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Review Article

To be a "Lymphomatoid Papulosis Type E" or not to be? That Is a Question

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Introduction

Lymphomatoid papulosis (LyP) Type E is a recently introduced subtype of LyP presenting with escar-like lesions and characterized with angiocentric invasion of dermal blood vessels by CD30 positive atypical lymphocytes resulting necrosis of their walls. Owing to its considerable histologic characteristics such as dense dermal infiltration of CD30 positive large atypical lymphocytes showing high mitotic activity, and angiodestructive invasion, it is challengible to discriminate LyP Type E to aggressive cutanoues lymphomas.

1. Histological classification of LyP

Primary cutaneous CD30 positive T-cell lymphoproliferative disorder (LPD), clinically characterized by a variable number of self-healing papulonodular lesions, with typical waxing and waning course, which represent the second most common form of cutaneous T-cell lymphoma [1]. Histologically, five different LyP Types have been delineated. LyP type A shows scatterd or grouped CD30 positive large pleomorphic or anaplastic lymphoid cells in the background of neutrophils and eosinophils, type B exhibits epidermotropic infiltrate of small lymphocytes, and type C displays cohesive sheets of atypical lymphoid cells with only a few admixed reactive cells. Type D is characterized by epidermotropic infiltrates of CD8 positive and CD30 positive atypical cells and mimics primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma. Histological features of four types of LyP were summarized in **Fig. 1.** Overlapping features can be found in individual lesions, and different lesions in the same patient may exhibit different histological types. Recently, angioinvasive LyP was identified as a new histological type and referred to as type E [2]. We recently reported a case of LyP type E showing diffuse CD56 and Granzyme-B positive immunophenotype in an immunocompetent 34-year-old man with a history of four year self-healing some erythematous nodules on his extrimities [3], which has been scarcely known that only three cases of CD56 positive LyP Type E developed in a 36-year-old woman with asymptomatic ulcerated papules on her neck, abdomen, and arm intermittently occurred for 10 years [4], a 40-year-old woman presenting disseminated skin lesions repeatly wax and wane clinical course for 20 years [5], and in a 76-year-old man menifested with right forearm lesions eventually scar-formed after 4 years [2], and discuss the clinicopathologic findings, differential diagnosis within the spectrum of CD30 positive LPD.

2. Typical scenario based on my experience

34-year-old man presented with a 4-year history of relapsing self-healing erythematous nodules on extremities. Until now, about 20 lesions have been occurred mainly in the limbs, and these lesions have developed 2-3 lesions at one time and improved spontaneously with mild scar. He denied notable weight loss, fever and lymphadenopathy. His laboratory test results were within normal ranges and anti-HIV antibody was negative. On physical examination, the patient had 2 well-defined erythematous nodules on the left distal arm and right proximal arm that rapidly evolve into ulceration **(Fig 2A,B)**. The central part manifested a hemorrhagic necrotic crust and had an eschar-like appearance **(Fig 2C)**. In view of the wax and waning nature of the lesions and the patient's medical history, incisional biopsy was subsequently performed. Histologic assessment showed a profound epidermal and superficial dermal necrosis due to vessel wall destruction by atypical lymphoid cells **(Fig 2E,F).** In deep dermis, marked lymphoid cell infiltration intervining subcutaneous fat, and destructing vessel walls noted **(Fig 2G,H)**. This lesion consisted of monotonous neoplastic lymphocytic cells with medium to large-sized slightly irregular nuclei, coarse chromatin, and prominent nucleoli **(Fig 2I)**. To explore these histologically considerable lymphocytic lesions, an immunohistochemical study was conducted: the medium to large-sized atypical lymphoid cells were positive for CD3, CD4, CD8, CD30, CD56, and Granzyme-B, but negative for CD20, CD79a, ALK, and Epstein-Barr virus encoded RNA in situ hybridization (EBER-ISH) . The Ki-67 labeling index was nearly 90% **(Fig 2J-P)**. Considering the unique clinical presentation and all of these histologic findings, the diagnosis of LyP Type E showing diffuse CD56 and Granzyme-B positive immunophenotype

was made. A systemic lymphoproliferative disorder could not be excluded and the patient was referred for a hematological opinion. Medical imaging and blood investigations excluded a systemic lymphoproliferative disorder and any underlying cause of immunosuppression. Regrettafully, a polymerase chain reaction (PCR) for T-cell receptor (TCR) gene rearrangements in our patient can not be done due to his refusal. At regular follow-ups, the patient remained asymptomatic, and reported no further episodes of skin problems and the lesions evolved over 2 months and healed with atrophic scars without any treatment **(Fig 2D)**.

Discussion

LyP is a chronic, recurrent, self-healing papulonodular eruption with a potential association with myosis fungoides, CD30 positive anaplastic large cell lymphoma, or Hodgkin disease. Microscopically, LyP is characterized by clusters of CD30 positive large and often anaplastic cells among heterogeneous inflammatory infiltrates. As newly introduced subtype of LyP, Type E, characterized clinically by oligolesional papules that evolve into necrotic eschar-like lesions with spontaneous regression and microscopically by typical angiocentric invasion of dermal blood vessels by CD30 positive atypical lymphocytes resulting necrosis of their walls [2]. Histologically, differential diagnosis of LyP type E includes nasal type extranodal NK/T-cell lymphoma, primary cutaneous T-cell lymphoma, primary cutaneous anaplastic large cell lymphoma. Nasal type extranodal NK/T-cell lymphoma is an aggressive lymphoma with angiocentric and angiodestructive infiltrates of CD3 positive, CD8 equvocal, CD56 positive, and necrosis, but in contrast to LyP type E, tumor cells usually lack expression of CD30 [6]. A subset of atypical cells express CD30 in nasal type extranodal NK/T-cell lymphoma, and in other T-cell or NK-cell tumors, but it is rarely expressed by the majority of atypical cells in these neoplasms. Moreover, it is linked to Epstein Barr virus (EBV) in virtually all cases, whereas none of LyP type E cases was associated with EBV as demonstrated by the absence of EBV assessed by in situ hybridization [7]. Finally, nasal type extranodal NK/T-cell lymphoma spreads to extracutaneous sites and has a poor prognosis [8]. Primary cutaneous T-cell lymphoma, which may present with angiocentric or subcutaneous infiltrates and ulcers, exhibit a poor prognosis, expresses dominant CD4 or CD8 positivity in tumor cells. In our case, atypical lymphoid cells stained for both CD4 and CD8 with indolent clinical course. LyP type E shares features with primary cutaneous anaplastic large cell lymphoma and borderline lesions, in which rarely angiocentric infiltrates [9]. This is probably the most challenging differential diagnosis as only a few or even a solitary lesion may be present at a given time, thus seriously limiting application of the general clue of multiple lesions in LyP versus a solitary lesion in anaplastic large cell lymphoma. The recurrent lesions are in favor for LyP but this feature may require follow-up. The overlapping features between LyP and primary cutaneous anaplastic large cell lymphoma, however, is emphasized by their categorization as part of the spectrum of CD30 positive LPD. LyP type E differs from anaplastic large cell lymphoma by angiocentric infiltrates of CD30 positive CD8 positive atypical lymphocytes [10, 11]. Several reports of cytotoxic T-cell origin in LyP have been known [2-5, 8, 12-16], but little has been knwon of clinical differences of LyP type E with CD56 and Granzyme-B expressed immnophenotype. The CD56, a monoclonal antibody against the neural cell adhesion molecule, was initially identified as a surface molecule of CD16 positive natural killer (NK) cells with the morphology of large granular lymphocytes. A CD56 is the archetypal phenotypic marker of natural killer cells but can actually be expressed by many more immune cells, including α/β T-cells, γ/δ T-cells, CD4 positivie T-cells, CD8 positive T-cells, dendritic cells, and monocytes. Common to all these CD56-expressing cell types are strong immunostimulatory effector functions, including T helper 1 cytokine production and an efficient cytotoxic capacity and these cells are found in various infectious, autoimmune, or malignant diseases [17]. Furthermore, in current clinical trials cancer patients with CD56 positive tumors are being treated with a CD56-targeting antibody drug [18], and increased CD56 positive T-cells seems to be effective to distinct populations of metastatic melanoma patients responding to anti-PD-L1 therapy [19]. Although cutaneous lymphomas expressing CD56, such as skin infiltration of acute myeloid leukemia, nasal type extranodal NK / T-cell lymphoma, and blastic NK-cell lymphoma, generally characterized by a highly aggressive clinical course and poor prognosis [8], according to several reports to date, CD56 positive immunophenotype in LyP seems to have an excellent prognosis like classic LyP. To date, four cases of CD56 positive LyP type E, including our case, also showed an excellent prognosis. Recently, we described a clinically and histologically LyP type E showing aberrant CD56 and Granzyme-B expression strongly, which presenting recurrent some papulonodular lesions with eschar-like change and scar formation throughout his extremities for years. These lesions follow an indolent course and has an excellent prognosis with spontaneous regression and recurrences, following a characteristic feature of LyP type E despites of strong CD56 and Granzyme B-positivity in tumor cells. As this is a newly introduced disease, little has been known about its clinical settings. . Unfortunately, no immunohistochemical markers or TCR gene rearrangement test mentioned above can lead a right diagnosis. Only eschar-like lesions showing wax and wane pattern clinically without lymphadenopathy are able to tell you the answer, therefore careful history taking and scrupulous physical examination are mandantory, which is already known as a way to be good physicians. More collective studies are necessary to unravel possible clinical differences, and to comparatively analyse histomorphology, and molecular alterations among LyP with / without CD56 positive immunophenotype, especially when it comes to CD56 positive LyP Type E.

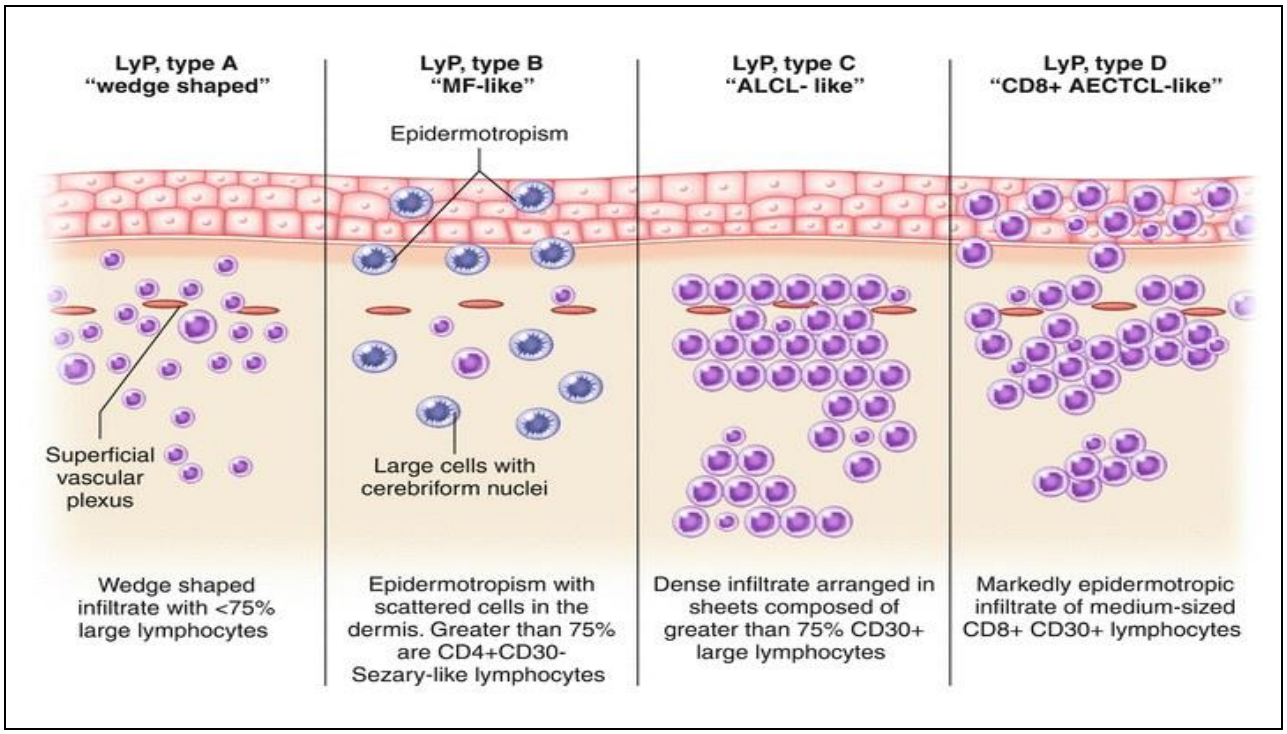

Figure 1

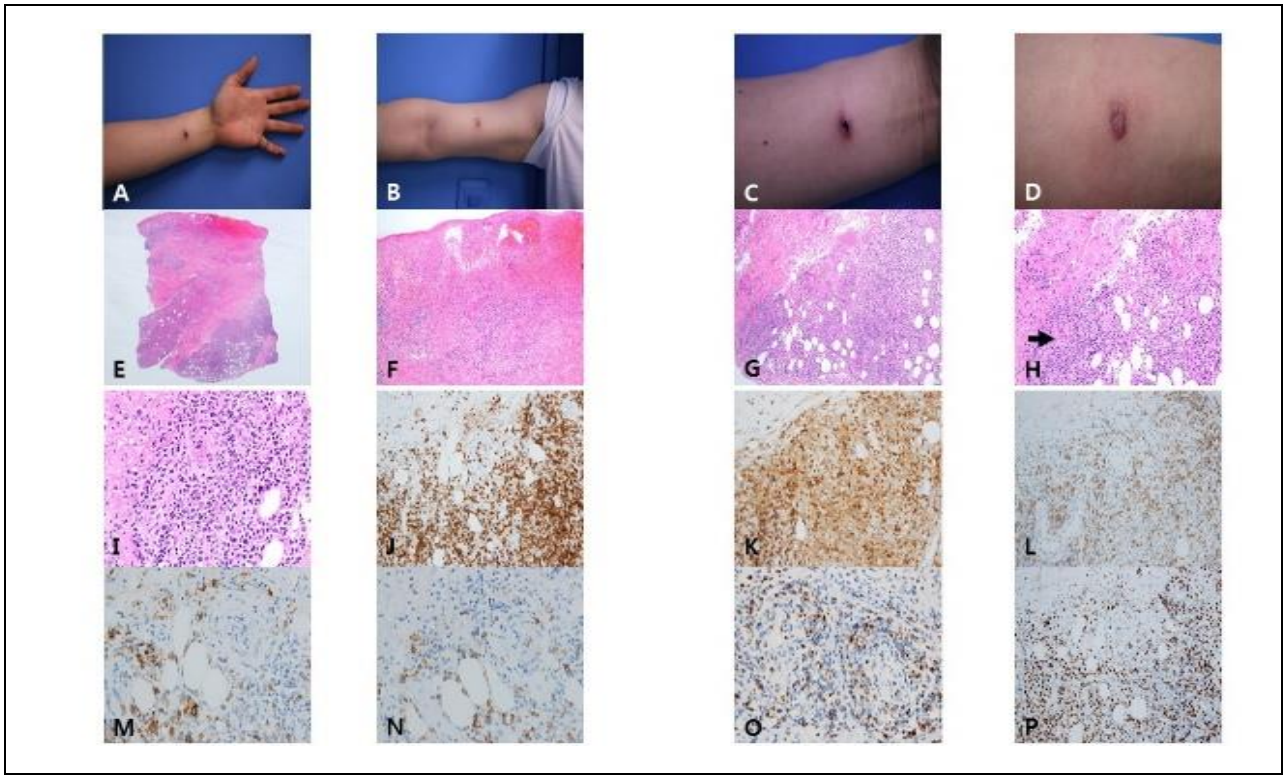

Figure 2. (A) Multiple papulonodular lesions developed at same time in left distal arm, and (**B)** Right proximal arm. (**C)** Erythematous nodule with a central eschar-like hemorrhagic crust on left distal arm. **D**.Residual scar after preceding ulcerative lesion. **(E)** Dense lymphoid cell infiltration from upper dermis to deep subcutaneous fat (H&E, x1.2). **(F)** Necrosis in upper dermis due to angiodestructive and angioinvasive infiltration with atypical lymphoid cells (H&E, x100). **(G)** Marked angioinvasion with atypical lymphoid cells in deep subcutaneous fat (H&E, x100), **(H)** which making vessel walls necrosis (arrow)(H&E, x200). **(I)** The medium to large-sized atypical lymphoid cells destructing vessel wall and intervining fat cells, which shows irregular nuclear contour, coarse chromatin, and relatively prominant nucleoli (H&E, x400). **(J)** CD3 positive (x200), **(K)**

CD4 positive (x200), **(L)** CD8 positive (x200), **(M)** CD30 positive (x400), **(N)** CD56 positive (x400), and **(O)** Granzyme-B positive atypical lymphoid cells (x400). **(P)** High proliferating ki-67 labeling index in these cells (x200).

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