Paraneoplastic pemphigus a retrospective case biology essay

Science, Biology

Dermatologica SinicaManuscript DraftManuscript Number: DSI-D-13-00010referral center in northern TaiwanArticle Type: Original Article*Manuscript without author detailsClick here to view linked ReferencesOriginal ArticlesParaneoplastic pemphigus: A retrospective case series in a referral center innorthern TaiwanAbstractBackground/Objectives GParaneoplastic pemphigus (PNP) is a rare mucocutaneousdisease with a high mortality rate. It is defined by polymorphic mucocutaneousmanifestations, particular histological features, characteristic results of direct andindirect immunofluorescence examinations, presences of specific auto-antibodies, andassociations with underlying neoplasms. However, currently, there is no existing studyregarding to the characteristics of PNP patients in Taiwan. In this study, we report acase series and try to figure out the specific presentations of PNP patients in Taiwan. Methods GWe retrospectively recruited PNP patients treated in a referral center innorthern Taiwan from 1998 to 2012. We collected the clinical manifestations, histopathological features, findings of direct and indirect immunofluorescence, resultsof immunoblotting, and all relevant clinical information. Results GEleven patients were identified with an average age of 62 years old. Polymorphic mucocutaneous manifestations were observed in almost all the patients. The most common presentation is pemphigus-like lesions, followed by lichenplanus-like lesions. All patients had recalcitrant oral mucosal lesions. Five and fourpatients had genital and eye involvements, respectively. The mostly associatedneoplasm is Castleman s disease, followed by malignant thymoma. Acantholysis isthe mostly observed histological features, followed by lichenoid dermatitis

andinterface dermatitis. Depositions of immunoglobulins or complements on the surfaceof keratinocytes or along basement membrane zone were found in eight and sevenpatients, respectively. Respiratory symptoms presented in eight patients. Despiteintensive treatments, seven patients expired. Conclusion GPatients with PNP in Taiwan is unique with a high association withCastleman s disease or malignant thymoma. Complete laboratory examinations andthorough investigations for occult neoplasms are mandatory to establish a diagnosis ofPNP in patients with high clinical suspicions. Key words: Castleman s disease, Lymphoma, Paraneoplastic pemphigus, ThymomaIntroductionParaneoplastic pemphigus (PNP), first reported by Anhalt et al1 in 1990, is a raremucocutaneous disease with a very high mortality rate. Clinically, it is characterizedby severe mucositis with polymorphic skin eruptions, occurring in patients withconcomitant neoplasms. In the literature, most common associated neoplasms werelymphoid neoplasms, including non-Hodgkin s lymphoma, chronic lymphocyticleukemia, and Castleman s disease. 2, 3In addition, several features, including histopathologic examination showingacantholysis 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, 230, 210, 190 and 170 kd are demonstrated to be characteristic for PNP. 4 Among them, theassociation with a lymphoid neoplasm, positive IIF results on rat bladder, andrecognition of envoplakin (210-kd) and/or periplakin (190-kd) upon IB are the mostsensitive and specific features in the diagnosis of

PNP. 5However, depositions of PNP autoantibodies were found in many tissues otherthan skin and epithelium, including kidney, uninary bladder, and muscles. 6 Besides, atleast five different clinical and immunopathological variants were identified, including pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like. Therefore, Nguyan et al. 6proposed a more encompassing term ��paraneoplastic autoimmune multiorgansyndrome (PAMS)��. In addition, several unusual cases were reported, includingpatients without a underlying neoplasm, 7 patients with lichenoid eruptions withoutdetectable autoantibodies, 8 and patients without mucosal involvement. 9 All of thesepoint out the complexity of the disease, the variety of mucocutaneous presentationsand organ involvements, and the need for further investigations. To date, only several case series have been reported in the literature due to rarityof the disease. In this study, we retrospectively collected PNP patients in a referralcenter in northern Taiwan and analyze the characteristics of this rare disease in thedomestic region. MethodsWe retrospectively recruited patients of PNP treated in the National Taiwan UniversityHospital from 1998 to 2012. The diagnosis of PNP was according to the criteriaproposed by Camisa and Helm, 10 including major criteria and minor criteria. Majorcriteria include polymorphous mucocutaneous eruption, concurrent internal neoplasia, and characteristic serum immunoprecipitation findings. Minor criteria include positivecytoplasmic staining of rat bladder epithelium by IIF, intercellular and BMZimmunoreactants on DIF of perilesional tissue, and acantholysis in biopsy specimenfrom at least one anatomic site of involvement. Patients must fulfill with three majoror two

major and two minor criteria to be diagnosed with PNP. For patients presented with lichenoid variant of PNP not meeting the Camisa andHelm��s criteria, we used the criteria proposed by Cummins et al., 8 which include thefollowing: (1) known or occult neoplasm; (2) extensive, refractory mucous membraneulcerations; (3) histologic examination for mucosa or skin revealing lichenoidinterface dermatitis; and (4) lichenoid or polymorphous blistering skin lesions and/orpulmonary involvement consistent with bronchiolitis obliterans (BO). We collected demographic data, associated malignancies, presentations ofcutaneous lesions, presences of mucosal involvements, histopathological features, results of DIF and IIF, findings of IB, systemic symptoms, treatments, complications, and outcomes of all the patients. ResultsPatient characteristicsEleven patients were recruited into this study. All patients were fulfilled with theCamisa and Helm��s criteria except two cases (Case 9 and 11). Both Case 9 and Case11, presenting with severe mucositis with predominant lichenoid skin eruptions, metthe Cummin��s criteria and were diagnosed as lichenoid variant of PNP. The averageage was 62 years old (range 30-86). Seven patients were male and the other fourpatients were female. The development of mucocutaneous lesions before orconcomitant with the diagnosis of underlying neoplasms was noted in six patients. Others presented with mucocutaneous manifestations months or years after thediagnosis of underlying neoplasms being made. Associated neoplasmsAll patients had at least one neoplasm. Two of them had two concomitant neoplasms. The most common associated neoplasm was Castleman��s disease (four cases, 36%), followed by malignant thymoma (three cases,

27%), follicular dendritic cell sarcoma(two cases, 18%) and non-Hodgkin��s lymphoma (two cases, 18%). Most associatedneoplasms were lymphoid neoplasms. Solid organ neoplasms were only encounteredin two patients. One was squamous cell carcinoma of the lung, and the other wasthyroid papillary microcarcinoma. For those presenting with concomitant neoplasms, one had follicular dendritic cell sarcoma arising from Castleman��s disease, and theother had both malignant thymoma and thyroid papillary microcarcinoma. Mucocutaneous manifestationsMucocutaneous manifestations of the patients were polymorphic (Figure 1 and Table1). All patients except one had more than one kind of mucocutaneous lesions. Themost common presentation was pemphigus-like, widespread, crusted erosions andulcerations (Figure 1A), which were observed in nine patients (82%). Pemphigoid-like lesions such as hemorrhagic blisters on the palms were onlyoccasionally found (Figure 1B). Infiltrative, purpuric, polygonal, flat-topped papulesand plaques (Figure 1C) or erosive lichenoid papules and plaques (Figure 1D) werethe second most common feature and were found in eight patients (73%). Fewpatients also presented with erythema multiforme (EM)-like targetoid lesions. Pemphigus-like lesions were the predominant manifestations in six patients, whileLP-like lesions were the predominant presentations in other five patients. All patients had extensive, refractory oral mucositis, involving lips, buccalmucosae, 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, includingparonychia (Figure 1H) and anonychia

(Figure 1I). Histopathology and immunopathologyThe patterns of histopathology varied and depended on the type of cutaneous lesionsbeing sampled. Seven of the patients received more than two skin biopsies. Of all theskin biopsies, acantholysis (Figure 2A), including suprabasal acantholysis orintra-epithelial acantholysis, was mostly observed and presented in nine patients(82%). Lichenoid dermatitis (Figure 2B), that was lichenoid infiltration with apoptotickeratinocytes, was noted in skin specimen from six patients (55%). Interfacedermatitis, that was basal vacuolar change with apoptotic keratinocytes (Figure 2C), was found in skin specimen from three patients (27%). Not surprisingly, to perform aclinico-pathological correlation, acantholysis was mostly found in pemphigus-likelesions and lichenoid dermatitis or interface dermatitis was mostly observed inclinically LP-like or EM-like lesions, respectively. For patterns of DIF findings, depositions of immunoglobulins or complementson the surface of keratinocytes (Figure 2D) were found in eight patients (73%). Lineardepositions of immunoglobulins or complements along BMZ (Figure 2E) werenoticed in seven patients (64%). Immunoglobulin M (IgM) cytoid bodies (Figure 2F)were observed in three patients (27%) having LP-like lesions. For results of IIFfindings, eight patients (73%) had positive serum anti-intercellular substance (ICS)antibodies using monkey esophagus as the substrates. Two of them also received IIFexaminations using rat bladder as the substrates and had positive staining on theepithelium of the bladder. No patients had detectable anti-BMZ antibodies in theirsera. ImmunoblottingImmunoblotting of serum samples were performed in five patients (Table 1). Twopatients had all characteristic bands corresponding to 250, 230, 210, 190, and 170-kdproteins. One had

antibodies reacted with 250 and 230-kd proteins, one had bands atmolecular weights of 190 and 210-kd, and another had only one band reacted with40-kd protein. Respiratory involvement and complicationsIn addition to mucocutaneous manifestations, systemic symptoms and complicationsoccurred frequently in PNP patients (Table 2). Respiratory symptoms, including drycough and dyspnea, were reported in eight patients (73%). Nevertheless, a diagnosisof BO was confirmed in only four patients (36%). Systemic infections were themostly encountered complications during the period of treatment, includingdisseminated tuberculosis, cryptococcemia, disseminated cytomegalovirus (CMV)infection, and herpetic keratitis. Two of the four above-mentioned patients with eyeinvolvement had severe corneal perforations (Figure 1G) and needed to receiveamniotic membrane transplantations to restore their visual acuity. Treatment and prognosisAll patients received high dose of systemic corticosteroids (Table 2). The maximaldosage was daily 2-4 mg per kilogram body weight. Intravenous immunoglobulin(IVIG) was used in three patients with a dosage of 2 gram per kilogram body weight. Rituximab infusions with a dosage of 375 mg per square-meter body surface area(mg/m2 BSA) were performed in two patients. Both patients had underlyinglymphomas. Cyclophosphamide and azathioprine were both used in two of thepatients. For treatments of underlying neoplasms, surgical interventions wereperformed in eight patients (73%). Chemotherapies were used in five patients (55%). Two of them had lymphomas. Two patients had follicular dendritic cell sarcomas, andanother one had squamous cell carcinoma of the lung. Radiotherapy was applied onone patient (9%) with invasive lymphoma. Only one patient did

not receive anytreatment for the underlying neoplasm because of the huge size of the tumor and poorgeneral condition. The prognosis of the patients was dismal. Seven patients expired within 1-2years after establishing the diagnosis of PNP. The mortality rate was 64%. All patientswith a confirmed diagnosis of BO passed away rapidly after development ofrespiratory symptoms. For those patients being alive, two of them had symptoms ofrespiratory distress, but none of them had a confirmed diagnosis of BO. DiscussionIn this study, we demonstrated characteristics of PNP patients in Taiwan. The mainfindings of this study are (1) polymorphic presentations of clinical andhistopathological features are observed in our patients, (2) the most commonassociated 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 previouslyreported case series (Table 3). Like the design of our study, Ohyma et al. 11 and Legeret al. 12 reported PNP cases based on a hospital-based or nationwide database withoutselection for a specific associated neoplasm or age groups. The average ages of thepatients in these two studies are similar with our study. The most common associatedneoplasm of these two studies, which is different with us, is non-Hodgkin��slymphoma and chronic lymphocytic leukemia, respectively. Like our findings, polymorphic mucocutaneous manifestations are also reported in these two studieswith pemphigus-like presentation as the most common mucocutaneous manifestation. The mortality rate and the extents of mucosal lesions are also similar except the ocularinvolvement, which is less frequently observed in our study. To clarify the reason of a higher

association of Castleman��s disease in our study, we compared our study with other previously reported case series with PNP patientsof Castleman��s disease (Table 3). Minouni et al. 13 reported fourteen cases in childrenand adolescents, in which twelve were associated with Castleman��s disease. Theyconclude that PNP in children and adolescents is most often a presenting sign ofoccult Castleman��s disease. This is consistent with one of our patients (Case 1), whopresented with longstanding mucocutaneous lesions since his adolescence and amediastinal Castleman��s disease complicated with focal follicular dendritic cellsarcoma was eventually identified more than 10 years later. Similar findings arereported in another two studies reporting PNP cases exclusively associated with14, 15Castleman��s disease. The average age in both studies is young. However, onlyone of the four patients with Castleman��s disease in our study is young. Therefore, ageof the patients in our study could not account for the higher association. The possiblereason is that there is genetic predisposition because around 77% of PNP patients areassociated with Castleman��s disease in China. 15 Although the ethnic groups inMainland China are more diverse than those in Taiwan, the majority of people arebelong to Han Chinese in both regions. Lichen planus-like lesions are the main presentations in PNP patients associated13-15with Castleman��s disease. Being consisted with this finding, three of four patientsassociated with Castleman��s disease in our study have LP-like lesions as their mainclinical manifestation. In addition, LP-like lesions present in all three patientsassociated with malignant thymoma in this study and are the predominant clinicalpresentations in two of them. Although the

association of pemphigus and thymoma iswell established, 16 pemphigus-like presentations are not the main finding in PNPpatients associated with malignant thymoma in this study. There are some reasonswhich could explain our observations. In addition to pemphigus, several reports have17, 18indicated that thymoma may be associated with lichen planusandgraft-versus-host-like diseases. 19 Moreover, thymoma has been linked to numerousautoimmune diseases, including myasthenia gravis, hypogammaglobulinemia, alopecia areata, pure red cell aplasia, and so on. 20 The fact that thymus is an importantimmune organ to maintain central tolerance is logical to explain the occurrence ofimmune dysregulation in the setting of thymic tumors. 21 A previous study hasprovided evidences to support this notion. They demonstrated circulatingCD45RA+CD8+ T cells is significantly increased in patients with thymoma comparedwith normal controls as well as intratumoral T cell development that is abnormallyskewed toward the CD8+ phenotype. 22 Therefore, we propose that these abnormalCD8+ T cells in patients with thymoma may account for the development of clinicalLP-like presentations and histopathological lichenoid infiltrations in our patients. However, further investigations are needed to confirm our hypothesis. The mortality rate of this study is 64%, which is comparable to the previousreports. Leger et al. 12 found 1-year overall survival rate was 49% which wasconsistent with our observation that most of the expired cases passed away within 1-2years after diagnosis. The development of respiratory symptoms might be the mostimportant risk factor for mortality in our study. Six of seven expired patients hadrespiratory symptoms, including dry cough and dyspnea. Four of them had aconfirmed

diagnosis of BO. In line with our finding, pulmonary injury withrespiratory failure has been demonstrated to be the cause of death in most PNPpatients associated with Castleman��s disease. 14 In addition, infections account for thecause of death in the majority of cases in another study, 12 which might be resultedfrom the use of high dose immunosuppressants. Indeed, high dose corticosteroidsand/or combined with other immunosuppressants or immunomodulators were used inall of our patients. Several episodes of infections were encountered in our patients asabove mentioned. We think that infections work synergistically with respiratoryinvolvements in these patients leading to a fatal outcome. In addition to these causesof death, PNP patients with EM-like skin lesions have been demonstrated to have amore severe and rapid fatal outcome. 12 Four patients with EM-like presentations inour study did have more refractory courses and all of them expired. In this study, treatments for PNP and treatments for underlying neoplasms seem12, 14not to affect the prognosis, which is consistent with previous studies. However, apromising outcome has been reported in a study composed of 22 PNP patientsassociated with Castleman��s disease, thymoma, and follicular dendritic cell sarcoma, who received surgical resections of their neoplasms. 23 Only 27% of the patientsexpired in that study. Of note, respiratory symptoms persisted in 13 patients. Thesimilar scenario occurred in Case 1 of this study, whose mucocutaneous lesionsbecame stationary after the operation despite the respiratory symptoms persisted. Nevertheless, another patient, Case 11 of our patients, experienced exacerbation ofrespiratory symptoms and development of myasthenia gravis after surgical removal ofmalignant thymoma. Four of our patients had eye

involvement. Two of them had severe cornealperforations and required an amniotic membrane transplantation. Corneal perforations24, 25or melting in PNP patients have been reported. The exact mechanism is still26 27undetermined. Both humoraland cellularmechanisms might be involved in thepathogenesis of the disease. Although the best treatment for this condition is not fullyinvestigated, amniotic membrane transplantations are the current standard oftreatment and work well in our patients to prevent symblephara and furtherdeterioration of visual acuity. Patients with PNP should monitor for the possibility ofeye involvements and evaluate whether corneal erosions or melting present. Earlyidentification with prompt management can reduce the risk of irreversible damage ofvisual acuity. In conclusion, our study is the first case series of PNP in Taiwan and outlines thecharacteristics of these patients. Polymorphic mucocutaneous presentations, frequentassociations with Castleman��s disease and malignant lymphoma, and a poor prognosiswith a high mortality rate indicate that a high clinical suspicion, a thoroughinvestigation for underlying neoplasm, and intensive treatments are mandatory tomanage patients with PNP.