelial membrane antigen (EMA).[111,115–118]

A monoclonal rearrangement of the TCR gene is detectable in 22–100% of LyP biopsies.[119–122] Steinhoff *et al.*[123] reported that all the CD30+ cells from patients with LyP lesions temporally separated during different biopsies were from a single T-cell clone. The same clonal rearrangement was also detected in the malignant lymphoma that subsequently presented in the same LyP patients.[61,82,123–125] On the other hand, Gellrich *et al.*[126] found that the CD30 cells were polyclonal in four LyP subtype A patients, while monoclonal cells were seen in the CD3-positive, CD30-negative cell population. Karai *et al.* identified a new form of LyP observed in 11 patients whose histology revealed a pagetoid reticulosis pattern with heavy epidermotropism and dense dermal infiltrates of CD3+ lymphocytes. At FISH, chromosomal rearrangements involving the DUSP22-IRF4 locus on 6p25.3 were found.[93]

Table 3 Lymphomatoid papulosis (LyP): histology

LyP type	Histopathology	Phenotype	Infiltrate characteristics	Lymphocyte morphology	Cells
A	Mixed cellular	CD4+	Dermal infiltrate with cells arranged in small clusters	Medium-sized to large (15–30 μm in diameter) anaplastic lymphoid cells with pleomorphic vesicular nuclei, prominent nucleoli and abundant cytoplasm. Mitotic figures are commonly seen	Neutrophils eosinophils histiocytes and plasma cells
B	Epidermotropic	CD4+, CD30+ (0–77%)	Epidermotropic infiltrate and band-like dermal infiltrate	Small- to medium-sized lymphocytes with pleomorphic enlarged and cerebriform nuclei	Fewer CD30+ large cells than type A and C; and few admixed inflammatory cells
C	Cohesive infiltrate	CD4+>CD8+	Nodular cohesive infiltrate	Large atypical lymphoid cells	Few reactive inflammatory cells
D	Epidermotropism	CD8+ (100%) CD30+ (90% of the cases)	Epidermotropic infiltrate	Atypical small- to medium-sized lymphocytes	Deep dermal perivascular component
E	Angiocentric and angiodestructive	CD8+ (70%)	Angiocentric and angiodestructive infiltrates	Medium-sized atypical lymphocytes with pleomorphic, moderately chromatin-dense nuclei	Extensive haemorrhagic necrosis and ulceration
F	Folliculotropic	CD4+, CD8+	Perifollicular infiltrates	Follicular Histology corresponds type A and C mucinosis	Neutrophils
LyP with DUSP22-IRF4 rearrangement		CD4−, CD8+ or CD4−, CD8−			

Types A to E are in the 2016 WHO classification of hematopoietic and lymphoid tumours[3] and in 2018 update of the WHO-European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas.[5] Type F has not been recognized.[53] EBV, Epstein–Barr virus; pcALCL, primary cutaneous anaplastic large cell lymphoma; sALCL, systemic anaplastic large cell lymphoma.

Primary cutaneous anaplastic large cell lymphoma (pcALCL) is typically composed of cohesive sheets of large CD30-positive tumour cells that show an anaplastic, pleomorphic, immunoblastic or Reed–Sternberg-like cytomorphology.[127] The immunophenotype is CD4+ and CD45RO with variable loss of CD2, CD5 and CD3. Cytotoxic molecules including granzyme B, TIA-1, perforin and cutaneous lymphocyte antigen are expressed in half of the cases.[128] CD158K (KIR3DL2), which is expressed on cells of pcALCL, can also be seen in transformed MF and Sézary syndrome.[129,130] Differing from systemic ALCL, the EMA and anaplastic lymphoma kinase (ALK) are rarely seen.[127,131,132] EMA immunoreactivity has been reported in few LyP and pcACLC cases, but it has been more frequently observed in secondary cutaneous lesions of systemic ALCL ($P = 0.01$).[118] The ALK protein, indicative of a t(2;5)(p23;q35) chromosomal translocation, is absent in 80–90% of pcALCL and is present in 60% of systemic ALCL.[133–136] Clonal rearrangement of TCR gamma genes is detected in 90% of the cases of ALCL.[122,137]

The expression of the multiple myeloma oncogene 1 (MUM1) and TNF receptor-associated factor 1 (TRAF1) has been reported to differentiate LyP from pcALCL.[138,139] TRAF1 was positive in 84% of LyP and in 7% of primary and secondary ACLCL.[139] Wada *et al.*[140] reported that MUM1/IRF4 (interferon regulatory factor 4) FISH has a 98% of specificity for pcALCL. They concluded that MUM1/IRF4 FISH positivity favours pcALCL over LyP ($P = 0.0005$). On the other hand, Kempf *et al.* reported that MUM1 expression was positive in 87% of 15 LyP biopsies, whereas it was present in only 10% of 20 pcALCL biopsies ($P = 0.002$).[138] Overall, studies do not support the use of TRAF1 and MUM1 as differential diagnostic markers for LyP vs. primary or secondary cACLC.[114,141–144]

Diagnosis

On the initial consultation, focus should be on skin examination with assessment of the haematolymphoid system. LyP diagnosis requires histopathologic confirmation within the clinical context (Fig. 4). Immunohistochemistry and TCR gene rearrangement analyses are critical adjuncts. Skin biopsies may need to be repeated for non-regressing or larger lesions. If a pcALCL or mycosis fungoides cannot be ruled out on clinical grounds, it should be considered as a borderline lesion. Laboratory work-up suggested but not restricted to CBC with differential, serum creatinine, liver profile, LDH, flow cytometry and possibly HTLV-1 assessment in the appropriate clinical context. In the event of palpable lymphadenopathy, imaging with computed tomography is recommended.

Treatment

Active non-intervention or a 'wait-and-see strategy' can be first line considering the benign course of the disease and the absence of evidence demonstrating therapeutic intervention changing either the course of the disease or preventing a second neoplasm.[145,146] However, in cases of single to a few localized papules, potent topical corticosteroids, intralesional steroids or

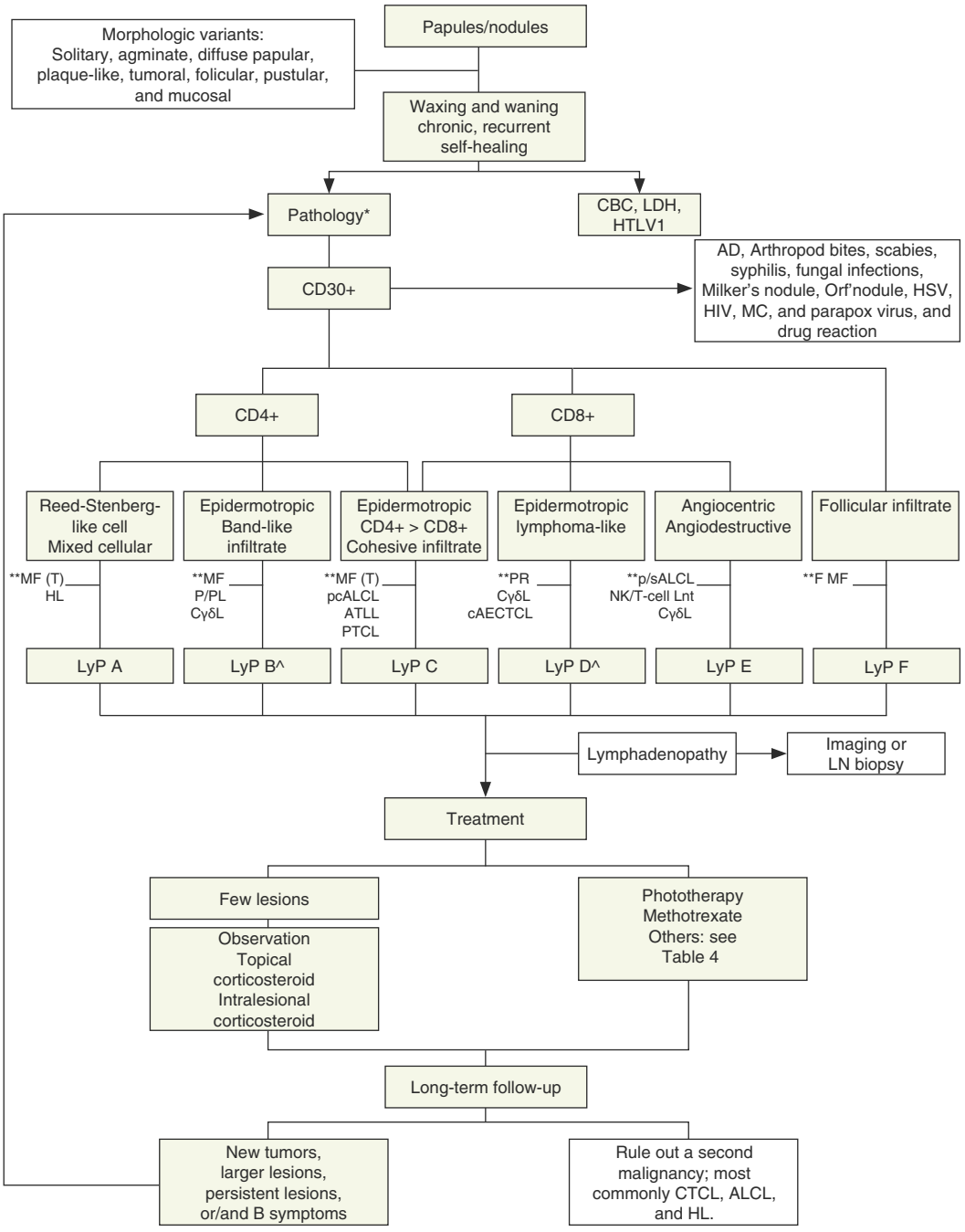

Figure 4 Diagnosis algorithm for lymphomatoid papulosis (LyP). AD, atopic dermatitis; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma; cAECTCL, cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma; CBC, count blood cells; CTCL, cutaneous T-cell lymphoma; CγδL, primary cutaneous gamma delta T-cell lymphoma; ENKTLNT, extranodal NK/T-cell Lymphoma, nasal type; F MF, follicular mycoses fungoides; HL, Hodgkin lymphoma; HP, histopathology; HSV, herpes simplex virus; LDH, lactate dehydrogenase; LN, lymph nodes; MC, molluscum contagiosum; MF (P/PL), mycoses fungoides patches/plaques stage; MF (T), mycoses fungoides transformation; p/s ALCL, primary and secondary ALCL; pcALCL, primary cutaneous ALCL; PR, pagetoid reticulosis. *Pathology should include immunohistochemical and T-cell gene rearrangement test. ^ CD30-negative entities: LyP type B and some cases of type D LyP. **Differential diagnosis by histopathology.

Table 4 Treatment recommendations in the literature

Best documented therapeutic approach†	
Topical corticosteroids	17, 51, 90, 146–148, 180–185
Methotrexate	17, 83, 90, 146, 147, 150, 152–155, 186–188
UVA, UVB	18, 90, 110, 118, 120, 139, 146, 147, 185, 189–193
Other lines therapies	
Topical	
Bexarotene	147, 194, 195
Carmustine	42, 196
Cytotoxic alkyl phospholipid hexadecyl-phosphocholine	197
Imiquimod	147, 198
Methotrexate	157
Nitrogen mustard	118, 147, 199
Photodynamic therapy	200, 201
Radiotherapy	46, 83, 89, 172, 181, 188, 202–204
Tacrolimus	189
Systemic	
Acyclovir	147, 172, 205, 206
Anti-CD30-antibody (SGN30)	207
Bexarotene	147, 172, 208
Brentuximab	147, 165
Erythromycin	182, 185
Etretinate	209
Extracorporeal photopheresis	155, 210
Interferon-alfa	171, 211, 212
Interferon-gamma	183, 213
Imatinib	34, 37, 38, 214
Isotretinoin	152
Mistletoe	215
Multiagent chemotherapy	172, 185, 208
Mycophenolic acid‡	146, 158
Penicillin	185, 204
Sulphones	185
Tetracyclines	182, 185, 204

†According to the European Organization for Research and Treatment of Cancer, International Society for Cutaneous Lymphomas and United States Cutaneous Lymphoma Consortium consensus recommendations.[145]
‡Recommendation from authors own experience.[146]
Modified from Kempf *et al.*[145]

surgical excision is viable therapeutic options (Table 4).[90,147,148] For those cases with widespread and disseminated disease or recurrent scarring lesions on cosmetically sensitive sites, the first-line treatment traditionally has included phototherapy or methotrexate.[149,150] In a comparison of different treatment options, Fernandez-de Misa *et al.*[90] reported no difference in either complete response (CR) or cutaneous relapse of LyP in patients treated with topical steroids, phototherapy or methotrexate.

Phototherapy

Clinicians have used both PUVA and narrowband UVb (311) with success in the treatment of LyP. As in other photosensitive disorders, PUVA generally out performs UVB nb 311, but as LyP is a recurring condition, and lifetime dose of PUVA needs to be limited with risk of subsequent skin cancers,[151] UVB nb 311 is typically the first-line phototherapy regimen.[18] De Souza reported eight paediatric patients treated with UVB nb 311 with a follow-up range from 1 to 13 years. They reported a CR in four cases, partial response (PR) in two cases and no response in two cases.[110] Kempf *et al.*[145] reported 19 patients treated with PUVA and demonstrated a 27% CR and a 68% PR. Thomsen *et al.*[152] reported six patients who responded well to PUVA, but as expected, relapsed after the treatment was stopped. According to our institution protocol for UVB nb 311 treatment LyP, therapy is performed three times weekly until lesions have disappeared and the patient is not developing any new lesions (typically 10–12 weeks). Once under control, light therapy is tapered down to two times per week for four more weeks and then once weekly for 4 weeks and then it is stopped. Phototherapy can be restarted with relapse, which eventually occurs in the majority of patients.

Methotrexate

Methotrexate is an effective treatment for many patients with LyP, but according to the EORTC, the International Society for Cutaneous Lymphomas and the United States Cutaneous Lymphoma Consortium, it is associated with a relapse rate of at least 40% after its discontinuation.[145] Thomsen *et al.* reported nine patients who successfully responded to methotrexate (2.5–25 mg q week over 5–18 months), but recurrence occurred in all but one patient when treatment was withdrawn.[152,153] Everett *et al.*[154] reported eight cases treated with methotrexate (2.5–15 mg q week) for 6–12 months and then followed these patients for 4–9 years and half of the patients had recurrences requiring retreatment with methotrexate. Vonderheid *et al.* reported 45 patients with long-term control on methotrexate at a median dose of 20 mg q week (range: 10–60 mg) over 39 months of treatment (median, range: 2–205). Methotrexate response was seen within 4 weeks, and long-term control was seen in 39 (87%) patients. Once the patients responded to weekly methotrexate, they were tapered to monthly treatments. After methotrexate was discontinued, ten patients remained free of LyP for a median of 127 months (range: 24–227).[155] Fernandez-De Misa *et al.*[90] detailed a case series of 48 patients treated with methotrexate (<20 mg weekly) resulting in 25 with CR, 21 with a PR and two that did not respond to the drug. Of those that had a CR, 92% had a relapse when off therapy.

Bruijn *et al.*[149] reported 28 patients that reached disease control after 3–4 weeks of methotrexate with two different approaches: eight patients were started on higher doses (15–22.5 mg weekly), and once they had achieved disease control the

dose was reduced; the other 18 patients were started on lower doses (7.5–10 mg q week) and titrated upward to achieve remission. Using the scoring system described by Vonderheid *et al.*,[155] they achieved an excellent disease control in 14 patients, with no new LyP lesions, and good control in 12 patients, with the development of a new lesions. The patients remained on medication for 1–216 months with a cumulative median dose of 1483 mg (range: 55–6362).[149] Newland *et al.* reported a total of 25 cases of LyP treated for 6 months with methotrexate 20–30 mg q week and then tapered over 2–6 additional months. With limited follow-up, 6 had CR, 16 were dose-dependent (recurrence on tapering) and three had disease progression while on methotrexate.[150] Wieser *et al.*[147] reported 15 of 54 patients that experienced a CR to methotrexate, with a recurrence rate of 27% on cessation of therapy. Yip *et al.* reported two paediatric patients treated with methotrexate for 1–4 years with recurrences upon discontinuation.[156]

Although most studies have used oral methotrexate, subcutaneous or intramuscular delivery is an alternative for those patients who are not responding to oral treatment, or who do not tolerate the gastrointestinal side-effects of the drug. Topical methotrexate applied daily on papules has been reported to be beneficial in a single case report.[157]

Mycophenolic acid derivatives

Mycophenolate mofetil (MMF; prodrug with gastric dissolution) and mycophenolic acid sodium (MPS; enteric coated) have been successfully used to treat LyP.[158] Champagne and Walsh reported successful results in 6 cases treated with MMF (2–2.5 g divided twice daily) and four patients treated with mycophenolic sodium (1440–1800 mg divided twice daily). Patients cleared after 5–6 weeks of treatment, whereas several of these patients had failed methotrexate.[158] In other study, 10 of 12 patients (83%) treated with MMF or MPS achieved complete clinical response with a mean dose of 1250 and 720 mg/day, respectively.[146]

Brentuximab

Brentuximab is a monoclonal antibody to CD30 conjugated to monomethyl auristatin E. It inhibits microtubule polymerization and causes G2/M cell cycle arrest leading to cell death. Brentuximab is US Food and Drug Administration (FDA) approved for the treatment of relapsed Hodgkin lymphoma and systemic ALCL with high overall response rates of 75% and 86%, respectively.[159,160] It is also FDA approved for the treatment of pcALCL or CD30-expressing mycosis fungoides who have received prior systemic therapy.[161,162] The European Medicines Agency has authorized its use in the above diseases, but indications are not as stringent, allowing its use also in the treatment of patients with CD30-positive cutaneous T-cell lymphomas, including LyP, and in patients who have received at least one previous treatment.[163]

Brentuximab may have a role in the treatment of severe or recalcitrant LyP. Duvic *et al.* reported nine LyP patients who responded to brentuximab therapy within 3–9 weeks of treatment. Five had a CR, and four had a PR. The median duration of response was 26 weeks[164] that was shorter than the duration of response seen earlier in studies with MF patients.[165] Wieser *et al.* reported 21 patients on brentuximab in which ten patients (47.6%) had a CR after only one to two infusions, with seven of these patients experiencing a relapse. Four patients had a PR, and seven had a non-response in this study.[147] Lewis *et al.*[166] reported on a similar study with all 12 patients showing a CR after the first dose, but five had a relapse within 12 weeks. The side-effect most commonly seen with brentuximab has been peripheral neuropathy in 42% (9 of 21) patients with LyP.[147] The Alcanza study, a phase 3 multicentre trial of brentuximab on CD30-positive cutaneous T-cell lymphoma, reported peripheral neuropathy in 67% of 66 patients.[167] Other side-effects reported include nausea, diarrhoea, fatigue, vomiting, alopecia, pruritus, maculopapular rash, progressive multifocal leukoencephalopathy, neuropathy causing diaphragmatic paresis leading to respiratory failure, vertigo and neutropenia.[166–169]

Other treatments

INF-α switches the cytokine pattern from Th2 cytokines to Th1. INF-α 2a has been successfully used in type E LyP.[170,171] Schmuth *et al.* reported 5 patients treated with INF-α subcutaneously three times weekly with good responses. Four patients had a CR, and one had a PR. The disease-free time after interferon therapy ranged from 1 to 11 years.[171] For the three patients who completed 12–13 months of treatment, there was not a relapse of the disease through their follow-up; however, relapse was seen in the two patients who completed only 5–7 months of treatment. Many therapeutic options have been trialled for LyP with case report evidence, and these are presented in Table 4.

Prognosis

Lymphomatoid papulosis is characterized by recurrent chronic crops of papules that can last months to years and have a tendency towards self-healing. Spontaneous remission can occur. Although it has a 10-year disease-specific survival of almost 100%,[18,42] approximately 20% of patients are at risk for developing a second lymphoid neoplasm such as mycosis fungoides, pcALCL and Hodgkin's lymphoma.[18,42,172] These associated neoplasms could appear at the same time, after or precede the onset of LyP.[85,172] Other haematologic conditions including variants of non-Hodgkin lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, myelodysplastic syndrome, chronic lymphoid leukaemia and hypereosinophilic syndrome have also been reported.[34,37,38,146,173–176] Bekkenk *et al.* reported a calculated risk for a systemic lymphoma after the onset of LyP of 4% and 12% within the first ten to 15 years, respectively.[18]

LyP subtypes A and D have been associated with a lower risk for a second malignancy, but types B and C have seen a higher risk.[147,177] Other prognostic markers for the development of a second lymphoid neoplasm include frequent recurrences of LyP lesions, facial involvement, older age, the expression of fascin by CD30+ large cells and a detectable T-cell clone.[178,179] As mentioned earlier, some cases have reported a clonal relationship between LyP and the second neoplasm.[85,123–125]

Conclusion

Lymphomatoid papulosis is a benign chronic skin condition that requires histopathology confirmation with immunophenotypic and genotypic assessment with the exclusion of malignancies. Treatment is directed based on the severity of the clinical presentation, in which active non-intervention is a reasonable option for localized or mild disease. Long-term follow-up is recommended for all LyP patients with the risk of secondary malignancies. Age-appropriate screening should be undertaken in all patients.

References

1 Macaulay WL. Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign–histologically malignant. *Arch Dermatol* 1968; **97**: 23–30.
2 Paulli M, Berti E, Rosso R *et al.* CD30/Ki-1-positive lymphoproliferative disorders of the skin–clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. *J Clin Oncol* 1995; **13**: 1343–1354.
3 Swerdlow SH, Campo E, Pileri SA *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; **127**: 2375–2390.
4 Willemze R, Jaffe ES, Burg G *et al.* WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–3785.
5 Willemze R, Cerroni L, Kempf W *et al.* The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019; **133**: 1703–1714.
6 Willemze R, Meyer CJ, Van Vloten WA, Scheffer E. The clinical and histological spectrum of lymphomatoid papulosis. *Br J Dermatol* 1982; **107**: 131–144.
7 Stein H, Mason DY, Gerdes J *et al.* The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985; **66**: 848–858.
8 Ralfkiaer E, Stein H, Wantzin GL, Thomsen K, Ralfkiaer N, Mason DY. Lymphomatoid papulosis. Characterization of skin infiltrates by monoclonal antibodies. *Am J Clin Pathol* 1985; **84**: 587–593.
9 Schwab U, Stein H, Gerdes J *et al.* Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. *Nature* 1982; **299**: 65–67.
10 Falini B, Pileri S, Pizzolo G *et al.* CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. *Blood* 1995; **85**: 1–14.
11 Werner B, Massone C, Kerl H, Cerroni L. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin. *J Cutan Pathol* 2008; **35**: 1100–1107.
12 Bhatt G, Maddocks K, Christian B. CD30 and CD30-targeted therapies in Hodgkin lymphoma and other B cell lymphomas. *Curr Hematol Malig Rep* 2016; **11**: 480–491.
13 Andreesen R, Osterholz J, Lohr GW, Bross KJ. A Hodgkin cell-specific antigen is expressed on a subset of auto- and alloactivated T (helper) lymphoblasts. *Blood* 1984; **63**: 1299–1302.
14 Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. *Blood* 1998; **92**: 1150–1159.
15 Mechtersheimer G, Moller P. Expression of Ki-1 antigen (CD30) in mesenchymal tumors. *Cancer* 1990; **66**: 1732–1737.
16 Griscelli F, Feraud O, Oudrhiri N *et al.* Malignant germ cell-like tumors, expressing Ki-1 antigen (CD30), are revealed during *in vivo* differentiation of partially reprogrammed human-induced pluripotent stem cells. *Am J Pathol* 2012; **180**: 2084–2096.
17 Nijsten T, Curiel-Lewandrowski C, Kadin ME. Lymphomatoid papulosis in children: a retrospective cohort study of 35 cases. *Arch Dermatol* 2004; **140**: 306–312.
18 Bekkenk MW, Geelen FA, van Voorst Vader PC *et al.* Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood* 2000; **95**: 3653–3661.
19 Namba H, Hamada T, Iwatsuki K. Human T-cell leukemia virus type 1-positive lymphomatoid papulosis. *Eur J Dermatol* 2016; **26**: 194–195.
20 Kempf W, Kadin ME, Dvorak AM *et al.* Endogenous retroviral elements, but not exogenous retroviruses, are detected in CD30-positive lymphoproliferative disorders of the skin. *Carcinogenesis* 2003; **24**: 301–306.
21 Kempf W, Kadin ME, Kutzner H *et al.* Lymphomatoid papulosis and human herpesviruses–A PCR-based evaluation for the presence of human herpesvirus 6, 7 and 8 related herpesviruses. *J Cutan Pathol* 2001; **28**: 29–33.
22 Kadin ME, Vonderheid EC, Weiss LM. Absence of Epstein-Barr viral RNA in lymphomatoid papulosis. *J Pathol* 1993; **170**: 145–148.
23 Kim YC, Yang WI, Lee MG *et al.* Epstein-Barr virus in CD30 anaplastic large cell lymphoma involving the skin and lymphomatoid papulosis in South Korea. *Int J Dermatol* 2006; **45**: 1312–1316.
24 Sangueza OP, Galloway J, Eagan PA, Braziel RM, Gulley ML. Absence of Epstein-Barr virus in lymphomatoid papulosis. An immunohistochemical and *in situ* hybridization study. *Arch Dermatol* 1996; **132**: 279–282.
25 Fernandez KH, Bream M, Ali MA *et al.* Investigation of molluscum contagiosum virus, orf and other parapoxviruses in lymphomatoid papulosis. *J Am Acad Dermatol* 2013; **68**: 1046–1047.
26 Schiemann WP, Pfeifer WM, Levi E, Kadin ME, Lodish HF. A deletion in the gene for transforming growth factor beta type I receptor abolishes growth regulation by transforming growth factor beta in a cutaneous T-cell lymphoma. *Blood* 1999; **94**: 2854–2861.
27 Haro R, Juarez A, Diaz JL, Santonja C, Manzarbeitia F, Requena L. Regional lymphomatoid papulosis of the breast restricted to an area of prior radiotherapy. *Cutis* 2016; **97**: E15–E19.
28 Samaraweera AP, Cohen SN, Akay EM, Evangelou N. Lymphomatoid papulosis: a cutaneous lymphoproliferative disorder in a patient on fingolimod for multiple sclerosis. *Mult Scler* 2016; **22**: 122–124.
29 Park JH, Lee J, Lee JH, Lee DY, Koh EM. Lymphomatoid papulosis in a patient treated with adalimumab for juvenile rheumatoid arthritis. *Dermatology* 2012; **225**: 259–263.
30 Matoula T, Nikolaou V, Marinos L *et al.* Lymphomatoid papulosis type D in a fingolimod-treated multiple sclerosis patient. *Mult Scler* 2016; **22**: 1630–1631.
31 Cohen V, Saber M, Provost N, Friedmann D. Lymphomatoid papulosis and fingolimod-A new connection? *Mult Scler* 2016; **22**: 1629–1630.
32 Outlaw W, Fleischer A, Bloomfeld R. Lymphomatoid papulosis in a patient with Crohn's disease treated with infliximab. *Inflamm Bowel Dis* 2009; **15**: 965–966.
33 Leo AM, Ermolovich T. Lymphomatoid papulosis while on efalizumab. *J Am Acad Dermatol* 2009; **61**: 540–541.
34 Garcia-Martinez P, Sitjas D, Llistosella E *et al.* Imatinib treatment of lymphomatoid papulosis associated with myeloproliferative

hypereosinophilic syndrome presenting the FIP1L1-PDGFRA fusion gene. *Acta Derm Venereol* 2017; **97**: 855–857.
35 Granel B, Serratrice J, Swiader L *et al.* Lymphomatoid papulosis associated with both severe hypereosinophilic syndrome and CD30 positive large T-cell lymphoma. *Cancer* 2000; **89**: 2138–2143.
36 Whittaker SJ, Jones RR, Spry CJ. Lymphomatoid papulosis and its relationship to "idiopathic" hypereosinophilic syndrome. *J Am Acad Dermatol* 1988; **18**(2 Pt 1): 339–344.
37 McPherson T, Cowen EW, McBurney E, Klion AD. Platelet-derived growth factor receptor-alpha-associated hypereosinophilic syndrome and lymphomatoid papulosis. *Br J Dermatol* 2006; **155**: 824–826.
38 Koury MJ, Newman JH, Murray JJ. Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; **115**: 587–589.
39 Kitano K, Ichikawa N, Shimodaira S, Ito T, Ishida F, Kiyosawa K. Eosinophilia associated with clonal T-cell proliferation. *Leuk Lymphoma* 1997; **27**: 335–342.
40 Mori M, Manuelli C, Pimpinelli N *et al.* CD30-CD30 ligand interaction in primary cutaneous CD30(+) T-cell lymphomas: a clue to the pathophysiology of clinical regression. *Blood* 1999; **94**: 3077–3083.
41 Tomaszewski MM, Lupton GP, Krishnan J, May DL. A comparison of clinical, morphological and immunohistochemical features of lymphomatoid papulosis and primary cutaneous CD30(Ki-1)-positive anaplastic large cell lymphoma. *J Cutan Pathol* 1995; **22**: 310–318.
42 Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol* 2003; **49**: 1049–1058.
43 Fujimura T, Lyu C, Tsuchiyama K, Aiba S. CD30-positive angioinvasive lymphomatoid papulosis (Type E) developing from parapsoriasis en plaque. *Case Rep Oncol* 2018; **11**: 850–854.
44 Heald P, Subtil A, Breneman D, Wilson LD. Persistent agmination of lymphomatoid papulosis: an equivalent of limited plaque mycosis fungoides type of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2007; **57**: 1005–1011.
45 Steinhoff M, Assaf C, Sterry W. Persistent agmination of lymphomatoid papulosis: not a new entity, but localized lymphomatoid papulosis. *J Am Acad Dermatol* 2008; **59**: 164–165; author reply 165.
46 Scarisbrick JJ, Evans AV, Woolford AJ, Black MM, Russell-Jones R. Regional lymphomatoid papulosis: a report of four cases. *Br J Dermatol* 1999; **141**: 1125–1128.
47 Gonzalez-Lopez MA, Gonzalez-Vela Mdel C, Caballero C, Consuegra G, Fernandez-Llaca H, Piris MA. Localized lymphomatoid papulosis. *Int J Dermatol* 2015; **54**: e98–e100.
48 Hsu YJ, Su LH, Hsu YL, Tsai TH, Hsiao CH. Localized lymphomatoid papulosis. *J Am Acad Dermatol* 2010; **62**: 353–356.
49 Wang T, Guo CL, Xu CC, Zhou XP, Liu YH, Zheng HY. Regional lymphomatoid papulosis in association with pseudoepitheliomatous hyperplasia: 13 years follow-up. *J Eur Acad Dermatol Venereol* 2015; **29**: 1853–1854.
50 Yancovitz M, Walters RF, Kamino H, Brown LH. Acral lymphomatoid papulosis. *J Am Acad Dermatol* 2010; **62**: 530–531.
51 Dalle S, Balme B, Thomas L. Lymphomatoid papulosis localized to the face. *Dermatol Online J* 2006; **12**: 9.
52 Kluk J, Child F, Robson A. Lymphomatoid papulosis with 6p25.3 rearrangement: a further case of the newly described variant. *Br J Dermatol* 2014; **171**: 1590–1592.
53 Kempf W, Kazakov DV, Baumgartner HP, Kutzner H. Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings. *J Am Acad Dermatol* 2013; **68**: 809–816.
54 Barnadas MA, Lopez D, Pujol RM, Garcia-Patos V, Curell R, de Moragas JM. Pustular lymphomatoid papulosis in childhood. *J Am Acad Dermatol* 1992; **27**: 627–628.
55 Chimenti S, Fargnoli MC, Pacifico A, Peris K. Mucosal involvement in a patient with lymphomatoid papulosis. *J Am Acad Dermatol* 2001; **44**(2 Suppl): 339–341.
56 Pujol RM, Muret MP, Bergua P, Bordes R, Alomar A. Oral involvement in lymphomatoid papulosis. Report of two cases and review of the literature. *Dermatology* 2005; **210**: 53–57.
57 Sciubba J, Said-Al-Naief N, Fantasia J. Critical review of lymphomatoid papulosis of the oral cavity with case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **90**: 195–204.
58 Sureda N, Thomas L, Bathelier E, Balme B, Depaepe L, Dalle S. Bullous lymphomatoid papulosis. *Clin Exp Dermatol* 2011; **36**: 800–801.
59 Schwartz Z, Coleman M, Toyohara JP, Freedman PD, Magro CM. Oral Lymphomatoid papulosis type C: a diagnostic pitfall, often confused with T-cell lymphoma. *Ann Diagn Pathol* 2017; **31**: 50–55.
60 Kadin ME. Lymphomatoid papulosis and associated lymphomas. How are they related? *Arch Dermatol* 1993; **129**: 351–353.
61 Chott A, Vonderheid EC, Olbricht S, Miao NN, Balk SP, Kadin ME. The dominant T cell clone is present in multiple regressing skin lesions and associated T cell lymphomas of patients with lymphomatoid papulosis. *J Invest Dermatol* 1996; **106**: 696–700.
62 Moura FN, Thomas L, Balme B, Dalle S. Dermoscopy of lymphomatoid papulosis. *Arch Dermatol* 2009; **145**: 966–967.
63 Caccavale S, Vitiello P, Mascolo M, Ciancia G, Argenziano G. Dermoscopy of different stages of lymphomatoid papulosis. *J Eur Acad Dermatol Venereol* 2018; **32**: e198–e200.
64 Bombonato C, Pampena R, Lallas A, Giovanni P, Longo C. Dermoscopy of lymphomas and pseudolymphomas. *Dermatol Clin* 2018; **36**: 377–388.
65 Piccolo V, Russo T, Agozzino M *et al.* Dermoscopy of cutaneous lymphoproliferative disorders: where are we now? *Dermatology* 2018; **234**: 131–136.
66 Ross NA, Truong H, Keller MS, Mulholland JK, Lee JB, Sahu J. Follicular lymphomatoid papulosis: an eosinophilic-rich follicular subtype masquerading as folliculitis clinically and histologically. *Am J Dermatopathol* 2016; **38**: e1–e10.
67 Kempf W. CD30+ lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. *J Cutan Pathol* 2006; **33** (Suppl 1): 58–70.
68 Kodama K, Fink-Puches R, Massone C, Kerl H, Cerroni L. Papular mycosis fungoides: a new clinical variant of early mycosis fungoides. *J Am Acad Dermatol* 2005; **52**: 694–698.
69 Noe MH, Drake A, Link BK, Liu V. Papular mycosis fungoides: report of two patients, literature review, and conceptual re-appraisal. *J Cutan Pathol* 2013; **40**: 714–719.
70 Uddin A, Bennett M, Nayeem K, Marren P, Abushaira H. A case of papular mycosis fungoides: new clinical variant of early mycosis fungoides. *J Eur Acad Dermatol Venereol* 2007; **21**: 685–687.
71 Brajon D, Bonnet N, Dales JP, Berbis P. Papular mycosis fungoides]. *Ann Dermatol Venereol* 2013; **140**: 455–458.
72 Martorell-Calatayud A, Botella-Estrada R, Sanmartin-Jimenez O, Requena C, Guillen-Barona C, Sangueza OP. Papular mycosis fungoides: two new cases of a recently described clinicopathological variant of early mycosis fungoides. *J Cutan Pathol* 2010; **37**: 330–335.
73 Kim SJ, Schaffer A, Lee HY, Seo JY, Park HJ. A case of papular mycosis fungoides: a new clinical variant of early mycosis fungoides. *Ann Dermatol* 2016; **28**: 383–384.
74 Liu ZH, Wang YL, Chen SY *et al.* Papular mycosis fungoides: a new clinic variant of early and benign mycosis fungoides? *J Clin Oncol* 2011; **29**: e381–e383.
75 Neri I, D'Acunto C, Pileri A, Reggiani C, Patrizi A. Papular mycosis fungoides: a new case expanding the spectrum of phenotypic and clinical findings. *G Ital Dermatol Venereol* 2011; **146**: 505–507.
76 Santamarina-Albertos A, Munoz-Martinez R, Alvarez-Gago T, Miranda-Romero A. Papular mycosis fungoides on the legs: a case report. *Actas Dermosifiliogr* 2014; **105**: 87–89.

77 Balta I, Akbay G, Eksioglu M, Astarci M, Ekiz O. Papular mycosis fungoides: a case report and review in the literature. *Indian J Dermatol* 2015; **60**: 107.

78 Vonderheid EC, Kadin ME. Papular mycosis fungoides: a variant of mycosis fungoides or lymphomatoid papulosis? *J Am Acad Dermatol* 2006; **55**: 177–180.

79 Vonderheid EC, Kadin ME, Telang GH. Commentary about papular mycosis fungoides, lymphomatoid papulosis and lymphomatoid pityriasis lichenoides: more similarities than differences. *J Cutan Pathol* 2016; **43**: 303–312.

80 Saggini A, Fink-Puches R, Cota C *et al.* Papular mycosis fungoides is a distinctive variant of early-stage mycosis fungoides: extended retrospective study with long-term follow-up. *Am J Surg Pathol* 2019; **43**: 1129–1134.

81 El Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. *Arch Dermatol* 2004; **140**: 441–447.

82 Zackheim HS, Jones C, Leboit PE, Kashani-Sabet M, McCalmont TH, Zehnder J. Lymphomatoid papulosis associated with mycosis fungoides: a study of 21 patients including analyses for clonality. *J Am Acad Dermatol* 2003; **49**: 620–623.

83 Christensen HK, Thomsen K, Vejlsgaard GL. Lymphomatoid papulosis: a follow-up study of 41 patients. *Semin Dermatol* 1994; **13**: 197–201.

84 Wood GS, Crooks CF, Uluer AZ. Lymphomatoid papulosis and associated cutaneous lymphoproliferative disorders exhibit a common clonal origin. *J Invest Dermatol* 1995; **105**: 51–55.

85 Basarab T, Fraser-Andrews EA, Orchard G, Whittaker S, Russel-Jones R. Lymphomatoid papulosis in association with mycosis fungoides: a study of 15 cases. *Br J Dermatol* 1998; **139**: 630–638.

86 Gallardo F, Costa C, Bellosillo B *et al.* Lymphomatoid papulosis associated with mycosis fungoides: clinicopathological and molecular studies of 12 cases. *Acta Derm Venereol* 2004; **84**: 463–468.

87 de la Garza Bravo MM, Patel KP, Loghavi S *et al.* Shared clonality in distinctive lesions of lymphomatoid papulosis and mycosis fungoides occurring in the same patients suggests a common origin. *Hum Pathol* 2015; **46**: 558–569.

88 Kempf W, Kazakov DV, Scharer L *et al.* Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. *Am J Surg Pathol* 2013; **37**: 1–13.

89 Saggini A, Gulia A, Argenyi Z *et al.* A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. *Am J Surg Pathol* 2010; **34**: 1168–1175.

90 Fernandez-de-Misa R, Hernandez-Machin B, Servitje O *et al.* First-line treatment in lymphomatoid papulosis: a retrospective multicentre study. *Clin Exp Dermatol* 2018; **43**: 137–143.

91 Pierard GE. A reappraisal of lymphomatoid papulosis and of its follicular variant. *Am J Dermatopathol* 1981; **3**: 179–181.

92 Kato N, Matsue K. Follicular lymphomatoid papulosis. *Am J Dermatopathol* 1997; **19**: 189–196.

93 Karai LJ, Kadin ME, Hsi ED *et al.* Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. *Am J Surg Pathol* 2013; **37**: 1173–1181.

94 Crowson AN, Baschinsky DY, Kovatich A, Magro C. Granulomatous eccrinotropic lymphomatoid papulosis. *Am J Clin Pathol* 2003; **119**: 731–739.

95 Jain N, Gutte R, Jadhav P, Khopkar U. Granulomatous and eccrinotropic lymphomatoid papulosis. *Indian J Dermatol Venereol Leprol* 2012; **78**: 82–84.

96 Ba W, Yang Y, Zhang Z *et al.* Lymphomatoid papulosis with folliculotropism, eccrinotropism and neurotropism. *J Cutan Pathol* 2018; **45**: 530–534.

97 Martires KJ, Cohen BE, Cassarino DS. CD30+ lymphoproliferative disorder with spindle-cell morphology. *J Cutan Pathol* 2016; **43**: 1041–1044.

98 Bellafiore S, Grenzi L, Simonetti V, Piana S. Pseudocarcinomatous hyperplasia hiding lymphomatoid papulosis: a "low-power view" pitfall. *Int J Surg Pathol* 2016; **24**: 232–236.

99 Samols MA, Su A, Ra S *et al.* Intralymphatic cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis: expanding the spectrum of CD30-positive lymphoproliferative disorders. *Am J Surg Pathol* 2014; **38**: 1203–1211.

100 Dore E, Swick BL, Link BK, Ghahramani GK, Liu V. Follicular lymphomatoid papulosis with follicular mucinosis: a clinicopathologic study of 3 cases with literature review and conceptual reappraisal. *J Cutan Pathol* 2017; **44**: 360–366.

101 Goodlad J. The many faces of lymphomatoid papulosis. *Diagn Histopathol* 2014; **20**: 263.

102 Kaudewitz P, Burg G, Stein H, Klepzig K, Mason DY, Braun-Falco O. Monoclonal antibody patterns in lymphomatoid papulosis. *Dermatol Clin* 1985; **3**: 749–757.

103 Wood GS, Strickler JG, Deneau DG, Egbert B, Warnke RA. Lymphomatoid papulosis expresses immunophenotypes associated with T cell lymphoma but not inflammation. *J Am Acad Dermatol* 1986; **15**: 444–458.

104 Varga FJ, Vonderheid EC, Olbricht SM, Kadin ME. Immunohistochemical distinction of lymphomatoid papulosis and pityriasis lichenoides et varioliformis acuta. *Am J Pathol* 1990; **136**: 979–987.

105 Zheng Y, Jia J, Tian Q *et al.* Lymphomatoid papulosis misdiagnosed as pityriasis lichenoides et varioliformis acuta: two case reports and a literature review. *Exp Ther Med* 2014; **8**: 1927–1933.

106 Cho-Vega JH, Vega F. CD30-negative lymphomatoid papulosis type D in an elderly man. *Am J Dermatopathol* 2014; **36**: 190–192.

107 Simo OC, Warren SJ, Mark L, Hoffmann K, Alomari AK. CD8-positive lymphomatoid papulosis (type D): some lesions may lack CD30 expression and overlap histologically with mycosis fungoides. *Int J Dermatol* 2019; **58**: 800–805.

108 Cardoso J, Duhra P, Thway Y, Calonje E. Lymphomatoid papulosis type D: a newly described variant easily confused with cutaneous aggressive CD8-positive cytotoxic T-cell lymphoma. *Am J Dermatopathol* 2012; **34**: 762–765.

109 Martires KJ, Ra S, Abdulla F, Cassarino DS. Characterization of primary cutaneous CD8+/CD30+ lymphoproliferative disorders. *Am J Dermatopathol* 2015; **37**: 822–833.

110 de Souza A, Camilleri MJ, Wada DA, Appert DL, Gibson LE, el-Azhary RA. Clinical histopathologic, and immunophenotypic features of lymphomatoid papulosis with CD8 predominance in 14 pediatric patients. *J Am Acad Dermatol* 2009; **61**: 993–1000.

111 Flann S, Orchard GE, Wain EM, Russell-Jones R. Three cases of lymphomatoid papulosis with a CD56+ immunophenotype. *J Am Acad Dermatol* 2006; **55**: 903–906.

112 Boulland ML, Wechsler J, Bagot M, Pulford K, Kanavaros P, Gaulard P. Primary CD30-positive cutaneous T-cell lymphomas and lymphomatoid papulosis frequently express cytotoxic proteins. *Histopathology* 2000; **36**: 136–144.

113 Kummer JA, Vermeer MH, Dukers D, Meijer CJ, Willemze R. Most primary cutaneous CD30-positive lymphoproliferative disorders have a CD4-positive cytotoxic T-cell phenotype. *J Invest Dermatol* 1997; **109**: 636–640.

114 Benner MF, Jansen PM, Meijer CJ, Willemze R. Diagnostic and prognostic evaluation of phenotypic markers TRAF1, MUM1, BCL2 and CD15 in cutaneous CD30-positive lymphoproliferative disorders. *Br J Dermatol* 2009; **161**: 121–127.

115 Moreau-Cabarrot A, Bonafe JL, Gorguet B, Andrieu H, Massip P. [Lymphomatoid papulosis and anaplastic giant-cell lymphoma]. *Ann Dermatol Venereol* 1994; **121**: 727–730.

116 Harvell J, Vaseghi M, Natkunam Y, Kohler S, Kim Y. Large atypical cells of lymphomatoid papulosis are CD56-negative: a study of 18 cases. *J Cutan Pathol* 2002; **29**: 88–92.

117 Bekkenk MW, Kluin PM, Jansen PM, Meijer CJ, Willemze R. Lymphomatoid papulosis with a natural killer-cell phenotype. *Br J Dermatol* 2001; **145**: 318–322.

118 Vergier B, Beylot-Barry M, Pulford K *et al.* Statistical evaluation of diagnostic and prognostic features of CD30+ cutaneous lymphoproliferative disorders: a clinicopathologic study of 65 cases. *Am J Surg Pathol* 1998; **22**: 1192–1202.

119 Weiss LM, Wood GS, Trela M, Warnke RA, Sklar J. Clonal T-cell populations in lymphomatoid papulosis. Evidence of a lymphoproliferative origin for a clinically benign disease. *N Engl J Med* 1986; **315**: 475–479.

120 el-Azhary RA, Gibson LE, Kurtin PJ, Pittelkow MR, Muller SA. Lymphomatoid papulosis: a clinical and histopathologic review of 53 cases with leukocyte immunophenotyping, DNA flow cytometry, and T-cell receptor gene rearrangement studies. *J Am Acad Dermatol* 1994; **1**: 210–218.

121 Whittaker S, Smith N, Jones RR, Luzzatto L. Analysis of beta, gamma, and delta T-cell receptor genes in lymphomatoid papulosis: cellular basis of two distinct histologic subsets. *J Invest Dermatol* 1991; **96**: 786–791.

122 Greisser J, Palmedo G, Sander C *et al.* Detection of clonal rearrangement of T-cell receptor genes in the diagnosis of primary cutaneous CD30 lymphoproliferative disorders. *J Cutan Pathol* 2006; **33**: 711–715.

123 Steinhoff M, Hummel M, Anagnostopoulos I *et al.* Single-cell analysis of CD30+ cells in lymphomatoid papulosis demonstrates a common clonal T-cell origin. *Blood* 2002; **100**: 578–584.

124 Wood GS. Analysis of clonality in cutaneous T cell lymphoma and associated diseases. *Ann N Y Acad Sci* 2001; **941**: 26–30.

125 Davis TH, Morton CC, Miller-Cassman R, Balk SP, Kadin ME. Hodgkin's disease, lymphomatoid papulosis, and cutaneous T-cell lymphoma derived from a common T-cell clone. *N Engl J Med* 1992; **326**: 1115–1122.

126 Gellrich S, Wernicke M, Wilks A *et al.* The cell infiltrate in lymphomatoid papulosis comprises a mixture of polyclonal large atypical cells (CD30-positive) and smaller monoclonal T cells (CD30-negative). *J Invest Dermatol* 2004; **122**: 859–861.

127 Krishnan J, Tomaszewski MM, Kao GF. Primary cutaneous CD30-positive anaplastic large cell lymphoma. Report of 27 cases. *J Cutan Pathol* 1993; **20**: 193–202.

128 Felgar RE, Macon WR, Kinney MC, Roberts S, Pasha T, Salhany KE. TIA-1 expression in lymphoid neoplasms. Identification of subsets with cytotoxic T lymphocyte or natural killer cell differentiation. *Am J Pathol* 1997; **150**: 1893–1900.

129 Ortonne N, Le Gouvello S, Mansour H *et al.* CD158K/KIR3DL2 transcript detection in lesional skin of patients with erythroderma is a tool for the diagnosis of Sezary syndrome. *J Invest Dermatol* 2008; **128**: 465–472.

130 Poszepczynska-Guigne E, Schiavon V, D'Incan M *et al.* CD158k/KIR3DL2 is a new phenotypic marker of Sezary cells: relevance for the diagnosis and follow-up of Sezary syndrome. *J Invest Dermatol* 2004; **122**: 820–823.

131 Morris SW, Kirstein MN, Valentine MB *et al.* Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science* 1994; **263**: 1281–1284.

132 ten Berge RL, Snijdewint FG, von Mensdorff-Pouilly S *et al.* MUC1 (EMA) is preferentially expressed by ALK positive anaplastic large cell lymphoma, in the normally glycosylated or only partly hypoglycosylated form. *J Clin Pathol* 2001; **54**: 933–939.

133 Montes-Mojarro IA, Steinhilber J, Bonzheim I, Quintanilla-Martinez L, Fend F. The pathological spectrum of systemic anaplastic large cell lymphoma (ALCL). *Cancers* 2018; **10**: 1–22.

134 Oschlies I, Lisfeld J, Lamant L *et al.* ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. *Haematologica* 2013; **98**: 50–56.

135 Wellmann A, Otsuki T, Vogelbruch M, Clark HM, Jaffe ES, Raffeld M. Analysis of the t(2;5)(p23;q35) translocation by reverse transcription-polymerase chain reaction in CD30+ anaplastic large-cell lymphomas, in other non-Hodgkin's lymphomas of T-cell phenotype, and in Hodgkin's disease. *Blood* 1995; **86**: 2321–2328.

136 Su LD, Schnitzer B, Ross CW *et al.* The t(2;5)-associated p80 NPM/ALK fusion protein in nodal and cutaneous CD30+ lymphoproliferative disorders. *J Cutan Pathol* 1997; **24**: 597–603.

137 Macgrogan G, Vergier B, Dubus P *et al.* CD30-positive cutaneous large cell lymphomas. A comparative study of clinicopathologic and molecular features of 16 cases. *Am J Clin Pathol* 1996; **105**: 440–450.

138 Kempf W, Kutzner H, Cozzio A *et al.* MUM1 expression in cutaneous CD30+ lymphoproliferative disorders: a valuable tool for the distinction between lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Br J Dermatol* 2008; **158**: 1280–1287.

139 Assaf C, Hirsch B, Wagner F *et al.* Differential expression of TRAF1 aids in the distinction of cutaneous CD30-positive lymphoproliferations. *J Invest Dermatol* 2007; **127**: 1898–1904.

140 Wada DA, Law ME, Hsi ED *et al.* Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. *Mod Pathol* 2011; **24**: 596–605.

141 Hernandez-Machin B, de Misa RF, Montenegro T *et al.* MUM1 expression does not differentiate primary cutaneous anaplastic large-cell lymphoma and lymphomatoid papulosis. *Br J Dermatol* 2009; **160**: 713.

142 Feldman AL, Law M, Remstein ED *et al.* Recurrent translocations involving the IRF4 oncogene locus in peripheral T-cell lymphomas. *Leukemia* 2009; **23**: 574–580.

143 Wasco MJ, Fullen D, Su L, Ma L. The expression of MUM1 in cutaneous T-cell lymphoproliferative disorders. *Hum Pathol* 2008; **39**: 557–563.

144 Kiran T, Demirkesen C, Eker C, Kumusoglu H, Tuzuner N. The significance of MUM1/IRF4 protein expression and IRF4 translocation of CD30(+) cutaneous T-cell lymphoproliferative disorders: a study of 53 cases. *Leuk Res* 2013; **37**: 396–400.

145 Kempf W, Pfaltz K, Vermeer MH *et al.* EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood* 2011; **118**: 4024–4035.

146 AbuHilal M, Walsh S, Shear N. Associated hematolymphoid malignancies in patients with lymphomatoid papulosis: a Canadian retrospective study. *J Cutan Med Surg* 2017; **21**: 507–512.

147 Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: treatment response and associated lymphomas in a study of 180 patients. *J Am Acad Dermatol* 2016; **74**: 59–67.

148 Paul MA, Krowchuk DP, Hitchcock MG, Jorizzo JL. Lymphomatoid papulosis: successful weekly pulse superpotent topical corticosteroid therapy in three pediatric patients. *Pediatr Dermatol* 1996; **13**: 501–506.

149 Bruijn MS, Horvath B, van Voorst Vader PC, Willemze R, Vermeer MH. Recommendations for treatment of lymphomatoid papulosis with methotrexate: a report from the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2015; **173**: 1319–1322.

150 Newland KM, McCormack CJ, Twigger R *et al.* The efficacy of methotrexate for lymphomatoid papulosis. *J Am Acad Dermatol* 2015; **72**: 1088–1090.

151 Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst* 1998; **90**: 1278–1284.

152 Thomsen K, Wantzin GL. Lymphomatoid papulosis. A follow-up study of 30 patients. *J Am Acad Dermatol* 1987; **17**: 632–636.

153 Lange Wantzin G, Thomsen K. Methotrexate in lymphomatoid papulosis. *Br J Dermatol* 1984; **111**: 93–95.

154 Everett MA. Treatment of lymphomatoid papulosis with methotrexate. *Br J Dermatol* 1984; **111**: 631.

155 Vonderheid EC, Sajjadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. *J Am Acad Dermatol* 1996; **34**: 470–481.

156 Yip L, Darling S, Orchard D. Lymphomatoid papulosis in children: experience of five cases and the treatment efficacy of methotrexate. *Australas J Dermatol* 2011; **52**: 279–283.
157 Bergstrom JS, Jaworsky C. Topical methotrexate for lymphomatoid papulosis. *J Am Acad Dermatol* 2003; **49**: 937–939.
158 Champagne T, Walsh S. Mycophenolic acid for lymphomatoid papulosis. *J Cutan Med Surg* 2013; **17**: 332–334.
159 de Claro RA, McGinn K, Kwitkowski V *et al.* U.S. Food and Drug Administration approval summary: brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma or relapsed systemic anaplastic large-cell lymphoma. *Clin Cancer Res* 2012; **18**: 5845–5849.
160 Younes A, Bartlett NL, Leonard JP *et al.* Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010; **363**: 1812–1821.
161 Richardson NC, Kasamon YL, Chen H *et al.* FDA approval summary: brentuximab vedotin in first-line treatment of peripheral T-cell lymphoma. *Oncologist* 2019; **24**: e180–e187.
162 U.S. Food and Drug Adminstration. FDA approves Brentuximab vedotin for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma, 2017. URL https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-brentuximab-vedotin-treatment-adult-patients-primary-cutaneous-anaplastic-large-cell (last accessed: 1 May 2019).
163 European Medicines Agency. Adcetris. Brentuximab vedotin, 2019. URL https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris (last accessed: 1 May 2019.
164 Ben m'rad M, Leclerc-Mercier S, Blanche P *et al.* Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. *Medicine (Baltimore)* 2009; **88**: 131–140.
165 Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J Clin Oncol* 2015; **33**: 3759–3765.
166 Lewis DJ, Talpur R, Huen AO, Tetzlaff MT, Duvic M. Brentuximab vedotin for patients with refractory lymphomatoid papulosis: an analysis of phase 2 results. *JAMA Dermatol* 2017; **153**: 1302–1306.
167 Prince HM, Kim YH, Horwitz SM *et al.* Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017; **390**: 555–566.
168 Carson KR, Newsome SD, Kim EJ *et al.* Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. *Cancer* 2014; **120**: 2464–2471.
169 Forero-Torres A, Holkova B, Goldschmidt J *et al.* Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. *Blood* 2015; **126**: 2798–2804.
170 Bilgic Temel A, Unal B, Erdi Sanli H, Duygulu S, Uzun S. A severe case of lymphomatoid papulosis type E successfully treated with interferon-Alfa 2a. *Case Rep Dermatol Med* 2017; **2017**: 3194738.
171 Schmuth M, Topar G, Illersperger B, Kowald E, Fritsch PO, Sepp NT. Therapeutic use of interferon-alpha for lymphomatoid papulosis. *Cancer* 2000; **89**: 1603–1610.
172 Kunishige JH, McDonald H, Alvarez G, Johnson M, Prieto V, Duvic M. Lymphomatoid papulosis and associated lymphomas: a retrospective case series of 84 patients. *Clin Exp Dermatol* 2009; **34**: 576–581.
173 Ribeiro-Silva A, Chang D, Arruda D, Felix PR. Lymphomatoid papulosis in a patient with Waldenstrom's macroglobulinemia. *J Dermatol* 2005; **32**: 132–136.
174 Lee YJ, Park JH, Lee JH, Lee DY. Lymphomatoid papulosis associated with multiple myeloma. *Int J Dermatol* 2016; **55**: e516–e518.
175 Rongioletti F, Basso GI, Sementa A, Gambini C, Rebora A. Follicular lymphomatoid papulosis and multiple myeloma. *Acta Derm Venereol* 1997; **77**: 403.
176 de SA, el-Azhary RA, Camilleri MJ, Wada DA, Appert DL, Gibson LE. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123 patients. *J Am Acad Dermatol* 2012; **66**: 928–937.
177 Nikolaou V, Papadavid E, Ekonomidi A *et al.* Association of clinicopathological characteristics with secondary neoplastic lymphoproliferative disorders in patients with lymphomatoid papulosis. *Leuk Lymphoma* 2015; **56**: 1303–1307.
178 Kempf W, Levi E, Kamarashev J *et al.* Fascin expression in CD30-positive cutaneous lymphoproliferative disorders. *J Cutan Pathol* 2002; **29**: 295–300.
179 Cordel N, Tressieres B, D'Incan M *et al.* Frequency and risk factors for associated lymphomas in patients with lymphomatoid papulosis. *Oncologist* 2016; **21**: 76–83.
180 Wolf P, Cohen PR, Duvic M. Ambivalent response of lymphomatoid papulosis treated with 8-methoxypsoralen and UVA. *J Am Acad Dermatol* 1994; **30**: 1018–1020.
181 Sina B, Burnett JW. Lymphomatoid papulosis. Case reports and literature review. *Arch Dermatol* 1983; **119**: 189–197.
182 Zirbel GM, Gellis SE, Kadin ME, Esterly NB. Lymphomatoid papulosis in children. *J Am Acad Dermatol* 1995; **33**(5 Pt 1): 741–748.
183 Kagaya M, Kondo S, Kamada A, Yamada Y, Matsusaka H, Jimbow K. Localized lymphomatoid papulosis. *Dermatology* 2002; **204**: 72–74.
184 Bories N, Thomas L, Phan A *et al.* Lymphomatoid papulosis in childhood: six case reports and a literature review. *Ann Dermatol Venereol* 2008; **135**: 657–662.
185 Sanchez NP, Pittelkow MR, Muller SA, Banks PM, Winkelmann RK. The clinicopathologic spectrum of lymphomatoid papulosis: study of 31 cases. *J Am Acad Dermatol* 1983; **8**: 81–94.
186 Lynch PJ, Saied NK. Methotrexate treatment of pityriasis lichenoides and lymphomatoid papulosis. *Cutis* 1979; **23**: 634–636.
187 Wantzin GL, Thomsen K, Brandrup F, Larsen JK. Lymphomatoid papulosis. Development into cutaneous T-cell lymphoma. *Arch Dermatol* 1985; **121**: 792–794.
188 Romero-Mate A, Martin-Fragueiro L, Minano-Medrano R, Martinez-Moran C, Arias-Palomo D, Borbujo J. Persistent agmination of lymphomatoid papulosis evolving to classical lesions of lymphomatoid papulosis. *J Am Acad Dermatol* 2009; **61**: 1087–1088.
189 Korpusik D, Ruzicka T. [Clinical course and therapy of lymphomatoid papulosis. Experience with 17 cases and literature review]. *Hautarzt* 2007; **58**: 870–881.
190 Calzavara-Pinton P, Venturini M, Sala R. Medium-dose UVA1 therapy of lymphomatoid papulosis. *J Am Acad Dermatol* 2005; **52**(3 Pt 1): 530–532.
191 Coelho JD, Afonso A, Feio AB. Regional lymphomatoid papulosis in a child–treatment with a UVB phototherapy handpiece. *J Cosmet Laser Ther* 2010; **12**: 155–156.
192 Errichetti E, Piccirillo A, Ricciuti F, Ricciuti F. Steroid-resistant localized lymphomatoid papulosis treated with local bath-PUVA therapy. *Indian J Dermatol* 2013; **58**: 163.
193 Gambichler T, Maushagen E, Menzel S. Foil bath PUVA in lymphomatoid papulosis. *J Eur Acad Dermatol Venereol* 1999; **13**: 63–65.
194 Krathen RA, Ward S, Duvic M. Bexarotene is a new treatment option for lymphomatoid papulosis. *Dermatology* 2003; **206**: 142–147.
195 Fujimura T, Furudate S, Tanita K *et al.* Successful control of phototherapy-resistant lymphomatoid papulosis with oral bexarotene. *J Dermatol* 2018; **45**: e37–e38.
196 Zackheim HS, Epstein EH Jr, Crain WR. Topical carmustine therapy for lymphomatoid papulosis. *Arch Dermatol* 1985; **121**: 1410–1414.
197 Dummer R, Krasovec M, Roger J, Sindermann H, Burg G. Topical administration of hexadecylphosphocholine in patients with cutaneous lymphomas: results of a phase I/II study. *J Am Acad Dermatol* 1993; **29**: 963–970.
198 Hughes PS. Treatment of lymphomatoid papulosis with imiquimod 5% cream. *J Am Acad Dermatol* 2006; **54**: 546–547.

199 Scheen SR 3rd, Doyle JA, Winkelmann RK. Lymphoma-associated papulosis: lymphomatoid papulosis associated with lymphoma. *J Am Acad Dermatol* 1981; **4**: 451–457.
200 Rodrigues M, McCormack C, Yap LM *et al.* Successful treatment of lymphomatoid papulosis with photodynamic therapy. *Australas J Dermatol* 2009; **50**: 129–132.
201 Arimatsu A, Tomii K, Fujiwara H, Hasegawa G, Shigehara Y, Tachibana T. Photodynamic therapy prevented the recurrence of lymphomatoid papulosis.. *Photodiagn Photodyn Ther* 2019; **25**: 334–335.
202 Cabanillas F, Armitage J, Pugh WC, Weisenburger D, Duvic M. Lymphomatoid papulosis: a T-cell dyscrasia with a propensity to transform into malignant lymphoma. *Ann Intern Med* 1995; **122**: 210–217.
203 Kaufmann T, Nisce LZ, Silver RT. Lymphomatoid papulosis: case report of a patient managed with radiation therapy and review of the literature. *Am J Clin Oncol* 1992; **15**: 412–416.
204 Thomsen K, Hjort G, Svendsen D. Lymphomatoid papulosis. *Dermatologica* 1972; **144**: 65–74.
205 Baumgartner G, Duschet P, Schwarz T, Partsch H, Gschnait F, Stacher A. Lymphomatoid papulosis: remission following intravenously administered acyclovir. *Dermatologica* 1986; **172**: 305–309.
206 Burg G, Klepzig K, Kaudewitz P, Wolf H, Braun-Falco O. Acyclovir in lymphomatoid papulosis and mycosis fungoides. *JAMA* 1986; **256**: 214–215.
207 Duvic M, Reddy SA, Pinter-Brown L *et al.* A phase II study of SGN-30 in cutaneous anaplastic large cell lymphoma and related lymphoproliferative disorders. *Clin Cancer Res* 2009; **15**: 6217–6224.
208 Perna AG, Jones DM, Duvic M. Lymphomatoid papulosis from childhood with anaplastic large-cell lymphoma of the small bowel. *Clin Lymphoma* 2004; **5**: 190–193.
209 Wyss M, Dummer R, Dommann SN *et al.* Lymphomatoid papulosis–treatment with recombinant interferon alfa-2a and etretinate. *Dermatology* 1995; **190**: 288–291.
210 Wollina U. Lymphomatoid papulosis treated with extracorporeal photochemotherapy. *Oncol Rep* 1998; **5**: 57–59.
211 Proctor SJ, Jackson GH, Lennard AL, Marks J. Lymphomatoid papulosis: response to treatment with recombinant interferon alfa-2b. *J Clin Oncol* 1992; **10**: 170.
212 Shang SX, Chen H, Sun JF, Xu XL. Regional lymphomatoid papulosis successfully controlled by interferon alpha-2b and nitrogen mustard solution. *Chin Med J (Engl)* 2013; **126**: 3194–3195.
213 Yagi H, Tokura Y, Furukawa F, Takigawa M. Th2 cytokine mRNA expression in primary cutaneous CD30-positive lymphoproliferative disorders: successful treatment with recombinant interferon-gamma. *J Invest Dermatol* 1996; **107**: 827–832.
214 Thuny C, Gaudy-Marqueste C, Nicol I *et al.* Chronic eosinophilic leukaemia revealed by lymphomatoid papulosis: the role of the FIP1-like 1-platelet-derived growth factor receptor alpha fusion gene. *J Eur Acad Dermatol Venereol* 2010; **24**: 234–235.
215 Seifert G, Tautz C, Seeger K, Henze G, Laengler A. Therapeutic use of mistletoe for CD30+ cutaneous lymphoproliferative disorder/lymphomatoid papulosis. *J Eur Acad Dermatol Venereol* 2007; **21**: 558–560.