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Motley and Sundry: Lymphomatoid Papulosis

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Abstract

Lymphomatoid Papulosis was initially scripted by Warren Macaulay as a selfhealing, rhythmical, paradoxical eruption, histological malignant and clinically benign. The disorder is comprised of chronic, relapsing, selfhealing papulo-nodular dermal eruptions portraying the histological aspects of a malignant lymphoma. Lymphomatoid papulosis (LyP) may classically define a clinical emergence of relapsing papulo-nodular lesions. Aberrant and enlarged lymphoid cells which elucidate an immune reactive CD30+ may describe the cyto-morphology of the disorder. Lymphomatoid papulosis may delineate a varied and expansive spectrum on histology. The microscopic categories commence with LyP A, LyP B and LyP C. Subsequently three addendum subtypes comprising of LyP D, LyP E and LyP with 6p25.3 mutation may be described. The revised World Health Organization (WHO) classification 2016/2017 may accord distinctive recognition to the latter three variants.

Keywords: Lymphomatoid papulosis; Malignant lymphoma; Haemorrhagic necrosis; Immune modulating

Introduction

Lymphomatoid Papulosis (LyP) may illustrate a benign lympho proliferative disorder or it may consecutively construe as a low grade malignant lymphoma. Lymphomatoid papulosis may be described as a disorder of obscure aetiology and pathogenesis. The interrelation betwixt CD30+ in conjunction with the interdependent ligand may be acknowledged for inducing the retrogression of LyP lesions [1,2]. Extraneous factors such as radiation therapy or the administration of immune modulating drugs such as Fingolimod may incite the disorder. Oncogenic viruses may not manifest within the lesions of LyP. However, endogenous retroviruses may be recognized within the lineage and histological remnants of the tumour cells [2]. Lymphomatoid Papulosis (LyP) may currently be considered as a Cutaneous T-Cell Lymphoma (CTCL) with a diminished malignant potential. It may simulate the clinical and histological aspects of a primitive cutaneous Anaplastic Large Cell Lymphoma (ALCL) along with the T Lymphocyte (LyT) variant which delineates an anomalous immune phenotype and cell clones of aberrant T-Cell Receptor (TCR) genes in an estimated two thirds to three fourths (60%-70%) individuals. LyP may account for approximately 15% of the Cutaneous T-Cell Lymphomas (CTCL) (Table 1).

Clinical types of LyP	Histological Aspects	Phenotype	Differential diagnosis	Distinctive criterion
Type A	Wedge shaped, disseminated infiltrate or clusters. Large atypical CD30+ lymphocytes Admixed histiocytes, neutrophils, eosinophils.	Predominantly CD4+	•Mycosis Fungoides. •Hodgkin's Lymphoma. •Anthropod bite reaction.	•Patches & plaques in MF versus papulo-nodular lesions in LyP. •Nodal Hodgkin's Lmphoma requires staging. •Clinical presentation for assessing pruritis.
Type B	Epidermotropic infiltrate of small to medium sized lymphocytes with variable CD30+ elucidation.	CD4+ (CD30-may be non-reactive)	•Mycosis Fungoides (patch/plaque stage).	•Patches & plaques in MF versus self-regressing papulo-nodular lesions in LyP.
Type C	Nodular cohesive infiltrate of large CD30+ a typical lymphocytes with a few reactive cells.	CD4+>CD8+	•Anaplastic large cell lymphoma (primary cutaneous or systemic form). •Mycosis Fungoides (transformation phase). •Peripheral T cell lymphoma (NOS-primary cutaneous or nodal). •Adult T cell lymphoma/leukaemia.	•Clinical presentation with solitary or grouped nodules in pc ALCL: staging in s ALCL. •Patches & plaques preceding tumours in MF. •Lack of CD30 or a few CD30+ cells & staging of tumour (PTCL). •Integration of HTLV1/2 in tumour cell genome.
Type D	Prominent epidermotropism of a typical lymphocytes delineating CD8+ and CD30+.	CD8+(100%)CD30 +(90%)	•Pagetoid Reticulosis (PR). •Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma.	•Localized or solitary erythematous or scaly lesion. •Multiple rapidly evolving plaques and nodules with erosions and necrosis.

Type E	Angio invasive infiltrates of atypical CD30+ lymphocytes. Haemorrhage, extensive necrosis and ulceration.	CD8+(70%)	•Extra-nodal NK/T cell lymphoma; nasal type. •Cutaneous gamma/delta lymphoma. •Anaplastic large cell lymphoma (angio invasive form).	• Association with EBV, secondary cutaneous involvement (staging). •IHC: Elucidation of TCR gamma delta with absence of TCR alpha/beta. •Clinical presentation with solitary or grouped nodules in pc ALCL: staging in s ALCL.
Key: MF: Mycosis Fungoides, pc ALCL: primary cutaneous Anaplastic Large Cell Lymphoma, s ALCL: systemic Anaplastic Large Cell Lymphoma, NK: Natural Killer, EBV: Epstein Barr virus, HTLV 1/2: Human T lymphotropic virus types 1 and 2, TCR: T Cell Receptor, TCL: T Cell Lymphoma, IHC: Immune Histochemistry.				

Table 1: Current terminology: Categories of Lymphomatoid Papulosis.

Clinical Aspects

Lymphomatoid Papulosis usually appears in adults, frequently in the fifth decade of life and it may rarely occur in children and young adults [2,3]. However, the disorder may depict a variable emergence with a mean age of 35-45 years. A male preponderance may be elucidated [2,4]. In spite of a stringent histological evaluation and follow up, one fifth (20%) of the individuals may progress to an overt malignant lymphoma or a non-lymphoid malignancy [5]. Lymphomatoid papulosis and adjunctive cutaneous lymphomas depict an obscure aetiology. The factors inciting the development of LyP may comprise of viral infections though the human T lymphotropic virus-1, Epstein Barr virus and Herpes simplex virus 1, 2 and 6 (HTLV 1, EBV,HSV1,2 and 6) may not be implicated [2,6]. Lymphomatoid papulosis may frequently expound reddish brown papules or nodules with progressive centroidal haemorrhagic necrosis and a spontaneous recovery within 3-8 weeks. The clinical evaluation may display a quantifiable minimal to hundreds of lesions with a variable evolution to the dermis. The lesions may configure groups within specified zones such as the central trunk or peripheral limbs. Additionally, a congregation of disseminated papules with miniature nodules may collocate the lesions of lymphomatoid papulosis [2].

A spontaneous regression may occur with the appearance of hypo-pigmented or hyper-pigmented lesions or atrophic varioliform scars. Alleviated lesions may enunciate an absence of scarring. Pustular lesions or ulcers may be infrequent. The discrete lesions of angio-invasive LyP type E may spontaneously retrogress within a span of weeks or months. A progressive eschar like necrosis with lesions extending up to 4 cm in magnitude may emerge. Occasional hypo-pigmented or hyper-pigmented varioloform scars may be identified with lesion reversal [2,3]. The persistence of nodular lesions, augmented magnitude of lesions, the appearance of B symptoms (fevers, weightloss, drenching night sweats) and lymph node enlargement may indicate a possible malignant transformation [7].

Attributes	**CD30+ALCL**	**Borderline**	**LyP**
Clinical Aspects			
Extent	Solitary>regional (exceptionally) diffuse	Regional	Regional/Diffuse
Lesion	Nodular, Tumours	Nodular	Papules/ papulo-nodular
Regression	Infrequent	Frequent	Consistent
Extra-cutaneous disease	25%-30%	Absent	Absent
Histological Aspects			
Wedge shaped infiltrate	Absent	Infrequent	Prominent
Sheets of CD30+ cells	Persistent	Miniature aggregates	Absent
Subcutaneous infiltrate	Present	Absent	Absent
Immune reactive CD30+	>75% of tumour cells	Miniature aggregates	Scattered CD30+ reactivity
Key: ALCL: Anaplastic Large Cell Lymphoma.			

Table 2: Demarcation betwixt Cutaneous CD30+ ALCL, Borderline Lesions and Lymphomatoid Papulosis.

The cutaneous lesion may gradually progress over a period of weeks to several years or decades [5]. Exceptional varieties of LyP may be constituted by the clinical variants "acral or mucosal" in addition to histological subtypes of follicular, syringotropic, granulomatous and spindle cell categories [1,3]. Follicular variant of lymphomatoid papulosis may elucidate pustular lesions clinically simulating a folliculitis Papular, self-limiting lesions may superimpose upon the patches of concomitant mycosis fungoides and may be addressed as "persistent agminated lymphomatoid papulosis" [1]. Oral mucosa may be infrequently involved with lymphomatoid papulosis. The lesions of

LyP predominantly localized to the dermis may frequently be asymptomatic. An estimated one fifths (20%) of the individuals displaying the LyP rash may be preceded or followed by adjunctive cutaneous or systemic lymphomas such as Mycosis Fungoides, primary Cutaneous Anaplastic Large Cell Lymphoma (C-ALCL) or Hodgkin's Lymphoma (Table 2).

Regression of lymphomatoid papulosis

The methodology of spontaneous retrogression of cutaneous lesions remains obscure. An interrelation of CD30+ immune molecule with its ligand (CD30 L) may incite the apoptosis of malignant T cells along with the retrogression of the tumor nodules [2,3]. The absence of transforming growth factor β (TGF β) inhibitor response on account of a mutation encoding type I transforming growth factor β (TGF β) receptor within the CD30+expressing tumor cells may be implicated in the progression of the tumour [1,3].

Variants of lymphomatoid papulosis

The five frequent histological variants (A-E) of lymphomatoid papulosis along with an explicit genotype with 6p25.3 genetic rearrangement may be enunciated [7,8]. The categories may be elucidated within the revised World Health Organization (WHO) classification 2016 [4]. Divergent histological subtypes may appear simultaneously in an individual. However, the LyP subcategories may not enunciate a particular prognostic or therapeutic connotation. LyP type A and C may be considered the frequent histological variants comprising of an estimated 80% of morphological diagnosis of LyP [3,8].

LyP type A: as a frequent category of lymphomatoid papulosis may incorporate an estimated three fourths (75%) of the detected LyP [3]. A wedge shaped dermal infiltrate of medium sized or enlarged, pleomorphic and anaplastic lymphoid cells may be elucidated, configuring miniature aggregates or a gross dissemination (Figures 1 and 2).

The pleomorphic/anaplastic cellular effusion may be commingled with inflammatory exudates comprising of innumerable neutrophils, eosinophils and histiocytes. The tumour cells may variably elucidate an immune reactive CD30+ [9] (Figures 3 and 4).

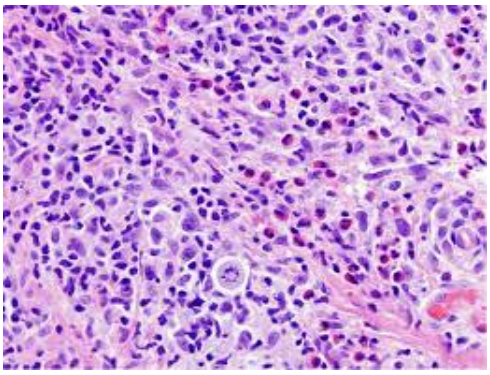

Figure 1: LyP-A infiltrate of lymphoid a typia admixed with inflammatory cells.

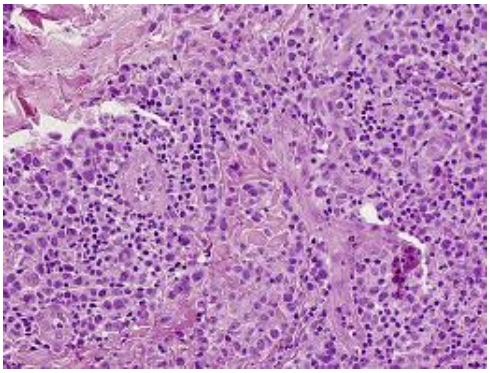

Figure 2: LyP-Dissemination of admixture of reactive cells and aberrant lymphocytes.

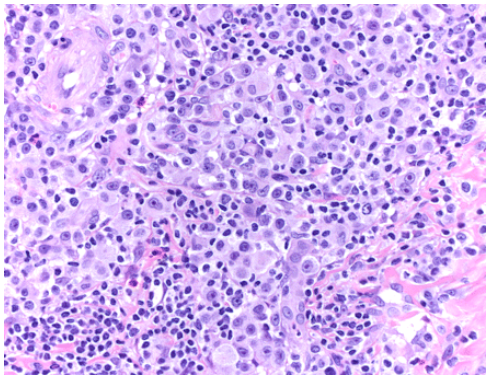

Figure 3: LyP Scattered anomalous lymphocytes with inflammatory exudates.

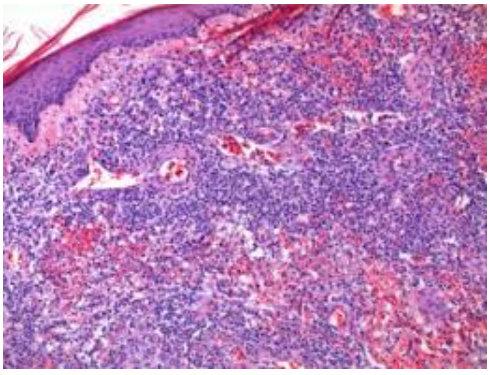

Figure 4: LyP Variable inflammatory exudates with anomalous lymphocytes.

LyP type B: may demonstrate an epidermotropic infiltrate composed of small to medium sized lymphocytes with a cerebriform nucleus. The cells may simulate the histology of a Mycosis Fungoides or a Sezary Syndrome. Immune reactivity to CD30+ may be lacking in LyP type B.

LyP type C: predominantly articulates a cohesive, nodular amalgamation of anomalous and enlarged lymphoid cells admixed with a minimal quantity of reactive inflammatory cells [9,10].

LyP type D: may represent a classical ingress of epidermotropic lymphocytes manifesting reactivity to CD8+ and CD30+ immune molecules. The cellular component may be atypical and composed of miniature to medium sized lymphocytes. A perivascular infiltrate of tumour cells embedded deep within the dermis may be elucidated (Figures 5-8).

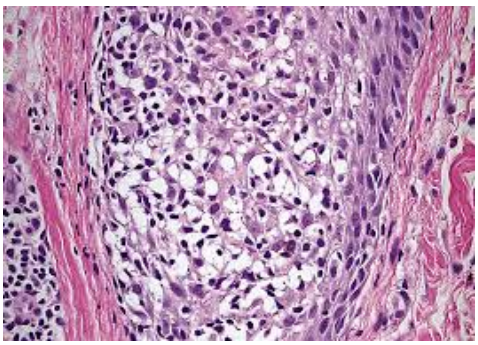

Figure 5: LyP- Atypical lymphocytes with histiocytes and neutrophils.

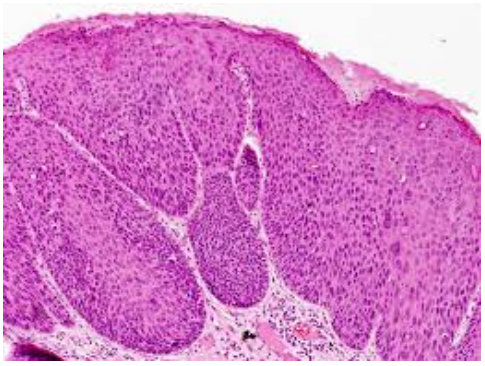

Figure 6: LyP-Dermal ingress of reactive and atypical lymphocytes.

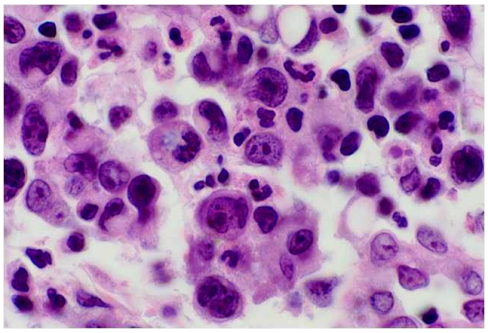

Figure 7: LyP-Anomalous lymphocytes with well dispersed nuclear chromatin and conspicuous nucleoli.

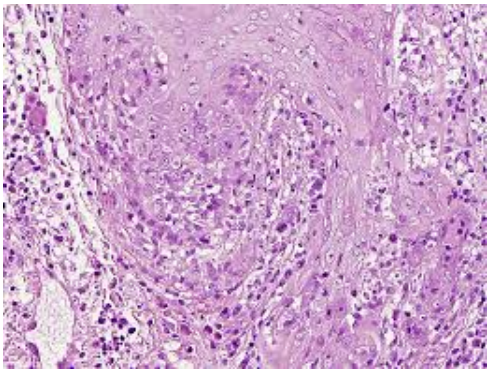

Figure 8: LyP- foci of necrosis with aberannt lymphoytes within the dermis.

LyP type E: or the angio-invasive variant may be characterized by angio-centric and angio- destructive infiltrates of tumour cells [11]. The infiltration of the vessel wall accompanied by the vascular occlusion may induce considerable haemorrhage, tissue necrosis and ulceration (Figure 9).

LyP type E on clinical grounds may depict a rapid progression of necrosis with an eschar like configuration. The necrotic eschar may be greater than the papulo-nodular lesions frequently delineated in LyP. Chromosomal rearrangements of the DUSP22/IRF4 genetic locus situated on gene 6p25.3 may be elucidated [6,7].

The histology of LyP type E may be similar to pagetoid reticulosis and demonstrates a predominant epidermotropism with superimposed intense infiltrates of miniature to medium sized CD30+ lymphocytes with a categorical congregation within the dermis. Particularly LyP type D and type E may be misdiagnosed as an aggressive lymphoma [9,10].

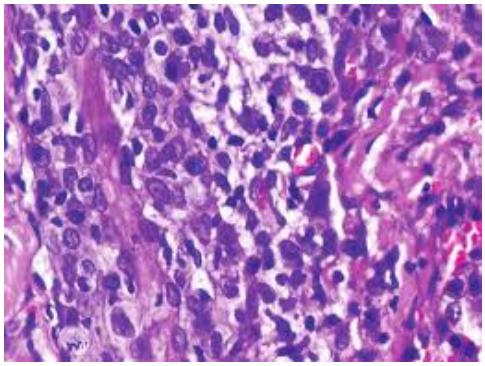

Figure 9: LyP- angiocentric variant with infiltration of the blood vessel wall.

Additional infrequent and exceptional histological categories of lymphomatoid papulosis may incorporate follicular LyP which exhibits a folliculotropism of immune reactive CD30+ atypical, enlarged and pleomorphic lymphocytes. The particular kind of LyP necessitates a demarcation from folliculitis or follicular mycosis fungoides on clinical and/or morphological grounds [12].

Apart from the above mentioned subclasses, rare morphological variants of LyP may be designated as the follicular, angiotropic, granulomatous and spindle cell LyP. The aberrant lymphoid cells delineated within the disorder may demonstrate the immune phenotype of activated T helper cells (CD25+, CD71+) with an immune reactive CD30+ (Figure 3). The particular immune marker (CD30+) may be persistently elucidated by the atypical lymphocytes detected within the LyP subtypes with the exception of LyP type B which generally delineates a varying proportion of CD30+ lymphoid cells [12].

The atypical lymphoid cellular component may concurrently exemplify a CD4+ immune phenotype. A CD8+ immune phenotype may be discerned with the instances of LyP type D (100%) and a majority of LyP type E in addition to the lesions detected in children [1]. The immune phenotype depicted by the anomalous lymphocytes may not influence the clinical course of the disease with its outcome (Figures 10-12).

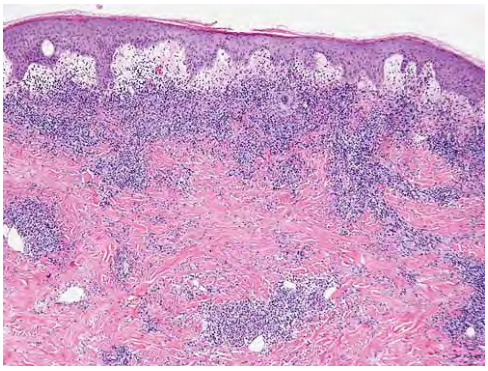

Figure 10: LyP-Strands of aberrant lymphocytes admixed with reactive cells.

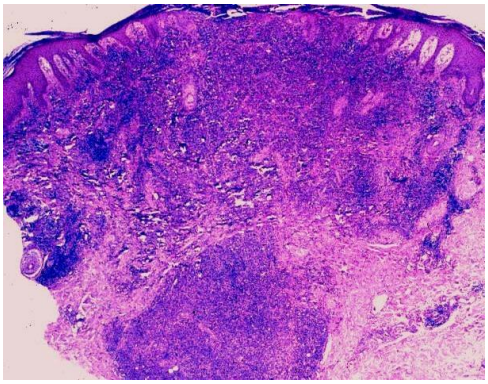

Figure 11: LyP-Dense dermal infiltrate of atypical lymphocytes.

Monoclonal rearrangement of the T Cell Receptor (TCR) genes may be expounded within 40%-90% of the instances of LyP [1,3]. Albeit, the lack of a T cell clone specific disease may not eliminate the clinical and morphological diagnosis of LyP. A singular molecular assay for the detection and categorization of a clone specific lymphomatoid papulosis may be inadequate [12,13]. Individual and discrete lesions of lymphomatoid papulosis may enunciate morphological attributes simulating and superimposed with adjunctive or coincident lesions.

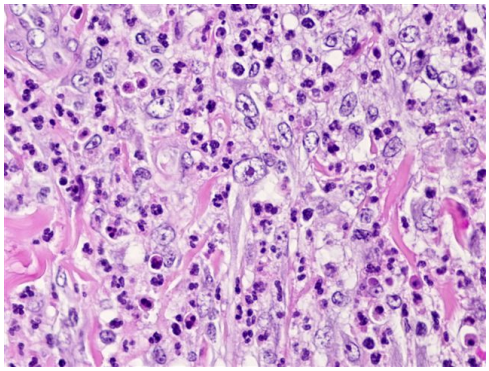

Figure 12: LyP- Aberrant lymphocytes with vesicular nuclei and prominent nucleoli.

A particular lesion of lymphomatoid papulosis may exemplify attributes identical to varying histological subtypes, thus rendering the recognition and categorization of the condition challenging [13,14]. The spectrum of histological variants of lymphomatoid papulosis may mandate an appropriate characterization in order to reduce probable misinterpretation and misrepresentation.

The current methodology of classifying and describing the lesions of lymphomatoid papulosis may incorporate pertinent aspects such as the collocation of histological subtypes, the articulate infiltration of tumor cells, the coexistent inflammatory effusion, the morphological attributes along with the phenotype of the neoplasm [3].

The histological draft while incorporating the variants of lymphomatoid papulosis may be designated as:

- LyP type A or a mixed cellular infiltrate
- LyP type D or an epidermotropic or pagetoid CD8+ immune reactive infiltrate

Suitable clinical attributes such as angio-centric or angio-invasive, CD8+ immune reactive or acral category may be appropriatelydescribed along with relevant genetic erudition may configure an addendum to the draft. The histological assessment in the absence of concomitant clinical/immune phenotypic/genetic correlation may be inadequate to correctly classify LyP. The final interpretation may mandate an appropriate clinical and pathological concordance.

Investigative assay

An extensive history with a comprehensive general physical examination, a complete blood count, liver function tests , a chest X-ray, computerized tomography of the abdomen and a bone marrow aspiration/biopsy may be mandated (with abnormal complete blood counts) [7]. The symbolic clinical appearance with evidentiary spontaneous retrogression of the discrete, individual lesions of LyP within weeks or months along with the typical morphology may assist the detection of the disorder [8].

The discernment of immune reactive CD30+Tcell lympho-proliferation may mandate a complete blood count along with a differential count, the usual serum chemistries and a serum Lactate

Dehydrogenase (LDH). A radiological staging or the bone marrow biopsy may not be a pre-requisite in patients elucidating classical clinical symptoms of LyP, an absence of enlarged lymph nodes with negative or inconclusive blood assay [3,8]. Extra cutaneous disease as discerned by the general physical examination or laboratory investigations may necessitate a radiological staging with an examination and biopsy of the enlarged lymph nodes [2,3].

Differential diagnosis

The variegated morphology of lymphomatoid papulosis with an immune reactive CD30+ may be elucidated by several lymphomas besides reactive inflammatory conditions (Figures 13 and 14). A distinction may be required from arthropod bite reaction, drug eruptions or pitryaisis lichenoides.

The diverse histological variants of LyP may simulate adjunct cutaneous and aggressive systemic lymphomas. Secondary cutaneous dissemination by systemic Anaplastic Large Cell Lymphoma (ALCL) may necessitate a demarcation from LyP [1].

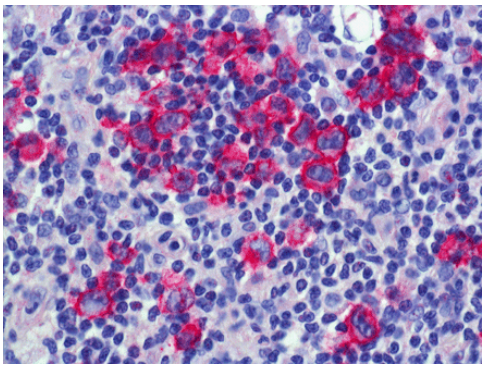

Figure 13: LyP-immune reactive CD30+ lymphocytes.

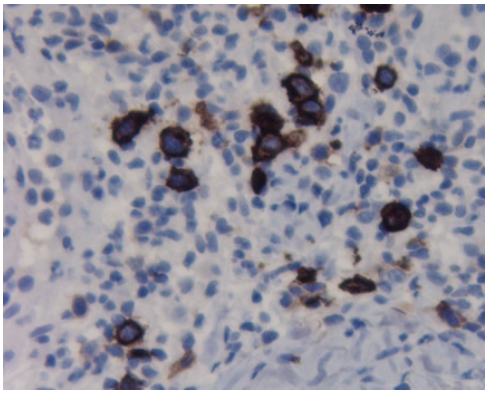

Figure 14: LyP-immune reactive CD30+ lymphocytes.

Immune suppressive conditions may require a distinction as the cutaneous CD30+ lympho-proliferative disease emerging in an immune deficient individual along with systemic forms of ALCL as these may delineate an inferior prognosis and mandate a chemotherapy with several drugs [11,14].

Lymphomatoid papulosis necessitates a differentiation from the dermal lesions of systemic Anaplastic Large Cell Lymphoma (ALCL), pertinent CD30+ cutaneous T cell lymphomas, mycosis fungoides, particular pseudo lymphomas, insect stings, viral infections, scabies, atopic dermatitis and associated lymphoid proliferations [1,7].

The determination of lymphomatoid papulosis and associated Cutaneous T-Cell Lymphoma (CTCL) may mandate a clinical corroboration along with a histological evaluation, an appropriate staging of the disease with a suitable immune-phenotypic assay [10]. `

The preliminary phase of distinction may employ the clinical criterion elucidated by surrogate conditions such as the Mycosis Fungoides, Mycosis Fungoides variant, Sezary syndrome and associated Cutaneous T-Cell Lymphoma (CTCL).

The clinical attributes may recognize the respective lesions in an estimated two thirds (65%) of instances of CTCL, as exemplified with Mycosis Fungoides and variants besides categorical patients of LyP with definitive clinical manifestations [1,3]. The subsequent phase of identification of LyP may require a histological evaluation in the form of skin biopsies along with the preferred immune reactivity for CD30+.

Lymphomatoid papulosis, Anaplastic Large Cell Lymphoma (ALCL) and an estimated one fourth (25%) of Cutaneous T Cell Lymphoma (CTCL) may suitably be identified with the morphological/immune phenotypic techniques. The implicated individuals may elucidate a superior prognosis.

Majority (90%) of the instances of Cutaneous T Cell Lymphoma (CTCL) may be appropriately addressed with the aforementioned mechanisms of identification which are characteristic of the disorder (Table 3).

The remaining (10%) categories may comprise of exceptional instances of T cell lymphoma such as a cutaneous peripheral lymphoma, subcutaneous panniculitis like lymphoma, epidermotropic aggressive cytotoxic CD8+ T cell lymphoma and associated lymphoid neoplasm [3,5].

Prognostic outcomes

Confined, dermal lesions of LyP may depict a favourable prognosis. Lymphomatoid papulosis may persist for an extended duration of months or years with a significant absence of elevated mortality [8]. A fraction of individuals afflicted with LyP may demonstrate a second lymphoid neoplasm especially Mycosis Fungoides, Hodgkin's lymphoma and anaplastic large cell lymphoma (cutaneous or nodal CD30+ ALCL).

The particular lymphoid neoplasm may be designated as "LyP associated malignant lymphomas" and appear preceding to, in concurrence with or subsequent to the preliminarily manifested LyP [14,15]. The incidence of "LyP associated malignant lymphomas" may range from 0%-62% in LyP inflicted individuals progressing to a second neoplasm [1,3].

An preference for elderly patients, the occurrence of histological LyP types B & C, lesions of LyP situated on the head, a frequent reoccurrence of LyP, a discernible T cell clone localized in the LyP lesions and elucidation of fascin by the CD30+ cell population may indicate an inferior prognosis of the "LyP associated malignant lymphomas" [12,15].

Diagnosis	Histology Inflammation/ Architecture	Phenotype	Appendix 1: Genotype	Appendix 2: Clinical Presentation
Lymphomatoid papulosis	Mixed cellular	CD4+	6p25.3	Generalized
	Epidermotropic	CD8+	NPM1-TYK2 gene fusion	Localized
	Pagetoid/Non-pagetoid	CD4-/CD8	-	Acral
	Cohesive	-	-	Mucosal/Oral
	Angio-invasive	CD56(optional)	-	Pustular
	Folliculotropic	TCR (optional)	-	-
	Syringotropic	-	-	-
	Granulomatous	-	-	-
	Intra-lymphatic	-	-	-
	Spindle cell	-	-	-

Table 3: Proposed contemporary terminology of Lymphomatoid papulosis.

Conclusion

As the prognosis of LyP is superior, a "wait and watch" strategy may be adopted. Active therapeutic intervention may not be able to modify the evolutionary course of the disease. The multiple, disseminated or stigmatizing lesions of LyP may be managed by ultraviolet light based therapy or a low dose methotrexate. A combined chemotherapeutic approach may be circumvented in LyP on account of probable emergence of a secondary lymphoid neoplasm. The therapeutic management of lymphomatoid papulosis may incorporate segments of short term, intensive chemotherapy. However, concurrent adverse reactions mandate an evaluation of the adopted regimen. Minimalistic lesions of LyP may not necessitate therapeutic intervention. The miniature lesions may benefit from the administration of low dose methotrexate, psoralen and ultraviolet A (PUVA) radiation, mechlorethamine, (nitrogen mustard), topical carmustine (BCNU) or a low dose etoposide.

Expansive dermal lesions may be self-limiting and disappear automatically within 4-12 weeks, however, may benefit from surgical eradication and/or radiotherapy. The progressive dermal lesions may terminate with spontaneous resolution. Monitoring may also be a pre-requisite in order to discern and appropriately treat the "LyP associated malignant lymphomas". The chemotherapeutic agent Brentuximab Vedotin (BV) may be efficacious in relapsing and refractory LyP. The potential adverse reactions may require a critical evaluation particularly with the employment of advantageous therapy for indolent lympho proliferative disorders such as lymphomatoid papulosis. The preliminary lesions or those elucidating an excellent prognosis may preferably be monitored by a dermatologist. LyP may mandate a long term and continuous surveillance on account of the innumerable reoccurrences. Nevertheless, the therapeutic modalities opted for the majority of lesions of lymphomatoid papulosis may be insufficient as the condition may recur following discontinuation of therapy.

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