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Case Report / Olgu Sunumu

Association of Epidermolysis Bullosa and Multiple Sclerosis: A Case Report and Literature Review

Epidermolizis Bülloza ve Multipl Skleroz Birlikteliği: Olgu Sunumu ve Literatür Taraması

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Abstract

Epidermolysis bullosa (EB) is a family of bullous disorders due to an absent basement component, which is usually associated with keratin gene mutations. The association of EB and multiple sclerosis (MS) was not reported. Herein, we aimed to report a known case of EB that presented a history of 20 days lower limb paresthesia and was eventually diagnosed with MS to highlight the association of a rare dermatologic disorder with MS.

Keywords: Epidermolysis bullosa, skin disease, multiple sclerosis

Öz

Epidermolizis bülloza (EB), genellikle keratin gen mutasyonları ile ilişkili bazal bileşen eksikliğinden kaynaklanan bülloz bir dermatolojik hastalık grubudur. Günümüzde EB ve nörolojik bozukluklar arasında ilişki raporlanmamıştır. Bu çalışmada, 20 günlük alt ekstremite parestezisi sonrası multipl skleroz (MS) tanısı alan bir EB olgusu bildirilmekte olup bu nadir dermatolojik hastalık grubunun MS ile ilişkisi vurgulanmaktadır.

Anahtar Kelimeler: Epidermolizis bülloza, deri hastalığı, multipl skleroz

Introduction

Epidermolysis bullosa (EB) encompasses heterogeneous inheritable skin disorders that are characterized by induced blistering of the skin and mucous membranes. According to the United States National EB Registry, the overall incidence and prevalence of EB is estimated to be 19.6 and 11.07 cases per one million live birth, respectively (1). EB comprises a remarkable variable spectrum of phenotypes, ranging from mild cutaneous fragility to severe cutaneous and extra-cutaneous involvement in which the joints, gastrointestinal, genitourinary, and respiratory system can be affected and results in a variable range of complications (2).

In addition, multiple sclerosis (MS) is a chronic disease that is characterized by inflammation and demyelination of the central nervous system (CNS) with various clinical and radiologic presentations. Despite the numerous advances in the discovery of the underlying genetic and environmental factors of the disease, the exact pathogenesis of MS remains unclear. However, strong evidence suggested immune-mediated responses, especially during the acute early phases of the disease (3).

The association of autoimmune neurological disorder and genetic bullous disorders as bullous pemphigoid has been well-described; however, to the best of our knowledge, neurologic complications of EB are not reported in the literature (4).

Herein, we aimed to describe a known case of EB that presented lower limb paresthesias with a final diagnosis of MS to highlight the association of a rare dermatologic disorder (EB) with MS.

Case Report

A 35-year-old white female patient presented with a 20-day history of lower limb paresthesia in a progressive fashion, which aggravated over a week before admission. The patient affirmed that

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symptoms worsen after a hot bath. She reported no associated band-like sensation, paresis, or sphincter impairment. Additionally, no evidence of Lhermitte's phenomenon was obtained.

The past medical history was positive for EB, hypothyroidism, and iron deficiency anemia. She also noticed a prior history of vision loss 5 years earlier, which subsided over a week without considerable medical therapy. Additionally, she was diagnosed with right optic neuritis due to unremarkable neuroimaging.

Her past surgical history was positive for finger amputation due to the underlying EB (Figure 1).

Her family history was unremarkable for neurological disorders.

Her neurological examination was notable for mild upper limb spasticity, generalized hyperreflexia, and bilateral upper plantar reflex. Furthermore, the sensory examination revealed a non-dermatomal decreased light touch, pain, and temperature sensation in the lower limbs. No sensory level was obtained. The remaining examinations were normal.

The brain magnetic resonance imaging (MRI) demonstrated a few non-enhancing ovoid T2 periventricular hyper-intense lesions. The cervical MRI revealed a small T2 lower cervical hyper-intense lesion without evidence of gadolinium enhancement on both sagittal and axial images (Figure 2).

Therefore, with a suspicion of a demyelinating attack, the patient underwent pulse steroid therapy with methylprednisolone at 1 gr/d for 3 consecutive days, which lead to a complete symptom recovery.

The following ancillary examinations were performed. A cerebrospinal fluid (CSF) analysis revealed 9 oligoclonal bands that are restricted to the CSF. The CSF was otherwise normal. Serum and CSF evaluation for inflammatory, metabolic, and infectious diseases, other than MS, was unrevealing. Eventually, based on the McDonald criteria, the patient was classified as relapse and remitting MS. Treatment started with dimethyl fumarate at 120 mg daily, which was titrated up to 240 mg twice a day. Additionally, in the absence of EB curative treatment, multidisciplinary care was targeted toward minimizing the risk of blister formation, wound care, symptom relief, and specific complications.

Discussion

EB is an inherited, heterogeneous group of rare autoimmune skin disorders that is characterized by skin and mucous membrane blistering through binding of autoantibodies to type VII collagen (COL7), a constituent of anchoring fibrils of the dermal-epidermal junction (5). Based predominantly on the plane of cleavage within the skin and the junctional, dystrophic and Kindler in which the EB simplex is considered as the most common subtype (1). Based on clinical features, it is divided into two clinical variants, the mechanobullous and the inflammatory (6).

As the genotype-phenotype correlations are not always shown in patients with EB, factors other than genetic mutations could play a role in the genesis of EB. In several patients with EB, high levels of anti-skin antibodies are found, such as desmoglein 1 (DSG1), DSG3, bullous pemphigoid 180 (BP180), BP230, and COL7, or higher level of interleukin (IL)-1β, IL-2, IL-6, IL-10, tumor necrosis factor-β, and interferon-γ, which are proportional to the disease severity and all suggested the presence of systemic inflammatory disorders (7,8). Based on the current data, the association of autoimmune neurological disorders and some subtypes of autoimmune bullous diseases are well described as few reports are notable for higher prevalence of MS among patients with Bullous pemphigoid (9). However, data on neurological disorders in associations with EB is limited. In 2015, the first report of peripheral nervous system (PNS) pathology and recessive dystrophic EB was published, which revealed a significant correlation of cutaneous mast cell numbers and degranulation in patients with EB with peripheral nerve pathology (10).

Contrarily, MS is a chronic demyelinating disease that affects 2.3 million people worldwide, which is thought to be an autoimmune disorder. Various immune disorders were reported in

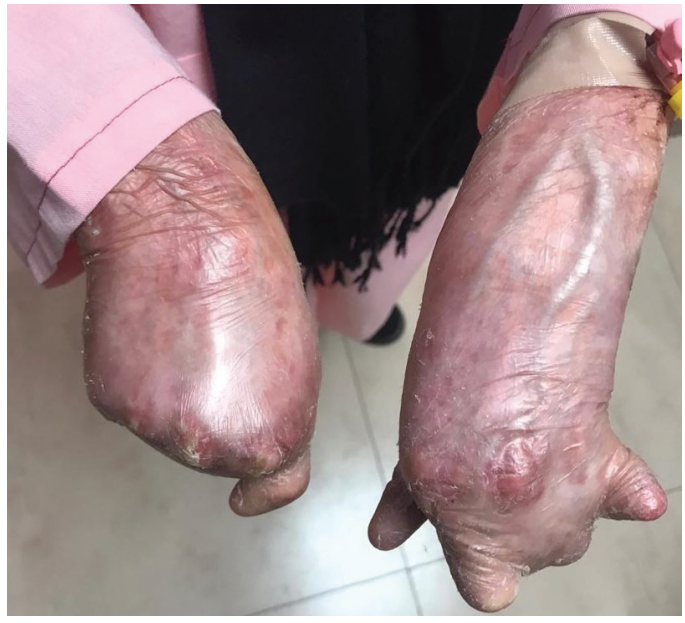

Figure 1. Amputation of fingers due to epidermolysis bullosa

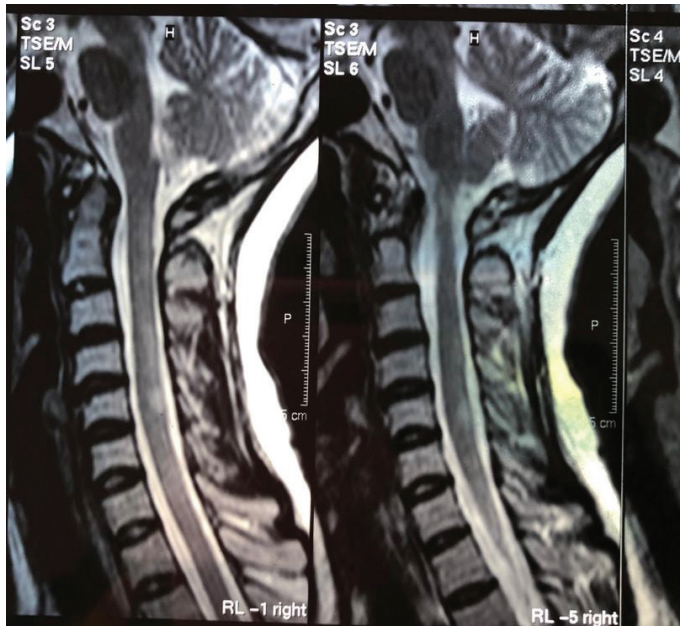

Figure 2. A small posterolateral T2 lower cervical hyper-intense lesion in the sagittal image

families with several members with MS that underline the common susceptibility of autoimmunity (11). Barcellos et al. (12) revealed the coexisting autoimmune disorder in 26% of families with a history of MS. Hashimoto thyroiditis, psoriasis, inflammatory bowel disease, and rheumatoid arthritis were the most common reported autoimmune disorders. Additionally, evidence indicated dermatological complications in MS. The epithelial isoform of Bullous pemphigoid antigen 1 (BPAG1) autoantibody has been detected in patients with MS. This antigen is one of the most common autoantigens of Bullous pemphigoid, which is also expressed in the neurons of the CNS, PNS, and Schwann cells. The specific BPAG1 variants are hypothesized to be novel targets of autoantibodies, such as in MS (13).

As previously mentioned, autoimmunity and inflammatory responses are frequently activated in EB, which seems to confirm that EB is a systemic disease and explains the extra-cutaneous involvement that is frequently observed in EB. Elevated levels of the pro-inflammatory cytokine IL-6 were believed to be observed in the initiation and propagation of inflammatory responses and in several autoimmune diseases, such as MS, which is mainly dependent on the Th17 differentiation. Moreover, pro-inflammatory cytokines are traditionally classified; however, IL-6 can also induce an anti-inflammatory cytokine profile, enhance IL-4/IL-10 production, decrease IL-1β secretion, and polarize human monocytes into an anti-inflammatory M2 phenotype under certain co-stimulatory conditions (14,15).

The reported case was unique since a rare autoimmune skin disorder was complicated with relapse-remitting MS. Our data cannot confirm a causal relationship between MS and EB; however, it suggests the association between two autoimmune disorders, which might occur in the context of a systemic pro-inflammatory state. Patients with EB present with cutaneous-mucous fragility, which is easily suspected when the lesions are on trauma-prone areas that impose a significant impact on MS management. The main limitation in clinical practice is evident for intravenous disease-modifying drugs (DMD) as they increase the probability of blistering lesions in each injection.

In conclusion, neurological complications in association with autoimmune bullous diseases as Bullous pemphigoid are reported; however, to the best of our knowledge, MS and EB were not reported in the literature. The uniqueness of our case was to highlight the association of MS and rare autoimmune disease and the importance of DMD election in management.

Ethics

Informed Consent: Consent form was filled out by the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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