Paraneoplastic pemphigus: A retrospective case series in a referral center in northern Taiwan

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A B S T R A C T

Background/Objectives: Paraneoplastic pemphigus (PNP) is a rare mucocutaneous disease with a high mortality rate. It is defined by polymorphic mucocutaneous manifestations, particular histological features, characteristic results of direct and indirect immunofluorescence examinations, presences of specific autoantibodies, and associations with underlying neoplasms. However, currently, there is no existing study regarding the characteristics of PNP patients in Taiwan. In this study, we report a case series and try to determine the specific presentations of PNP patients in Taiwan.

Materials and methods: PNP patients treated in a referral center in northern Taiwan from 1998 to 2012 were retrospectively recruited. The clinical manifestations, histopathological features, findings of direct and indirect immunofluorescence, results of immunoblotting, and all relevant clinical information were collected.

Results: Eleven patients were identified with an average age of 62 years. Polymorphic mucocutaneous manifestations were observed in almost all patients. The most common presentation was pemphigus-like lesions, followed by lichen planus-like lesions. All patients had recalcitrant oral mucosal lesions. Five and four patients had genital and eye involvements, respectively. The mostly associated neoplasm is Castleman's disease, followed by malignant thymoma. Acantholysis is the mostly observed histological features, followed by lichenoid dermatitis and interface dermatitis. Depositions of immunoglobulins or complements on the surface of keratinocytes or along basement membrane zone were found in eight and seven patients, respectively. Respiratory symptoms presented in eight patients. Despite intensive treatments, seven patients expired.

Conclusion: PNP in Taiwanese patients has a high association with Castleman's disease or malignant thymoma. Complete laboratory examinations and thorough investigations for occult neoplasms are mandatory to establish a diagnosis in patients with clinical suspicions of PNP.

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Introduction

Paraneoplastic pemphigus (PNP), first reported by Anhalt et al.1 in 1990, is a rare mucocutaneous disease with a very high mortality rate. Clinically, it is characterized by severe mucositis with polymorphic skin eruptions, occurring in patients with concomitant neoplasms. In the literature, most common associated neoplasms were lymphoid neoplasms, including non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Castleman's disease.2-3

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In addition, several features, including: histopathologic examination showing acantholysis and interface dermatitis; positive direct immunofluorescence (DIF) findings at the keratinocyte cell surfaces and/or along the basement membrane zone (BMZ); positive indirect immunofluorescence (IIF) results using different epithelia; and serum immunoblotting (IB) revealing a complex of five proteins of 250 kD, 230 kD, 210 kD, 190 kD, and 170 kD are demonstrated to be characteristic for PNP.4 Among them, the association with a lymphoid neoplasm, positive IIF results on rat bladder, and recognition of envoplakin (210 kD) and/or periplakin (190 kD) upon IB are the most sensitive and specific features in the diagnosis of PNP.

However, depositions of PNP autoantibodies were found in many tissues other than skin and epithelium, including kidney, urinary bladder, and muscles.5 At least five different clinical and immunopathological variants have been identified, including
lichenoid variant of PNP. The average age was 62 years (range, 30–86 years). Seven patients were male. The development of mucocutaneous manifestations months or years after the underlying neoplasms was noted in six patients. Others presented with cutaneous lesions prior to or concomitant with the diagnosis of underlying neoplasms being made.

Materials and methods

Patients with PNP treated in the National Taiwan University Hospital from 1998 to 2012 were retrospectively recruited. The diagnosis of PNP was according to the criteria proposed by Camisa and Helm, including major criteria and minor criteria. Major criteria include polymorphous mucocutaneous eruption, concurrent internal neoplasia, and characteristic serum immunoprecipitation findings. Minor criteria include positive cytoplasmic staining of rat bladder epithelium by IIF, intercellular and BMZ immunoreactants on DIF of perilesional tissue, and acantholysis in biopsy specimen from at least one anatomic site of involvement. To be diagnosed with PNP, patients must fulfill three major or two major and two minor criteria.

For patients presented with the lichenoid variant of PNP not meeting the Camisa and Helm’s criteria, we used the criteria proposed by Cummins et al. which include the following: (1) known or occult neoplasm; (2) extensive, refractory mucous membrane ulcerations; (3) histologic examination for mucosa or skin revealing lichenoid interface dermatitis; and (4) lichenoid or polymorphous blistering skin lesions and/or pulmonary involvement consistent with bronchiolitis obliterans (BO).

The demographic data, associated malignancies, presentations of cutaneous lesions, presentations of mucosal involvements, histopathological features, results of DIF and IIF, findings of IB, systemic symptoms, treatments, complications, and outcomes of all the patients were collected.

Results

Patient characteristics

Eleven patients were recruited into this study. All patients fulfilled the Camisa and Helm criteria except two cases (Cases 9 and 11), who presented with severe mucositis with predominant lichenoid skin eruptions, met the Cummin’s criteria and were diagnosed as lichenoid variant of PNP. The average age was 62 years (range, 30–86 years). Seven patients were male. The development of mucocutaneous lesions prior to or concomitant with the diagnosis of underlying neoplasms was noted in six patients. Others presented with mucocutaneous manifestations months or years after the diagnosis of underlying neoplasms being made.

Associated neoplasms

All patients had at least one neoplasm. Two of them had two concomitant neoplasms. The most common associated neoplasm was Castleman’s disease (4 cases, 36%), followed by malignant thymoma (3 cases, 27%), follicular dendritic cell sarcoma (2 cases, 18%), and non-Hodgkin’s lymphoma (2 cases, 18%). Most associated neoplasms were lymphoid neoplasms. Solid organ neoplasms were only encountered in two patients. One was squamous cell carcinoma of the lung, and the other was thyroid papillary microcarcinoma. For those presenting with concomitant neoplasms, one had follicular dendritic cell sarcoma arising from Castleman’s disease, and the other had both malignant thymoma and thyroid papillary microcarcinoma.

Mucocutaneous manifestations

Mucocutaneous manifestations of the patients were polymorphic (Figure 1 and Table 1). All patients except one had more than one kind of mucocutaneous lesion. The most common presentation was pemphigus-like, widespread, crusted erosions and ulcerations (Figure 1A), which were observed in nine patients (82%). Pemphigoid-like lesions such as hemorrhagic blisters on the palms were only occasionally found (Figure 1B). Infiltrative, purpuric, polygonal, flat-topped papules and plaques (Figure 1C) or erode lichenoid papules and plaques (Figure 1D) were the second most common feature and were found in eight patients (73%). Few patients also presented with erythema multiforme (EM)-like targetoid lesions. Pemphigus-like lesions were the predominant manifestations in six patients, while LP-like lesions were the predominant presentations in the other five patients.

All patients had extensive, refractory oral mucositis, involving lips, buccal mucosae, and tongues (Figure 1E). Genital erosions were found in five patients (45%; Figure 1F), and eye involvements were observed in four patients (36%; Figure 1G). In addition, other less common manifestations were also encountered, including paronychia (Figure 1H) and anonychia (Figure 1I).

Histopathology and immunopathology

The patterns of histopathology varied and depended on the type of cutaneous lesions being sampled. Seven of the patients received more than two skin biopsies. Of all the skin biopsies, acantholysis (Figure 2A), including suprabasal acantholysis or intraepithelial acantholysis, was mostly observed and presented in nine patients (82%). Lichenoid dermatitis (Figure 2B), that was lichenoid infiltration with apoptotic keratinocytes, was noted in skin specimen from six patients (55%). Interface dermatitis, which was basal vacuolar change with apoptotic keratinocytes (Figure 2C), was found in skin specimen from three patients (27%). Not surprisingly, to perform a clinicopathological correlation, acantholysis was mostly found in pemphigus-like lesions and lichenoid dermatitis or interface dermatitis was mostly observed in clinically LP-like or EM-like lesions, respectively.

For patterns of DIF findings, deposition of immunoglobulins or complement on the surface of keratinocytes (Figure 2D) was found in eight patients (73%). Linear deposition of immunoglobulins or complement along the BMZ (Figure 2E) was noted in seven patients (64%). Immunoglobulin M (IgM) cytid bodies (Figure 2F) were observed in three patients (27%) having LP-like lesions. For results of IIF findings, eight patients (73%) had positive serum anti-intercellular substance (ICS) antibodies using monkey esophagus as the substrates. Two of them also received IIF examinations using rat bladder as the substrates and had positive staining on the epithelium of the bladder. No patients had detectable anti-BMZ antibodies in their sera.

Immunoblotting

Immunoblotting of serum samples were performed in five patients (Table 1). Two patients had all characteristic bands corresponding to proteins of 250 kD, 230 kD, 210 kD, 190 kD, and 170 kD. One had
Table 1
Summary of the patients.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Cutaneous lesions</th>
<th>Associated neoplasms</th>
<th>Pathology</th>
<th>DIF</th>
<th>IIF</th>
<th>IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>M</td>
<td>LP, PV</td>
<td>CD, FDCS</td>
<td>Acantholysis, Lichenoid dermatitis</td>
<td>IgG: ICS+, IgM: cytoid body+</td>
<td>ICS+</td>
<td>170, 190, 210, 230, 250</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>F</td>
<td>PV, EM</td>
<td>NHL</td>
<td>Acantholysis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>ICS+</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>PV, EM</td>
<td>CD</td>
<td>Acantholysis, Interface dermatitis</td>
<td>IgG, IgA, C3: ICS+, IgM: BMZ+, linear</td>
<td>ICS+ (bladder+)</td>
<td>230, 250</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>F</td>
<td>LP, PV</td>
<td>CD</td>
<td>Acantholysis, Interface dermatitis</td>
<td>IgM: cytoid body+</td>
<td>ICS+</td>
<td>170, 190, 210, 230, 250</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>M</td>
<td>LP, EM</td>
<td>CD</td>
<td>Acantholysis (focal)</td>
<td>IgG, IgA, C3: ICS+, IgM: BMZ+, linear</td>
<td>ICS+</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>PF, LP</td>
<td>Thymoma</td>
<td>Acantholysis, Lichenoid dermatitis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>ICS+</td>
<td>190, 210</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>PV, LP</td>
<td>Thymoma</td>
<td>Acantholysis, Lichenoid dermatitis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>ICS+</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>M</td>
<td>LP</td>
<td>Thymoma</td>
<td>Lichenoid dermatitis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>ICS+ (bladder+)</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>86</td>
<td>M</td>
<td>PV, LP</td>
<td>Lung SCC</td>
<td>Lichenoid dermatitis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>ICS+</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>76</td>
<td>M</td>
<td>PV, EM</td>
<td>NHL</td>
<td>Acantholysis, Interface dermatitis</td>
<td>IgG: ICS+, C3: BMZ+, linear</td>
<td>Nil</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>M</td>
<td>LP, PV</td>
<td>Thymoma, Thyroid Ca</td>
<td>Lichenoid dermatitis</td>
<td>Nil</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

BMZ = basement membrane zone; BP = bullous pemphigoid; C3 = complement 3; CD = Castleman’s disease; DIF = direct immunofluorescence; E = eye; EM = erythema multiforme; F = female; FDCS = follicular dendritic cell sarcoma; G = genital; IB = immunoblotting; ICS = intercellular substance; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IIF = indirect immunofluorescence; LP = lichen planus; M = male; NA = not applicable; NHL = non-Hodgkin’s lymphoma; O = oral; PF = pemphigus foliaceus; PV = pemphigus vulgaris; Thyroid Ca = thyroid papillary microcarcinoma.

The order of the lesions listed in the column is based on the order of predominance in the individual patient.

Acantholysis is defined as a feature of basal vacuolation with dyskeratotic cells, while lichenoid dermatitis is applied to the finding composed of a dense band-like infiltration at upper dermis along with basal vacuolation and dyskeratotic cells.

Figure 1
Clinical presentations of patients with paraneoplastic pemphigus. (A) Pemphigus-like, widely distributed, crusted erosions on the trunk in Case 9; (B) hemorrhagic blisters on the palms in Case 10; (C) numerous lichen planus-like, erythematous or purplish, flat-topped, papules and plaques on the trunk in Case 5; (D) crusted erosive papules and plaques, which healed with residual hyperpigmentations, on the palms in Case 1; (E) recalcitrant crusted erosions and ulcers on the lips and the tongue in Case 8; (F) several erosions on the glans penis in Case 5; (G) corneal perforation in Case 6; (H) paronychia on the big toe in Case 11; and (I) anonychia affecting all finger nails in Case 1.
antibodies that reacted with 250 kD and 230 kD proteins, one had bands of 190 kD and 210 kD proteins, and another had only one band that reacted with the 40 kD protein.

**Respiratory involvement and complications**

In addition to mucocutaneous manifestations, systemic symptoms and complications occurred frequently in PNP patients (Table 2). Respiratory symptoms, including dry cough and dyspnea, were reported in eight patients (73%). Nevertheless, a diagnosis of BO was confirmed in only four patients (36%). Systemic infections were the mostly encountered complications during the period of treatment, including disseminated tuberculosis, cryptococcemia, disseminated cytomegalovirus (CMV) infection, and herpetic keratitis. Two of the four above-mentioned patients with eye involvement had severe corneal perforations (Figure 1G) and needed to receive amniotic membrane transplantations to restore their visual acuity.

**Table 2** Treatment, complications, and prognosis of the patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Respiratory symptoms</th>
<th>BO Treatment</th>
<th>Treatment for neoplasm</th>
<th>Prognosis and follow-up duration (Mo)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>CS</td>
<td>S, C/T</td>
<td>Survived, 58</td>
<td>Anonychia</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>CS, RTX</td>
<td>S, C/T</td>
<td>Died, 11</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>CS, IVIG</td>
<td>Nil</td>
<td>Died, 24</td>
<td>Cryptococcemia</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>CS, IVIG</td>
<td>S</td>
<td>Died, 9</td>
<td>Nil</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>CS</td>
<td>S</td>
<td>Died, 8</td>
<td>Corneal perforation</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>CS, CYC, AZA</td>
<td>S</td>
<td>Died, 4</td>
<td>Corneal perforation, CMV</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>CS, CYC, IVIG</td>
<td>S, C/T</td>
<td>Survived, 69</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>CS</td>
<td>S, R/T</td>
<td>Survived, 59</td>
<td>Hip fracture</td>
</tr>
<tr>
<td>9</td>
<td>–</td>
<td>CS</td>
<td>C/T</td>
<td>Died, 14</td>
<td>Herpetic keratitis</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>CS, RTX</td>
<td>C/T</td>
<td>Died, 1</td>
<td>Nil</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>CS, PE, AZA</td>
<td>S</td>
<td>Survived, 12</td>
<td>Myasthenia gravis</td>
</tr>
</tbody>
</table>

AZA = azathioprine; BO = bronchiolitis obliterans; C/T = chemotherapy; CMV = cytomegalovirus infection; CS = corticosteroids; CYC = cyclophosphamide; IVIG = intravenous immunoglobulin; Mo = month; PE = plasma exchange; RTX = rituximab; R/T = radiotherapy; S = surgery.

**Discussion**

In this study, we demonstrated characteristics of PNP patients in Taiwan. The main findings of this study are: (1) polymorphic presentations of clinical and histopathological features are observed in our patients; (2) the most common associated neoplasm is Castleman’s disease, followed by malignant thymoma; and (3) a poor prognosis and a high mortality rate are noted.
We compared the characteristics of our PNP patients with several previously reported case series (Table 3). Similar to the design of our study, Ohyma et al. and Leger et al. reported PNP cases based on a hospital-based or nationwide database without selection for a specific associated neoplasm or age groups. The average ages of the patients in these two studies were similar to our study. Unlike our study, the most common associated neoplasms of these two studies were non-Hodgkin’s lymphoma and chronic lymphocytic leukemia, respectively. Akin to our findings, polymorphic mucocutaneous manifestations are also reported in these two studies with pemphigus-like presentation as the most common mucocutaneous manifestation. Another case series reported by Choi et al. describing 12 Korean patients with paraneoplastic pemphigus has a very similar result regarding the most common associated neoplasms (Table 3). However, the most common mucocutaneous presentation in this study was EM-like lesions rather than pemphigus-like lesions. Among all studies mentioned above, the mortality rate and the extents of mucosal lesions are similar except the ocular involvement, which is less frequently observed in our study.

To clarify the reason for a higher association of Castleman’s disease in our study, we compared our study with other previously reported case series with PNP patients of Castleman’s disease. Minouni et al. reported 14 cases in children and adolescents, of which 12 were associated with Castleman’s disease. They concluded that PNP in children and adolescents is most often a presenting sign of occult Castleman’s disease. This is consistent with one of our patients (Case 1), who presented with longstanding mucocutaneous lesions since his adolescence and a mediastinal Castleman’s disease complicated with focal follicular dendritic cell sarcoma was eventually identified more than 10 years later. Similar findings were reported in another two studies reporting PNP cases exclusively associated with Castleman’s disease. The average age in both studies was young. However, only one of the four patients with Castleman’s disease in our study is young. Therefore, age of the patients in our study could not account for the higher association. The possible reason is that there is genetic predisposition because around 77% of PNP patients are associated with Castleman’s disease in China. Although the ethnic groups in Mainland China are more diverse than those in Taiwan, the majority of people are Han Chinese in both regions.

LP-like lesions are the main presentations in PNP patients associated with Castleman’s disease. Consistent with this finding, three of four patients associated with Castleman’s disease in our study have LP-like lesions as their main clinical manifestation. In addition, LP-like lesions present in all three patients were associated with malignant thymoma in this study and were the predominant clinical presentations in two of them. Although the association of pemphigus and thymoma is well established, pemphigus-like presentations are not the main finding in PNP patients associated with malignant thymoma in this study. There are some explanations for our observations. In addition to pemphigus, several reports have indicated that thymoma may be associated with LP and graft-versus-host-like diseases. Moreover, thymoma has been linked to numerous autoimmune diseases, including myasthenia gravis, hypogammaglobulinemia, alopecia areata, and pure red cell aplasia. The fact that thymus is an important immune organ to maintain central tolerance may explain the occurrence of immune dysregulation in the setting of thymic tumors. A previous study provided evidence to support this notion, demonstrating that circulating CD45RA CD8 T cells are significantly increased in patients with thymoma compared with normal controls, and intratumoral T cell development that is abnormally skewed toward the CD8 phenotype. Therefore, we propose that these abnormal CD8 T cells in patients with thymoma may account for the development of clinical LP-like presentations and histopathological lichenoid infiltrations in our patients. However, further investigations are needed to confirm our hypothesis.

The mortality rate of this study was 64%, which is comparable to the previous reports. Leger et al. found that the 1-year overall survival rate was 48%, which was consistent with our observation that most nonsurvivors died within 1 year after diagnosis. The development of respiratory symptoms might be the most important risk factor for mortality in our study. Six of seven expired patients had respiratory symptoms, including dry cough and dyspnea. Four of them had a confirmed diagnosis of BO. In line with our finding, pulmonary injury with respiratory failure has been demonstrated to be the cause of death in most PNP patients associated with Castleman’s disease. In addition, infections account for death in the majority of cases in another study, which might have resulted from the use of high dose immunosuppressants. Indeed, high-dose corticosteroids and/or combined with other immunosuppressants or immunomodulators were used in all of our patients. Several episodes of infections were encountered in our patients as above mentioned. We think that infections work synergistically with respiratory involvement in these patients leading to a fatal outcome. In addition to these causes of death, PNP patients with EM-like skin lesions have been demonstrated to have a more severe and rapid fatal outcome. Four patients with EM-like presentations in our study did have more refractory courses and all of them died.

In this study, treatments for PNP and treatments for underlying neoplasms did not seem to affect the prognosis, which is consistent with previous studies. However, a promising outcome has been reported in a study composed of 22 PNP patients associated with Castleman’s disease, thymoma, and follicular dendritic cell sarcoma, who received surgical resections of their neoplasms. Only 27% of the patients died in that study. Of note, respiratory symptoms persisted in 13 patients. The similar scenario occurred in Case 1 of this study, whose mucocutaneous lesions became stable after the operation despite the respiratory symptoms persisted. Nevertheless, another of our patients, Case 11, experienced exacerbation of respiratory symptoms and development of myasthenia gravis after surgical removal of a malignant thymoma.

Four of our patients had eye involvement. Two of them had severe corneal perforations and required an amniotic membrane transplantation. Corneal perforations or melting in PNP patients have been reported. The exact mechanism is still undetermined. Both humoral and cellular mechanisms might be involved in the pathogenesis of the disease. Although the best

Table 3 Comparison of the present study with previously reported case series of paraneoplastic pemphigus in the literature.

<table>
<thead>
<tr>
<th>Present study</th>
<th>Ohyma et al.</th>
<th>Leger et al.</th>
<th>Choi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case number</td>
<td>11</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>Average age (y)</td>
<td>62</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td>The first three most commonly associated neoplasms</td>
<td>CD, NHL</td>
<td>CD, NHL</td>
<td>CD, FDCS</td>
</tr>
<tr>
<td>The most common skin lesion</td>
<td>Pemphigus-like</td>
<td>Pemphigus-like</td>
<td>Pemphigus-like</td>
</tr>
<tr>
<td>Mucosa involvement</td>
<td>Oral: 100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Genital: 45</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Ocular: 36</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Respiratory symptom</td>
<td>73</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>64</td>
<td>68</td>
<td>50</td>
</tr>
</tbody>
</table>

Data are presented as % unless otherwise specified. CD = Castleman’s disease; CLL = chronic lymphocytic leukemia; EM = erythema multiforme; FDCS = follicular dendritic cell sarcoma; LP = lichen planus; NA = not applicable; NHL = non-Hodgkin’s lymphoma.
treatment for this condition is not fully investigated, amniotic membrane transplants are the current standard of treatment and work well in our patients to prevent symblephara and further deterioration of visual acuity. Patients with PNP should be monitored for the possibility of eye involvement and evaluate whether corneal erosion or melting is present. Early identification with prompt management can reduce the risk of irreversible damage of visual acuity.

In conclusion, to the best of our knowledge, our study is the first case series of PNP in Taiwan and outlines the characteristics of these patients. Polymorphic mucocutaneous presentations, frequent associations with Castleman’s disease and malignant lymphoma, and a poor prognosis with a high mortality rate indicate that a high clinical suspicion, a thorough investigation for underlying neoplasm, and intensive treatments are mandatory to manage patients with PNP.

References