Exfoliative Erythroderma: An Unusual Presentation of Paraneoplastic Pemphigus Associated with Castleman’s Disease

Thirawut Sirikham\textsuperscript{a, b}, Weeratian Tawanwongsri\textsuperscript{b}, Suthinee Rutnin\textsuperscript{b}, Kumutnart Chanprapaph\textsuperscript{b}, Vasanop Vachiramon\textsuperscript{b}

\textsuperscript{a}Division of Dermatology, Department of Medicine, Suratthani Hospital, Suratthani, Thailand; \textsuperscript{b}Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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Abstract
We report a 23-year-old woman who presented with generalized scaly erythematous rash predominantly on the upper trunk and hemorrhagic stomatitis. The histopathologic and immunopathologic findings were consistent with the diagnosis of paraneoplastic pemphigus. Castleman’s tumor was diagnosed with computed tomography and exploratory laparotomy. A partial clinical improvement was observed after complete tumor removal and intravenous immunoglobulin administration. However, the patient died as a result of septicemia.

Introduction
Paraneoplastic pemphigus (PNP) is an uncommon autoimmune blistering disease characterized by intractable stomatitis, polymorphous cutaneous eruption, and neoplasm. It was
first described by Anhalt et al. in 1990 [1]. The exact pathogenesis of PNP is still unclear. However, the tumor may cause immune dysregulation leading to autoantibody production targeting epidermal cell surface antigens such as desmoplakin I (250 kD), bullous pemphigoid antigen I (230 kD), desmoplakin II (210 kD), envoplakin (210 kD), periplakin (190 kD), plectin (500 kD), and a 170-kD protein. This condition presents most frequently between the age of 45 and 70 years, but also occurs in the younger age group. Apart from skin and oral mucosa involvement, PNP can affect the gastrointestinal and respiratory tract epithelium. The prognosis is generally poor. Progression of malignant tumors may be inevitable. Moreover, sepsis complications and bronchiolitis obliterans are frequent causes of mortality in PNP.

Case Report

A 23-year-old female was referred to our university-based hospital with generalized skin rash and oral ulcer for 6 weeks. The rash first appeared on the trunk and gradually progressed to involve all extremities as well as the face. There was no history of recent upper respiratory tract infection. She had no underlying skin disease or systemic disease and did not take any medication. She was treated with intravenous dexamethasone 20 mg daily, intravenous acyclovir, and oral azithromycin for 5 days by a local dermatologist without clinical improvement.

On examination, temperature was 37.3°C, pulse 92 beats per minute, blood pressure 130/70 mm Hg, and respiratory rate 20 breaths per minute. Dermatologic examination showed generalized scaly erythema with multiple foci of atypical targetoid lesions on the trunk and all extremities as well as the face. Bilateral conjunctival injection, scaly hemorrhagic crusted erosion on both upper and lower lips, as well as mild erosion on bilateral buccal mucosa and genital site were noted (Fig. 1). Lymph nodes were palpable. The remaining examinations were unremarkable.

A 4-mm punch biopsy was performed on a lesion of the chest. Routine histopathology demonstrated superficial perivascular infiltration (predominately consisting of lymphocytes and eosinophils), mild epidermal hyperplasia, basal vacuolization, exocytosis, scattered necrotic keratinocyte, as well as prominent melanophages (Fig. 2). Direct immunofluorescence study showed intercellular deposition of IgG resembling chicken wire feature and linear basement membrane zone staining with IgG and C3 (Fig. 3).

Blood samples for indirect immunofluorescence test disclosed circulating IgG autoantibodies directed against transitional epithelial cells of rat bladder. Anti-desmoglein 1 and anti-desmoglein 3 via the enzyme-linked immunosorbent assay technique were 47.97 U/mL and >200 U/mL (normal <20 U/mL), respectively. Anti-BP180 was >200 RU/mL (normal <20 RU/mL) and anti-BP230 was negative. Herpes simplex virus type 1 and 2 DNA, Venereal Disease Research Laboratory, Treponema pallidum hemagglutination assay, as well as Mycoplasma titer were all negative. We were unable to perform immunoblotting, but given the clinical, histopathologic, as well as direct and indirect immunofluorescence results, the diagnosis was consistent with PNP. Computed tomography with contrast of the chest and abdomen revealed a 6.7 × 5.5 cm, markedly enhancing oval-shaped structure at the left para-aortic region surrounded by dilated vessels. According to the computed tomographic findings, a provisional diagnosis of Castleman’s disease (CD) was made.

The patient was treated with intravenous immunoglobulin (IVIG) 2 g/kg/day over 5 consecutive days and surgical removal of the tumor. The pathologic findings were compatible with hyaline-vascular type CD. Although there was substantial improvement in the truncal lesions 10 days after IVIG administration, the lesions on acral area and the oral lesions were
refractory to treatment. Two weeks after the complete 5-day course of IVIG, the patient died as a result of Staphylococcus and Acinetobacter septicemia.

**Discussion**

Varied morphologic presentations of PNP have been described, including erythematous macules, flaccid blisters and erosions (pemphigus-like), tense blisters (pemphigoid-like), erythema multiforme-like lesions, lichenoid eruptions (lichen planus-like), and graft-versus-host-like eruptions [2–4]. However, intractable hemorrhagic stomatitis is typically reported as the hallmark feature of this disorder. In adult patients, the three most common neoplasm associated with PNP were non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and CD [5]. However, Ohzono et al. [6] described malignant solid tumor as one of the most common neoplasms associated with PNP. Nearly three-fourths of CD are found in the mediastinum, followed by the retroperitoneal regions and pelvis [7, 8]. CD, discovered by Benjamin Castleman in 1954 [9], originally described a male patient with prolonged fever, nonproductive cough, and mediastinal lymph node hyperplasia resembling thymoma [10]. Three subtypes of CD were later classified. The most common subtype of CD was hyaline-vascular lesion followed by plasmacytoid subtype and mixed subtype [11]. Corresponding to the finding in our patient, the hyaline-vascular subtype often presents as a solitary mass, albeit the plasmacytoid subtype is characterized by multifocal involvement [12].

The pathophysiologic mechanism of PNP has not been well established. It was hypothesized that lymphoid neoplasms cause immune dysregulation leading to autoantibody production and immune cross-reaction against tumor with the epidermal cell surface antigens [13]. Interferon-gamma, interferon-omega, interleukin-6, and interleukin-12 were also described as playing crucial roles in the pathogenesis [14, 15].

Early total tumor resection is mandatory to achieve resolution of unicentric CD [12, 16]; otherwise, the patients – particularly with erythema multiforme-like skin lesions with extensive skin or mucosal involvement – may face a poor prognosis. The major causes of death included bronchiolitis obliterans followed by sepsis and gastrointestinal bleeding [17]. Systemic corticosteroids, immunosuppressive agents, or IVIG should be commenced as an additional treatment. In patients with severe infection, IVIG should be considered. The reported benefits of IVIG included temporary improvement of skin lesions and prevention of respiratory complications [18, 19]. An antibody titer reduction of up to 43% has been report after 4 weeks of IVIG alone for PNP [20]. This reflects good immunologic response for IVIG. Clinical response and achievement of cutaneous and mucosal improvement, however, may take longer.

Our patient, diagnosed with PNP associated with CD, presented with exfoliative dermatitis with some features of atypical target lesions. To the best of our knowledge, exfoliative erythroderma is an exceedingly rare presentation of PNP. Dermatopathologic study together with immunopathology plays a crucial role in achieving the accurate diagnosis of PNP, allowing prompt management for this fatal disease. Further study focusing on pathogenesis with targeted therapy remains still a glimmer of hope for a treatment with better outcomes.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The patient gave written informed consent for publication of his case (including publication of images). The study was done according to the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T. Sirikham and W. Tawanwongsri collected the data and wrote the initial manuscript draft. S. Rutnin wrote the pathologic description and manuscript. K. Chanprapaph wrote the manuscript and did language editing. V. Vachiramon evaluated and revised the manuscript and is the corresponding author. All authors provided critical feedback and contributed to the final version of the manuscript.

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Fig. 1. Hemorrhagic crust, scaly erosion on the lips, and generalized erythroderma with some foci of atypical target lesions on the face, trunk, and upper extremities (a, b).
Fig. 2. Superficial perivascular infiltration (predominately consisting of lymphocytes and eosinophils), mild epidermal hyperplasia, basal vacuolization, exocytosis, scattered necrotic keratinocytes, and prominent melanophages. Hematoxylin-eosin, original magnification ×400.

Fig. 3. Direct immunofluorescent study showed intercellular deposition of IgG resembling chicken wire feature and linear basement membrane zone staining with IgG (a) and C3 (b).