Case Report
Olgu Sunumu

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Pemphigus vulgaris in a patient with primary hypogammaglobulinemia: A case report

Primer hipogamaglobulinemili bir hastada pemfigus vulgaris: Bir olgu sunumu

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Abstract

Pemphigus vulgaris (PV) is a rare autoimmune disorder characterized by blisters on the mucous membranes and skin. Autoimmunity is an important complication developing in predominantly antibody deficiencies, which is a subgroup of primary immunodeficiencies (PID). Herein, we present a patient with PV who had primary antibody deficiency and whose disease relapsed during the maintenance period of conventional immunosuppressive treatments but progressed to remission following high-dose intravenous immunoglobulin therapy. Thus, we aimed to create awareness for the study of primary immunodeficiencies in rare autoimmune bullous diseases.
Keywords: Pemphigus vulgaris, primary antibody deficiency, primary immune deficiency

Öz

Pemfigus vulgaris (PV), deri ve mükoz membranlarda büllerin varlığı ile karakterize, nadir görülen otoimmün bir hastalıktır. Otoimmünite, özellikle primer immün yetmezliklerin bir alt grubu olan antikor eksikliklerinde gelişen önemli bir komplikasyondur. Burada, PV ile birlikte primer antikor eksikliği olan ve geleneksel immünosüpresif tedavilerin idame döneminde nükseden ancak yüksek doz intravenöz immünoglobulin tedavisi ile remisyona giren PV'li bir olgu sunulmaktadır. Bu olgunun sunumu ile nadir görülen otoimmün büllöz hastalıklarda primer immün yetmezliklerin araştırılması için farkındalığın geliştirilmesi amaçlanmıştır.
Anahtar Kelimeler: Pemfigus vulgaris, primer antikor eksikliği, primer immün yetmezlik

Introduction

Pemphigus vulgaris (PV) is the most common and potentially life-threatening subtype of pemphigus observed in the 4th to the 6th decade of life without any sex predilection[1]. The characteristic features of PV are blister formation and erosions of the skin and mucous membranes. Although the etiology of PV is generally unknown, the immunoglobulin G (IgG) autoantibodies against desmosomal structural proteins, known as desmoglein 1 (DSG1) and DSG3, play important roles in mucocutaneous blister formation, causing loss of cell-to-cell adhesion among squamous epithelial cells. Thus far, the association between PV and predominantly antibody deficiency (PAD) has rarely been reported. In a recently published article, serum antibody levels were investigated in bullous autoimmune dermatoses, and low IgG2 and IgG3 levels were found in patients with bullous pemphigoid (BP) or PV[2]. Various autoimmune diseases develop based on PADs[3]. In this report, we present a patient with PAD-associated PV that was refractory to conventional treatments.

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Case Report

A 72-year-old woman presented to our outpatient clinic with painful ulcerous lesions in the mouth and ruptured blisters on the skin on various body parts. According to the patient, the skin lesions had appeared 3 months after the oral lesions. Due to the mouth lesions she was unable to eat and lost 7 kg in the last month. Simultaneous with mouth sores, bleeding developed in the whites of the eyes. Despite anti-infective and immunosuppressive treatments by different centers, the lesions gradually spread, and the patient's quality of life remained impaired. Verbal informed consent was obtained from patient.

Physical examination: Erosive exudative lesions on erythematous bases were observed on the buccal mucosa (Figure 1a). Widespread erosions were also seen on mucosal surfaces of the upper and lower lips, palate, and tongue. The gingival mucosa was crimson in color and appeared edematous. Moreover, white patches were observed on the tongue caused due to oral thrush. Various ruptured bullous lesions were inspected on nearly all body parts, notably under the breasts, arms, legs, and groin (Figure 1b). Dimensions of the lesions varied from 0.5x0.5 cm (smallest) to 4x5 cm (largest). Nikolsky's sign was positive in the newly developed bullous lesions. There were crusted and inflamed lesions on the patient's scalp.

Laboratory findings: Results of the routine blood test were abnormal, depicted as follows: White blood cell count, 13.2×10^3 cells/mm^3 (4.5-11×10^3); neutrophil count, 9.8×10^3 cells/mm^3 (2-7.8×10^3); fasting glucose, 120 mg/dL (74-106); uric acid, 7.2 mg/dL (2.5-6); blood urea nitrogen, 23 mg/dL (6-20); glomerular filtration rate, 57 mL/min/1.73 m^2 (>60); total protein, 5.9 g/dL (6-8.1); C-reactive protein, 54 mg/L (0-5); erythrocyte sedimentation rate, 84 mm/h (0-15).

While the IgG level was below the lower limit of the reference range [IgG, 4.8 g/L (7-16)], IgA and IgM levels were close to the lower limit of the reference range [IgA, 0.98 g/L (0.7-5); IgM, 0.34 g/L (0.3-2.9); IgE, 11.9 IU/Ml (<87), respectively] at the time of diagnosis. In the retrospective analysis of the laboratory results of the patient, the levels of major serum IGS4 months ago were also similar to those of the recent measurements. The percentages of lymphocyte subsets were within the reference range.

The titers of autoantibodies directed against DSG1 and DSG3 in the patient's serum were 2.81 and 9.91, respectively (reference range, negative for <1; positive for ≥1). Biopsy could not be performed because the patient presented to the clinic in the midst of the Coronavirus disease-2019 pandemic; therefore, strict measures were taken at the hospitals.

Diagnosis: According to the clinical and laboratory results, the patient was diagnosed with PV, an autoimmune bullous disease that developed over PAD. Considering the serum levels of major Ig isotypes, the underlying immunodeficiency was categorized as probable common variable immunodeficiency (CVID) in accordance with the diagnosis algorithm suggested by Ameratunga et al.[4] and the European Society for Immunodeficiencies criteria[5]. According to these criteria, apart from susceptibility to infection, autoimmune manifestation is accepted as an adequate clinical finding for diagnosis. Essentially, our patient had no history of severe infection. Since primary hypogammaglobulinemia is the characteristic sign of CVID, secondary causes of hypogammaglobulinemia were excluded by evaluating clinical and laboratory findings of the case (e.g., B-cell malignancies, protein-losing enteropathies, malabsorption, nephrotic syndrome, and immunosuppressive medications such as corticosteroids and chemotherapy).

Treatment and clinical course: As per the recommendations of international boards, intravenous immunoglobulin (IVIG) treatment was started at the dose of 600 mg/kg every 4 weeks because of hypogammaglobulinemia[4,5]. For the treatment of PV, oral immunosuppressive agents were initiated, such as cyclosporine (CYS) 200 mg/day divided into two doses and methylprednisolone (MP) in 1 mg/kg/day in a single dose. The dose titrations of these drugs were adjusted according to the clinical response. Vitamin D and calcium supplements were administered along with to the specific treatments.

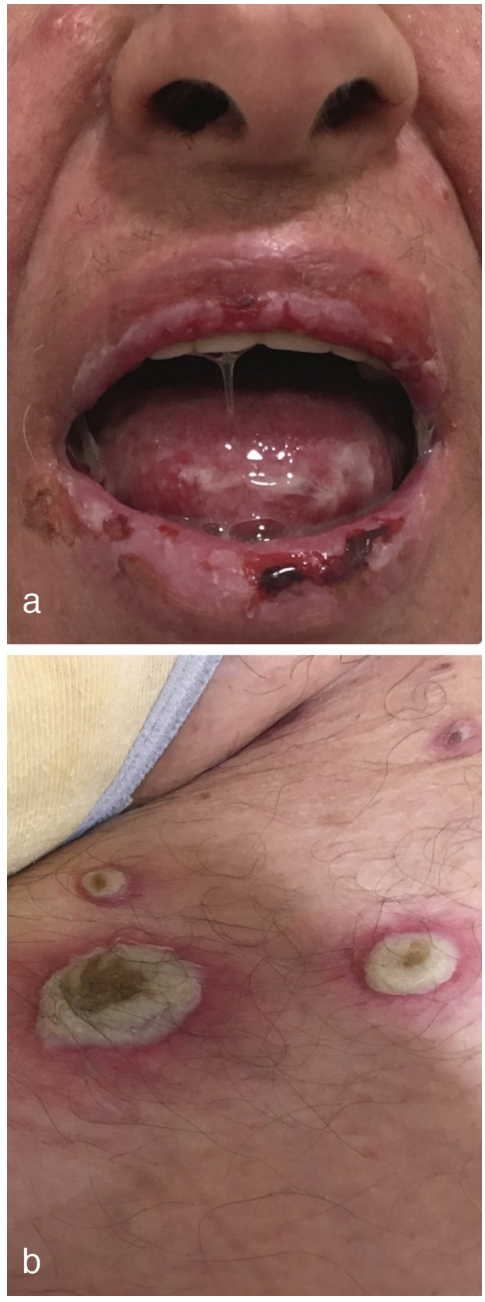

Figure 1. (a) Erosive exudative lesions on the buccal mucosa. **(b)** Ruptured bullous lesions on the legs and groin

In addition to systemic treatment, anti-ulcer and antifungal topical treatments were prescribed for mucosal and cutaneous lesions. The patient received strict oral care.

The doses of immunosuppressive drugs were gradually reduced after the desired clinical response was obtained, and the lesions regressed. While the patient was on maintenance treatment with 8 mg MP once a day and 50 mg CYS in two divided doses, the disease recurred on day 54 of the treatment. Bullous lesions were observed on the face and in the mouth (Figure 2a). As there were metabolic complications, CYS was replaced with 720 mg mycophenolic acid (MPA) orally administered into two doses daily. The dose of MP was increased to 1 mg/kg daily as a single dose. As the first period of treatment, the doses of immunosuppressive agents were gradually titrated to the maintenance doses according to the clinical response. Thus, the doses of the immunosuppressive agents were decreased to 360 mg/day as divided into two doses for MPA and a single dose of 8 mg/day for MP. Although remarkable clinical improvement was achieved with this treatment regimen, new precursor lesions appeared in the mouth and body on day 104 of the treatment. The titers of anti-DSG1 and anti-DSG3 autoantibodies in the patient's serum persisted to 3.58 and 5.97, respectively. Thereupon, high-dose IVIG treatment at 2 g/kg while maintaining immunosuppressive therapy was decided. Therefore, the total IVIG dose was divided into 4 days. After this intervention, all mucosal and cutaneous lesions related to PV were completely resolved (Figure 2b). The treatment with MPA and MP was continued at maintenance doses without any significant side effects till date.

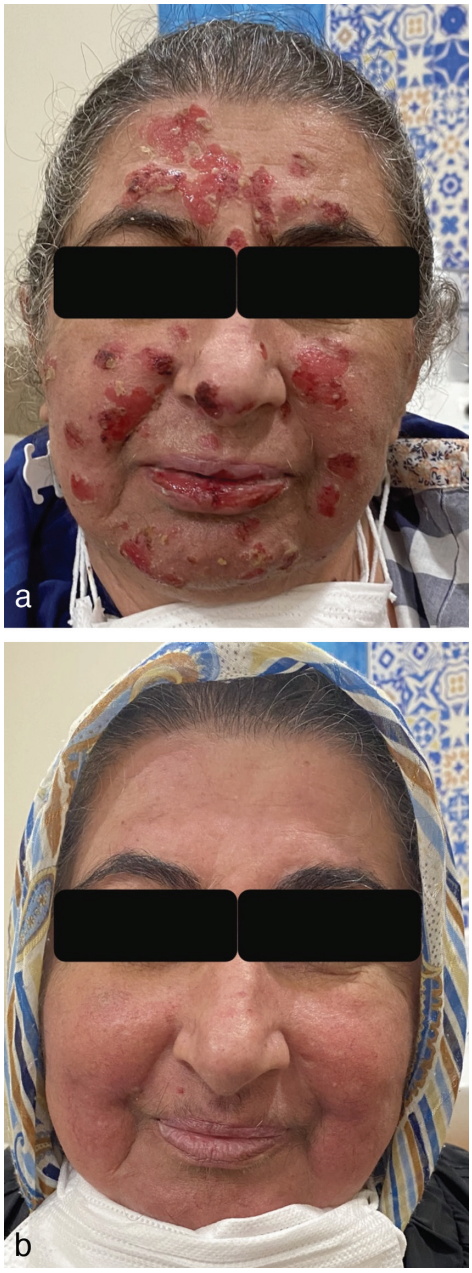

Figure 2. (a) Recurrence after initial immunosuppressive treatment. **(b)** Completely resolved mucosal and cutaneous lesions after change in immunosuppressive treatment protocol

During the first recurrence, hyperglycemia (fasting glucose, 285 mg/dL) and hypercholesterolemia (total cholesterol, 356 mg/dL) developed while CYS and MP were used simultaneously. Cushingoid appearance occurred following a high MP dose. Additionally, the levels of thyroid-stimulating hormone and anti-thyroid peroxidase were increased to 9.29 mU/L and 122.8 IU/mL, respectively. In addition to oral formulations of atorvastatin and levothyroxine, subcutaneous insulin treatment was initiated for the treatment of diabetes mellitus, hyperlipidemia, and Hashimoto's thyroiditis. The levels of fasting glucose and cholesterol were regulated by these treatments. At the final lab test, thyroid function tests were within the normal limits. Thus, while the clinical signs of hypothyroidism had completely regressed, cushingoid appearance partially persists.

Discussion

CVID characterized by hypogammaglobulinemia is classified into the third main group of primary immunodeficiencies (PIDs) according to the Phenotypical Classification Table of Inborn Errors of Immunity currently suggested by the International Union of Immunological Societies expert committee[6]. CVID is the most frequent symptomatic PID in adults with an incidence of 1:50,000 to 25,000. Recurrent infections and autoimmunity are the characteristic features of this disorder[7]. Immune cytopenia, rheumatoid arthritis, systemic lupus erythematosus, vasculitis, psoriasis, vitiligo, and immune enteropathies are common complications during the disease course. Lymphoproliferation, granulomas, and lymphoid malignancies are other complications in this highly heterogeneous disease.

Genetic cause can be detected in 25% of the patients[8]. CVID includes not only antibody deficiency but also T-cell defects. Thus, severe autoimmune disorders may develop because of immune dysregulation, primarily in late-onset disease. In this respect, CVID is evaluated into the group of primary immune regulatory disorders (PIRDs) with a tendency to cause autoimmune diseases and have T- and B-cell defects together[7]. Tregopathies, late onset or profound combined immunodeficiencies, are included in the PIRD group.

Herein, we present a patient with PV that progressed to PID. The causes of paraneoplastic pemphigus (PNP) were investigated because of the older age and presence of PID. To reveal the common causes of PNP, lymphoid malignancies and thymoma were investigated by appropriate radiologic, biochemical, and immunologic examinations. However, no evidence related to the PNP was found. Thus, we

excluded an important disease that should be considered for differential diagnosis[9].

In the literature search, PV has not been documented to be associated with CVID. Only a case of a woman with CVID who developed PNP after receiving radiotherapy for relapsed non-Hodgkin's lymphoma has been reported so far[9]. In a recent report, serum IgG1 and IgG4 levels were elevated in patients with PV and BP compared with healthy controls, whereas serum IgG2 and IgG3 levels were decreased in patients with PV and BP[2]. Accordingly, researchers suggested that IgG2 level should be measured before immunosuppressive treatment in patients with BP. Although mycophenolate mofetil (MMF) and MPA were recommended as a first-line adjuvant immunosuppressive agent for the corticosteroid-sparing effect according to the European Dermatology Forum and British Association of Dermatologists guidelines, CYS was preferred instead of these agents in consideration of the patient's clinical features and mechanism of action of drugs[10,11]. Since the patient was immunodeficient, CYS, which has an immunosuppressive effect by the downregulation of NFAT in T-cells, was evaluated as first-line adjuvant drug. On the contrary, MPA exerted immunosuppressive effect on the humoral and cellular immunity by the inhibition of the *de novo* pathway of purine synthesis in T-cell and B-cell lineages and accordingly suppressing their proliferations. In addition, as MPA is well tolerated than MMF in terms of gastrointestinal side effects, this drug was selected as a first-line adjuvant drug for the case[11].

Herein, we report the first case of PV that developed in a patient with CVID. Although autoimmune skin disorders are one of the common manifestations of CVID, the absence of such reported cases is possibly due to the lack of awareness of PID among physicians[12]. This report primarily aims to highlight that PID should be evaluated in elderly patients with autoimmune bullous disease. Otherwise, mortality and morbidity rates may increase due to delayed diagnosis, and insufficient or inappropriate treatments may lead to devastating results.

Ethics

Informed Consent: Verbal informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.H.M., T.E., M.T., Concept: U.H.M., Design: U.H.M., Data Collection or Processing: U.H.M., Analysis or Interpretation: U.H.M., Literature Search: U.H.M., T.E., M.T., Writing: U.H.M., T.E., M.T.

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