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ORIGINAL ARTICLE

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

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ABSTRACT

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]

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.[5]

However, depositions of PNP autoantibodies were found in many tissues other than skin and epithelium, including kidney, urinary bladder, and muscles.[6] At least five different clinical and immunopathological variants have been identified, including

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pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus (LP)-like. Therefore, Nguyan et al.[6] proposed a more encompassing term "paraneoplastic autoimmune multiorgan syndrome". In addition, several unusual cases were reported, including patients without a underlying neoplasm,[7] patients with lichenoid eruptions without detectable autoantibodies,[8] and patients without mucosal involvement.[9] All of these emphasize the complexity of the disease, the variety of mucocutaneous presentations and organ involvements, and the need for further investigations.

To date, only a few case series have been reported in the literature due to the rarity of the disease. In this study, we retrospectively collected PNP patients in a referral center in northern Taiwan and analyzed the characteristics of this rare disease in the domestic region.

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,[10] 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,[8] 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, presences 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 erosive 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 clinico-pathological 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) cytoid 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

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