Coexistence of Discoid Lupus Erythematosus and Paraneoplastic Pemphigus: A Case Report and Literature Review

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Abstract: Pemphigus and lupus erythematosus are both B-cell-mediated autoimmune diseases, dependent on autoreactive CD4+ T lymphocytes to modulate autoimmune B-cell response. Many forms of pemphigus have been reported to occur in association with systemic lupus erythematosus (SLE) as well as other autoimmune diseases. However, it remains unclear whether this association occurs because of a shared immunopathogenesis or the coexistence may be coincidental. We hereby present a case report of discoid lupus erythematosus and paraneoplastic pemphigus associated with marginal zone lymphoma in a 54-year-old Thai man who had persistent oral erosions for 1 year together with generalized polymorphic cutaneous eruptions for 2 months. Simultaneous occurrence of paraneoplastic pemphigus and discoid lupus erythematosus without SLE has never been reported in the same individual. Hydroxychloroquine, immunosuppressive agents including prednisolone and azathioprine together with chemotherapy were given to treat these conditions.

Keywords: paraneoplastic pemphigus, discoid lupus erythematosus, cutaneous lupus erythematosus, autoimmune bullous disease, non-Hodgkin lymphoma, marginal zone lymphoma

Introduction

Pemphigus and lupus erythematosus (LE) are classified as B-cell-mediated autoimmune diseases, both depending on autoreactive CD4+ T lymphocytes to modulate autoimmune B-cell response.1 Many forms of pemphigus have been anecdotally reported to occur in association with LE as well as other autoimmune diseases, but the pathogenic mechanism remains unclear.2-18 Previous reports have demonstrated cases with pemphigus foliaceus (PF) or pemphigus vulgaris (PV) in association to discoid lupus erythematosus (DLE).11,12 To date, there has been only one reported case of paraneoplastic pemphigus (PNP) associated with SLE.3 To the best of our knowledge, we present the first case of DLE and PNP associated with marginal zone lymphoma. This is a 54-year-old Thai man who had persistent oral erosions for 1 year and generalized polymorphic cutaneous eruptions for 2 months. An additional literature review on cases with pemphigus and LE has been performed. The search of English-language publications was conducted using MEDLINE, EMBASE and Scopus as electronic databases. The citations were identified with the use of a combination of the following text words: “pemphigus”, “paraneoplastic pemphigus”, “lupus erythematosus”, “SLE”, “CLE”, and “case report” from inception of each database to August 2022. Review of articles also included the abstracts of all references retrieved from the search.

Case Presentation

A 54-year-old Thai man with no known underlying medical conditions visited our institution with a 1-year history of persistent multiple painful oral erosions. He also developed generalized pruritic skin lesions on the scalp, face, right ear,
trunk, both upper and lower extremities for 2 months. He lost 8 kg of weight within 6 months due to poor intake, but
denied of any constitutional or systemic symptoms. He had an 8-pack-year history of smoking without a significant
history of sun exposure. The patient was otherwise healthy.

Physical examination revealed multiple painful erosive patches on the lower lip, gingiva, buccal mucosa, tongue, hard
palate, and genitalia as well as various forms of cutaneous lesions. Firstly, there were multiple, well-defined, erythemato-
sous to purplish plaques, with overlying crusted erosions on the forehead. Secondly, there were multiple ill-defined,
erythematous papules, some coalescing into plaques and overlying with group of erosions and scattered bullae on both
upper extremities (Figure 1A–D). Thirdly, there was a well-demarcated, erythematous atrophic plaque with follicular
plugging and peripheral hyperpigmentation on the right concha (Figure 2A). Lastly, there were multiple, well-defined,
purplish plaques, with overlying whitish scales and few erosions on scalp, face, upper chest, upper back and both lower
legs (Figure 2B). Dermoscopic examination revealed thick, whitish and yellowish scales, follicular keratotic plugs,
erythematous background with peripheral purplish-brown area on the scalp lesion (Figure 2C).

Skin biopsies were taken from two sites: the forehead and upper back. Histopathological examination from the forehead
revealed suprabasal separation with acantholytic keratinocytes and focal lichenoid lymphocytic infiltration with melano-
phages (Figure 3) suggestive of paraneoplastic pemphigus (PNP). Direct immunofluorescence (DIF) showed intercellular
deposition of IgG (Figure 4A) and C3. There was also granular deposition of IgG, IgM and C3 at perieccrine areas
(Figure 4B). Indirect immunofluorescence using rat bladder substrate was positive for intercellular deposition as well.
Moreover, histopathological examination from the upper back revealed focal lichenoid, superficial and deep perivascular lymphocytic infiltration in association with irregular epidermal hyperplasia. There was also perifollicular interface changes with scattered basal necrotic keratinocytes, compatible with hypertrophic discoid lupus erythematosus (DLE) (Figure 5).

Laboratory tests, composing of complete blood count, renal function, liver function test, and urinalysis, were within normal limits. Anti-nuclear antibody (ANA) was also negative. Enzyme-linked immunosorbent assay (ELISA) for anti-desmoglein-1 autoantibody was positive (153.33; reference range 0–20 U/mL) at the time of the initial diagnosis. However, ELISA for anti-desmoglein-3, anti-BP180, anti-BP230, and anti-type VII collagen autoantibody were negative. To evaluate for associated tumor, computed tomography (CT) scan of the chest and whole abdomen with intravenous contrast media was performed and showed an infiltrative soft-tissue mass surrounding the periaortic and aortocaval regions with extension to involve the right psoas muscle (Figure 6). CT-guided biopsy was done for histopathology and immunohistochemistry which confirmed the diagnosis of marginal zone lymphoma.

Based on the clinical manifestation and investigation findings, this patient had coexistence of DLE and PNP associated with marginal zone lymphoma. The patient was initially treated with prednisolone (20 mg/day), azathioprine 50 mg/day for PNP together with hydroxychloroquine 200 mg/day for DLE. After the diagnosis of marginal zone lymphoma was made, chemotherapy (CVP regimen) with of cyclophosphamide, vincristine and prednisolone plus rituximab was administered.

**Discussion**

DLE is the most common clinical subtype of CCLE. It is categorized as localized (above the neck) or generalized (above and below the neck, typically over the extensor forearms and hands) form. Approximately 80% of DLE patients appear...
as localized form, while less than 20% of DLE patients have generalized skin lesions which are more likely to develop features of clinically significant systemic lupus erythematosus (SLE).\textsuperscript{19,20} Hypertrophic DLE is regarded as a rare variant of DLE, representing 2% of all lesions of CCLE, and is characterized histologically by irregular epidermal hyperplasia associated with features of classic CCLE, including interface changes.\textsuperscript{21,22}

PNP is a rare mucocutaneous autoimmune disease associated with neoplasm.\textsuperscript{23} Tumors associated with PNP are either benign or malignant neoplasms which can be hematologic or non-hematologic in origin.\textsuperscript{24} PNP mostly affects

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**Figure 5** Histopathological examination of hypertrophic DLE showing focal lichenoid, superficial and deep perivascular lymphocytic infiltration with marked epidermal hyperplasia (H&E, ×4); perifollicular interface changes with necrotic basal keratinocytes (inset, ×40).

**Figure 6** Computed tomography (CT) scan of chest and whole abdomen demonstrating infiltrative soft-tissue mass surrounding the periaortic and aortocaval regions with extension to involve the right psoas muscle (red arrow).
adults between 45 and 70 years of age with no gender differences, but it may also be found in children and adolescents.\textsuperscript{25–27} Intractable stomatitis and polymorphous cutaneous eruptions, including blisters and lichenoid dermatitis, are characteristic clinical features caused by both humoral and cell-mediated immunity, respectively.\textsuperscript{28} Pathologic findings are presence as acantholytic blisters and interface dermatitis, which sometimes coexist in the same lesion.\textsuperscript{28,29} Immunofluorescence is a useful technique in the diagnosis of PNP. In particular, indirect immunofluorescence using rat bladder is a highly specific method to differentiate PNP from other pemphigus groups that do not harbor anti-plakin autoantibodies.\textsuperscript{28,30,31}

According to literature review of DIF in dermatologic diseases, perieccrine and apocrine immunofluorescence findings may add diagnostic sensitivity in DIF evaluation, particularly of LE and subepidermal immunobullous disease, in which findings at the epidermis or dermo-epidermal junction are uninterpretable.\textsuperscript{32} However, the presence of immunoreactants in adnexal structures, such as IgG and C3 deposition in the intercellular space of hair follicles or sweat ducts, can be found in PNP.\textsuperscript{33} DIF report of our case showed not only epidermal intercellular deposition that can be found in PNP but also periadnexal granular deposition that was a characteristic of CCLE. In addition, clinical manifestation of the right ear, compatible with concha sign and dermoscopic findings of the scalp lesion supported the diagnosis of DLE as well.\textsuperscript{34,35}

The presence of any autoimmune diseases increases the probability of additional ones occurring during the disease’s course because they can share common immunopathogenic mechanisms and risk factors which explain why several diseases can coexist.\textsuperscript{36} CLE-alone is also associated with a risk of non-SLE autoimmune diseases.\textsuperscript{37} To date, many forms of pemphigus have been reported to occur in association with both CLE and SLE.\textsuperscript{2–18} Table 1 summarizes the data on patients with pemphigus in association with lupus erythematosus (LE) and other autoimmune diseases. In general, pemphigus and SLE are both B-cell-mediated autoimmune diseases, dependent on autoreactive CD4+ T lymphocytes to modulate B-cell response.\textsuperscript{1} Two novel regulatory genes, interferon regulatory factor 8 (IRF8) and signal transducer and activation transcription 1 (STAT1), have been identified as genetic markers that are significantly associated with pemphigus and SLE.\textsuperscript{38} Nevertheless, there is still a shortage of knowledge about autoimmune diseases that appear concurrently with CLE. The pathogenetic function of autoantibodies and B cells in CLE, particularly in solitary DLE, is lacking.\textsuperscript{39} There is, however, strong evidence for a function of cytotoxic T cell-mediated immune reaction,\textsuperscript{40–42} whereas the pathogenesis of PNP is driven by both humoral and cell-mediated immune responses.\textsuperscript{28} In cell-mediated immunity, autoreactive CD8+ T cells contributing to the formation of lichenoid dermatitis and CD56+ cells are detected within the dermo-epidermal junction of PNP lesions.\textsuperscript{43–45} Variable genetic factors and genetic susceptibility polymorphisms have been observed in PNP and DLE.\textsuperscript{24,46} Nonetheless, the coexistence of PNP and DLE in the same patient has never been reported, so it remains to be determined whether this association occurs because of a shared immunopathogenesis as mentioned previously or merely a coincidental finding.

Prognosis of PNP is poor and mortality is high, with 1-year, 2-year, and 5-year overall survival rate of 49%, 41% and 38%, respectively, depending on the underlying cause.\textsuperscript{46}

There is currently no standard treatment for PNP due to the absence of randomized controlled trials.\textsuperscript{24} However, it is vital to define and treat the associated neoplasms.\textsuperscript{47} In patients with benign and operable tumor, a surgical cure is often the best chance of inducing remission.\textsuperscript{48} Nonetheless, in PNP with malignant neoplasms, reducing the tumor burden may not lead to disease control.\textsuperscript{46} The most widely used treatment for mucocutaneous lesions is systemic corticosteroid with or without other immunosuppressive agents including cyclosporine, cyclophosphamide, azathioprine and mycophenolate mofetil.\textsuperscript{46,49} Other treatments that have shown promising effects are intravenous immunoglobulin (IVIg), plasmapheresis, rituximab, ibritinib, alemtuzumab and tocilizumab.\textsuperscript{28,50–56} In addition to photoprotection and smoking cessation, the first-line treatment of DLE is topical or intralesional corticosteroids, topical calcineurin inhibitor and systemic antimalarial therapy for individuals who do not respond to topical and intralesional treatments, or with extensive disease.\textsuperscript{57} Nevertheless, the therapeutic options having benefit for both PNP and DLE consist of mycophenolate mofetil, IVIg and rituximab.\textsuperscript{28,57} For marginal zone lymphoma, there are many different chemotherapy regimens, dependent on individual fitness of the patients, including rituximab/bendamustine, rituximab/cyclophosphamide/doxorubicin/vincristine/predni-sone (R-CHOP), rituximab/cyclophosphamide/vincristine/prednisone (R-CVP) or rituximab/fludarabine.\textsuperscript{58} In our case, we advised for photoprotection, smoking cessation and prescribed systemic corticosteroid, azathioprine and systemic antimalarial drug to control mucocutaneous lesions of PNP and DLE. R-CVP regimen was administered for marginal zone lymphoma with significant clinical improvement (Figure 7).
| Study                  | Age/Sex | Race or Ethnicity | Type of Pemphigus | Type of LE | Association to Other Autoimmune Diseases | Onset of Pemphigus Related to LE | Onset of Pemphigus Related to Other Autoimmune Diseases | Pemphigus Treatment | LE and Other Autoimmune Diseases’ Treatment | Course and Outcome |
|------------------------|---------|-------------------|-------------------|------------|-------------------------------------------|----------------------------------|--------------------------------------------------------|---------------------|---------------------------------------------|-------------------|
| Our case               | 54/M    | Thai              | PNP               | DLE        | –                                         | Simultaneous                     | –                                                      | P, AZA, R-CVP       | HCQ                                         | Improved          |
| Mascaró JM Jr et al    | 35/M    | Caucasian         | PNP               | SLE        | PM                                        | After 12 years                    | Preceded by 4 years                                   | Sx (Pelvic Castleman disease) | P, AZA, CYC, CSA | PNP, SLE, PM: remission                   |
| Nanda et al            | 45/F    | Arab              | PV                | SLE        | –                                         | Preceded by 11 months             | –                                                      | P, D                | NR                                          | PV: relapsed after remission for 8 months |
| Somorin et al          | 32/F    | African           | PV                | SLE        | –                                         | Preceded by 5 years               | –                                                      | P, CS                | CS                                          | PV, SLE: under controlled          |
| Kuchabal et al         | 15/F    | Indian            | PV                | SLE        | –                                         | Preceded by 7.5 years             | –                                                      | P, CS                | CS                                          | PV, SLE: under controlled          |
| Fong and Chan          | 59/F    | Chinese           | PV                | SLE        | –                                         | After 4 months                    | –                                                      | P, AZA               | P                                           | PV: improved SLE: NR                  |
| Hidalgo-Tenorio et al  | 46/M    | Caucasian         | PV                | SLE        | –                                         | After 1 year                      | –                                                      | P                   | P, HCQ                                      | SLE: improved PV: resolved           |
| Calebotta A et al      | 35/F    | NR                | PV                | SLE        | –                                         | After 1 year                      | –                                                      | P                   | P                                           | Lost to follow-up                |
| Malik M et al          | 57/M    | NR                | PV                | SLE/MCTD   | –                                         | Preceded by 4 years               | –                                                      | P, AZA, TAC, IVlg   | P, HCQ, NSAIDs, amlodipine               | PV, SLE/MCTD: under controlled |
|                        | 43/F    | NR                | PV                | SLE        | –                                         | Simultaneous                      | –                                                      | P, D, IVlg           | Sym                                         | PV: under controlled               |
|                        | 57/F    | NR                | PV                | SLE        | –                                         | Simultaneous                      | –                                                      | D, IVlg              | Sym                                         | PV: remission for 5 years SLE: under controlled |
|                        | 49/F    | NR                | PV                | SLE        | –                                         | Preceded by 3 years               | –                                                      | P, AZA, D, MTX, IVlg | Nifedipine                               | PV, SLE: under controlled          |
|                        | 23/F    | NR                | PV                | SLE        | –                                         | Preceded by 6 years               | –                                                      | D, AZA, G, TAC, MYC, CYC, MTX, IVlg      | Sym                                         | PV, SLE: under controlled          |
|                        | 71/M    | NR                | PV                | SLE/MCTD   | –                                         | Preceded by 2 years               | –                                                      | P, D, MTX, IVlg      | P, HCQ, Nifedipine                        | PV: remission for 2 year SLE/MCTD: under controlled |

Table 1 Data on Patients with Pemphigus in Association with Lupus Erythematosus and Other Autoimmune Diseases
| Age | Gender | Race | Disease | Disease | Duration | Therapy | Management | Remission | Other Treatments |
|-----|--------|------|---------|---------|----------|---------|------------|-----------|-----------------|
| 63/F | NR | PV | SLE | – | Preceded by 2 years | – | P, AZA, MTX, IVlg | P, MTX, HCQ | PV: SLE: under controlled |
| 35/M | NR | PV | SLE/MCTD | – | Preceded by 6 years | – | P, AZA, D, IVlg | P, AZA, MTX, HCQ, NSAIDs, propranolol, oxycodone | PV: remission for 1 year SLE/MCTD: active |
| 41/F | NR | PV | SLE | – | Preceded by 1.5 years | – | P, IVlg | P, AZA, HCQ | PV: remission for 3 years SLE: active |
| 37/F | NR | PV | SLE | – | Simultaneous | – | P, D | Sym | PV: under controlled SLE: active |
| Thongprasom K et al\textsuperscript{11} | 36/F | Thai | PV | DLE | Amniopathic DM, AA | Preceded by 2 months | Preceded AA by 1 month Preceded Amniopathic DM by 1 year | P, FAO | DLE: DOX, D, CQ, MTX, Colchicine, Alternative therapy Amniopathic DM, AA: NR | PV: remission DLE: partially resolved Amniopathic DM, AA: NR |
| Bilgic Temel A et al\textsuperscript{12} | 54/M | NR | PF | DLE | – | After 4.5 years | – | NR | NR | NR |
| Ng PP et al\textsuperscript{13} | 49/F | Chinese | PF | SLE | – | After (not to mention timing) | – | P | P | PF: SLE: under controlled |
| Sawamura S et al\textsuperscript{14} | 65/F | Japanese | PF | SLE | MG, autoimmune thyroiditis | Simultaneous | Simultaneously Detected with thyroiditis Preceded MG by 4 months | P | P, CSA, CYC | Under controlled |
| Ngo et al\textsuperscript{15} | 27/F | African-American | PE | SLE | – | Simultaneous | – | NR | NR | NR |
| Itoh K et al\textsuperscript{16} | 34/F | Japanese | PE | SLE | MG | After 12 years | Simultaneously detected | CS | MG: thymectomy, anticholinesterase, PEX, CS SLE: CS | Improved |
| Aschenmann DP et al\textsuperscript{17} | 68/F | African-American | PE | SLE | – | After 8 years | – | NR | NR | NR |
| Marinović et al\textsuperscript{18} | 44/F | Caucasian | PH | SLE | – | Preceded by 2 years | – | Local therapy | P, AZA | NR |

Abbreviations: AA, alopecia areata; AZA, azathioprine; CS, corticosteroids; CSA, cyclosporine; CQ, chloroquine; CYC, cyclophosphamide; D, dapsone; DLE, discoid lupus erythematosus; DM, dermatomyositis; DOX, doxycycline; F, female; FAO, fluocinolone acetonide 0.1% Orabase; G, gold; HCQ, hydroxychloroquine; IVlg, intravenous immunoglobulin; M, male; MCTD, mixed connective tissue disease; MG, myasthenia gravis; MTX, methotrexate; MYC, mycophenolate mofetil; NR, not reported; NSAIDS, non-steroidal anti-inflammatory drugs; P, prednisolone; PE, pemphigus erythematosus; PEX, plasmapheresis; PF, pemphigus foliaceus; PH, pemphigus herpetiformis; PM, polymyositis; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris; R-CVP, rituximab/cyclophosphamide/vincristine/prednisolone; SLE, systemic lupus erythematosus; Sx, surgery; Sym, symptomatic therapy; TAC, tacrolimus.
Conclusion
We report a case of co-occurrence of discoid lupus erythematosus and paraneoplastic pemphigus associated with marginal zone lymphoma in a middle-aged Thai man. Owing to the rarity of the coexistence of these two conditions, definitive explanation to pathogenesis of the association is lacking. Further studies are warranted.

Ethics Approval and Consent to Participate
This article was performed in accordance with the principles of Declaration of Helsinki. Ethical review and approval were not required to publish the case details in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for publication of this case report and any accompanying images as per our standard institutional rules.

Disclosure
The authors report no conflicts of interest in this work.

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Figure 7 Improvement of PNP lesions of the oral mucosa (A) and DLE lesions of the upper back (B) after treatment.
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