CASE REPORT

Paraneoplastic Pemphigus and Myasthenia Gravis associated with Unicentric Castleman Disease: A Case Report

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Background: Paraneoplastic pemphigus is a rare autoimmune blistering skin disease presenting with intractable erosive stomatitis and polymorphic cutaneous lesions including pemphigus-like lesions, bullous pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like manifestations. Associated neoplasms are non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease. The mortality rate of this disease was high.

Case Report: The authors reported a case of a 24-year-old man who had paraneoplastic pemphigus and myasthenia gravis associated with unicentric Castleman disease. He presented with stomatitis and ulcerated lichenoid lesions on his hands and feet, along with paronychial involvement and nail dystrophy for many months. Histopathological findings from the skin lesions showed vacuolar interface dermatitis. Direct immunofluorescence demonstrated deposition of IgG and C3 at the dermo-epidermal junction. Indirect immunofluorescence using rat bladder epithelium revealed circulating IgG antibodies in the intercellular space. Additionally, he had ptosis and proximal muscle weakness due to myasthenia gravis and left upper quadrant abdominal mass, with histological confirmation of unicentric Castleman disease, hyaline vascular type. The diagnosis of paraneoplastic pemphigus and myasthenia gravis associated with unicentric Castleman disease was made. He had initially been treated with prednisolone and mycophenolate mofetil. Tumor removal was later performed. Mucocutaneous lesions and weakness gradually improved within three months after the operation. Currently, the disease has been well controlled with prednisolone.

Conclusion: Paraneoplastic pemphigus can present as intractable stomatitis and lichen planus-like lesions. High suspicion can lead to proper investigations to confirm the diagnosis and subsequently seek an associated neoplasm. The treatment includes treatment of associated neoplasm and a combination of systemic corticosteroids with immunosuppressants, including mycophenolate mofetil for this patient.

Keywords: Paraneoplastic pemphigus; Myasthenia gravis; Castleman disease; Case report

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Paraneoplastic pemphigus (PNP) is a rare autoimmune blistering skin disease associated with various neoplasms, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease[1]. Here, the authors reported a case of paraneoplastic pemphigus and myasthenia gravis associated with unicentric Castleman disease, in which the patient presented with intractable stomatitis and ulcerative lichenoid lesions on the hands and feet, along with paronychial involvement.

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Case Report

A 24-year-old man presented with persistent oral erosions for 1 year. Three months later, he developed painful genital erosions and ulcerated skin lesions on both hands and feet, accompanied by paronychia and nail dystrophy. He went to see a doctor at a nearby hospital. Skin biopsies from the left hand and genital area were performed, and the results were consistent with lichen planus. Methotrexate was prescribed but discontinued because of recurrent pneumonia. Prednisolone 40 mg/day was then initiated for 3 months but no significant improvement in his condition was detected.

Seven months later, the patient noticed diplopia, dysphagia, and proximal muscle weakness. He also reported a weight loss of 8 kg over 6 months. New rashes had developed on his trunk. The patient was referred to

Srinagarind Hospital, Khon Kaen University, in February 2022 for further management.

The patient denied any past medical history. He stopped smoking and drinking alcohol 3 months before admission.

The physical examination revealed a hyposthenic-built man with stable vital signs. Hemorrhagic crusting on the lips (Figure 1A) and erosions on the buccal mucosa were observed. No conjunctivitis or other ocular inflammations was detected. Additionally, there were erythematous maculopapular rashes with minimal scaling on the trunk (Figure 1B), ulcerated violaceous erythematous plaques on the hands, particularly prominent on the dorsal surfaces of the interphalangeal and metacarpophalangeal joints (Figure 1C), as well as on the feet. Erosive erythematous patches were also present on the genitalia. Paronychial involvement with dystrophic nails on both hands and feet was noted (Figure 1D). During abdominal examination, a palpable firm-consistency mass, 8 cm in diameter, with a smooth surface was detected in the left upper quadrant. Neurological examination showed an alert patient with pupils of 3 mm diameter reacting to light in both eyes, full extraocular movement, bilateral ptosis, no facial palsy, proximal muscle weakness graded at 4/5, normoreflexia, and intact sensation.

Skin biopsies on the right 2nd finger and chest wall were performed. A histological examination from the right 2nd finger revealed mild acanthotic epidermis, basal vacuolar degeneration with scattered necrotic keratinocytes, and superficial perivascular lymphocytic infiltrate accompanied by melanophages. Colloid bodies were also noted in the papillary dermis (Figure 2A). The section from the chest wall revealed basal vacuolar degeneration and scattered necrotic keratinocytes. Superficial perivascular lymphocytic infiltrate with hemosiderin was observed (Figure 2B). Direct immunofluorescence (DIF) showed positive for IgG and complement (C3) at the dermo-epidermal junction. Indirect immunofluorescence (IIF) using rat bladder epithelium showed positive for IgG anti-intercellular space (Figure 2C).

The complete blood count and blood chemistry were normal. The viral hepatitis profile, anti-HIV, anti-nuclear antibody, anti-dsDNA, rapid plasma reagin, and anti-Treponema pallidum tests were all negative. Chest radiography showed no abnormalities. Electrodiagnosis revealed a post-synaptic neuromuscular junction disorder compatible with generalized myasthenia gravis. The blood test for anti-acetylcholine receptor IgG was positive. Abdominal computed tomography revealed a 7x7.1x9.8 cm circumscribed vividly enhancing mass with intralesional calcification in the left upper quadrant of the abdomen, with an unidentifiable organ of origin, likely indicating an intraperitoneal lesion (Figure 3A). An open laparotomy was performed, revealing a mass in the left upper quadrant of the abdomen. The tumor was completely removed, and the gross

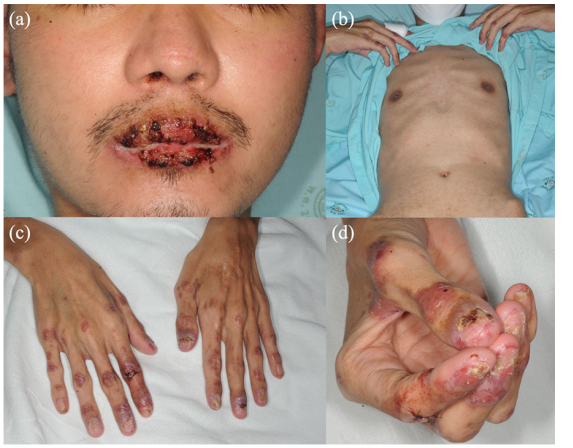

Figure 1. A) Hemorrhagic crusting on lips. B) Erythematous maculopapular rash with minimal scale on the trunk. C) Ulcerated violaceous erythematous plaques on hands which were prominent on the dorsal surface of interphalangeal and metacarpophalangeal joints. D) Paronychial involvement with dystrophic nails of hands.

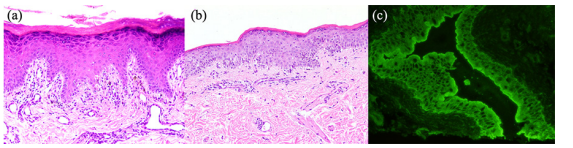

Figure 2. A) Skin from the right second finger revealed mild acanthotic epidermis, basal vacuolar degeneration with scattered necrotic keratinocytes, and superficial perivascular lymphocytic infiltrate accompanied by melanophages. Colloid bodies were also noted in the papillary dermis. B) Skin from the chest wall revealed basal vacuolar degeneration and scattered necrotic keratinocytes. Superficial perivascular lymphocytic infiltrate with hemosiderin was observed. Haematoxylin and eosin, original magnification A) ×400; B) ×100. C) Indirect immunofluorescence (rat bladder epithelium) showed positive for IgG anti-intercellular space.

appearance of the cross-section revealed a well-encapsulated homogeneous mass (Figure 3B). Histopathology was compatible with unicentric Castleman disease, hyaline vascular type (Figure 3C and 3D).

Prednisolone 60 mg/day and mycophenolate mofetil 1.5 g/day were started, and tumor removal was performed. Mucocutaneous lesions gradually improved within 3 months after the surgery. Pyridostigmine was used initially for myasthenia gravis treatment and discontinued within 2 months after the surgery due to marked improvement in weakness. Currently, he is taking prednisolone 40 mg/day, and the disease is well under control.

Discussion

Paraneoplastic pemphigus (PNP) or paraneoplastic autoimmune multiorgan syndrome (PAMS) is a rare autoimmune blistering skin disease associated with various neoplasms[1]. The proposed immunopathogenesis involved the generation of neoplasm-induced autoreactive T-cells, followed by subsequent humoral immune response

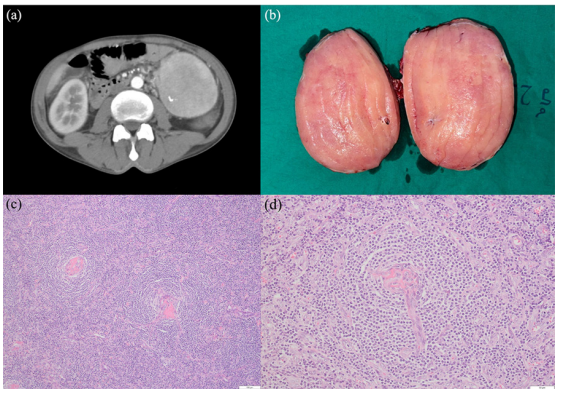

Figure 3. A) Abdominal computed tomography showed a 7×7.1×9.8 cm circumscribed vividly enhancing mass with intralesional calcification at LUQ abdomen. B) The gross appearance of the cross-section revealed a well-encapsulated homogenous mass. C) Histopathology from enlarged lymph node revealed large follicles with small, regressed germinal centers and expanded mantle zones that resemble "onion skin". Interfollicular areas contained many sclerotic high endothelial venules. D) This follicle exhibited a hyaline-vascular lesion, also called a "lollipop" lesion, involving a large radial blood artery with sclerosis and a regressed germinal center. Haematoxylin and eosin, original magnification (c) ×100; (d) ×200.

Table 1. Revised diagnostic criteria for PNP requiring three major, or two major and two minor criteria[5].

Major criteria
1. Mucous membrane lesions with or without cutaneous involvement
2. Concomitant internal neoplasm
3. Serologic evidence of anti-plakin antibodies: immunoprecipitation, immunoblot, ELISA, indirect immunofluorescence on transitional epithelium
Minor criteria
1. Acantholysis and/or lichenoid interface on histopathology, ± necrotic keratinocytes
2. Direct immunofluorescence showing intercellular and/or basement membrane staining

(antibody-dependent cell-mediated cytotoxicity) and cell-mediated immune response (cell-mediated cytotoxicity) against various target antigens[2]. Several target desmosomal and hemidesmosomal antigens were identified, listed in order of decreasing frequency: envoplakin, periplakin, desmoplakin, desmoglein 3, BP 230, alpha-2-macroglobulin-like 1, desmoglein 1, BP 180, desmocollin, laminin 3-3-2, and collagen VII alpha chain[3]. However, the characteristic autoantibodies are anti-plakin antibodies[4]. The diagnosis of PNP relies on clinical manifestations, histopathological findings, and biochemical features including DIF, IIF, immunoblot, immunoprecipitation, and enzyme-link immunosorbent assay (ELISA). Recently, a proposed revised criteria for diagnosis has emerged, capable of capturing more cases of paraneoplastic pemphigus compared to the previously commonly used criteria by Camisa and Helm[5]. The revised diagnostic criteria for PNP is shown in Table 1.

Typically, nearly all patients have extensive and intractable erosive stomatitis initially and subsequently develop polymorphic cutaneous lesions. The variety of skin lesions with different morphologies depends on the predominant immunopathogenesis, encompassing pemphigus-like lesions (mainly driven by antibody-dependent cell-mediated cytotoxicity), bullous pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like, and lichen planus-like manifestations (largely influenced by cell-mediated cytotoxicity)[1]. Features favoring the diagnosis of paraneoplastic pemphigus over pemphigus vulgaris included polymorphic skin lesions, notably lichenoid lesions, involvement of the palms and soles, and paronychia. Interestingly, our patient exhibited all three of these distinct features.

Various histopathologic features have been reported ranging from lichenoid interface only (21.1%), acantholysis only (28.7%), and both lichenoid interface and acantholysis (41.9%), with or without necrotic keratinocytes, depending on the cutaneous morphology[5]. The histopathology of our patient was consistent with the skin findings, which were lichenoid interface changes in lichen planus-like lesions. Positive DIF was seen in 77.7% with various findings: intercellular (27%), intercellular and junctional (42.6%), and junctional (4.5%) deposition of IgG and/or C3[5]. Our patient's DIF result fell into the minority of cases, showing positive IgG and C3 only at the basement membrane zone. This finding correlated with lichenoid interface changes observed in histopathology. However, it might be attributed to weak and focal intercellular deposition, as explained in previous studies[6]. Evidence of anti-plakin autoimmunity was demonstrated by a positive IIF on rat bladder transitional epithelia in 67.2% to 74% of cases[5,7]. Other methods used to detect anti-plakin antibodies include ELISA, immunoblot, and immunoprecipitation, each exhibiting variable sensitivity and specificity[7].

Reported associated neoplasms, arranged in order of decreasing frequency, are non-Hodgkin lymphoma (38.6%), chronic lymphocytic leukemia (18.4%), Castleman disease (18.4%), sarcoma (6.2%), thymoma (5.5%), Waldenstrom macroglobulinemia (1.2%), Hodgkin lymphoma (0.6%), and melanoma (0.6%)[8]. Cases of PNP with carcinoma were reported but were far less common than lymphoproliferative neoplasms. Various HLA genetic susceptibilities in PNP were described across different races and ethnicities[4].

Unicentric Castleman disease is classified as a lymphoproliferative disorder characterized by the enlargement of a lymph node at a single anatomical site. Common locations include the chest (29%), neck (23%), abdomen (21%), and retroperitoneum (17%)[9]. Castleman disease is associated with the overproduction of cytokines and interleukins, activating T-cells, subsequently

differentiating B-cells into plasma cells, and ultimately leading to the production of autoantibodies. These immunopathogenic mechanisms can explain associated autoimmune phenomena such as peripheral neuropathy, systemic lupus erythematosus, and myasthenia gravis. Most reported cases of myasthenia gravis associated with Castleman disease were of the unicentric type and exhibited the hyaline vascular histological subtype in the mediastinum[10,11].

There was only one previous case report of paraneoplastic pemphigus associated with Castleman disease and myasthenia gravis. However, both patients died (one from respiratory failure caused by bronchiolitis obliterans and another from ventricular arrhythmia)[12,13].

The treatment for paraneoplastic pemphigus includes managing the associated neoplasm, systemic steroid therapy, which can be combined with immunosuppressants such as cyclophosphamide, mycophenolate mofetil, azathioprine, and cyclosporine, as well as the use of anti-CD20 rituximab[8]. Intravenous immunoglobulin and plasmapheresis have been used in some cases[14]. The mortality rates in PNP was high with reported mortality between 50 to 80%[4]. Various poor prognostic factors were described in literature such as the presence of anti-envoplakin antibodies, bronchiolitis obliterans, toxic epidermal necrolysis-like features, bullous pemphigoid-like features, age more than 42, and body surface area involvement over 17.5%[3,15].

Conclusion

The authors reported a rare case of paraneoplastic pemphigus and myasthenia gravis associated with unicentric Castleman disease. The treatment included tumor removal and a combination of prednisolone with mycophenolate mofetil. Currently, he is taking prednisolone 40 mg/day, and the disease is well under control.

What is already known on this topic?

Paraneoplastic pemphigus is a rare autoimmune blistering skin disease associated with various neoplasms including Castleman disease and associated with a high mortality rate.

What this study adds?

To the best of our knowledge, this is the first case report of a patient diagnosed with paraneoplastic pemphigus and myasthenia gravis associated with unicentric Castleman disease, who has survived for 2 years following the diagnosis.

Ethics approval

This report was approved by the Center for Ethics in Human Research, Khon Kaen University (HE671005). Informed consent was obtained, and the patient consented to the publication of the pictures and related clinical information.

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Conflicts of interest

The authors declared no conflict of interests.

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