A Potential Link between Amyotrophic Lateral Sclerosis and Bullous Pemphigoid: Six New Cases and a Systematic Review of the Literature

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Abstract

Objective  Bullous pemphigoid in amyotrophic lateral sclerosis (BP-ALS) is rare and poorly understood. We herein assessed the association between ALS and BP using clinical and biological findings.

Methods  The clinical features of six new BP-ALS cases were described and collated with cases from a systematic literature review.

Results  Our six cases were combined with three other published cases. The mean disease duration (from ALS onset to the occurrence of BP) was 5.6±3.1 years. All patients had limb-onset ALS. Four of the 9 patients received riluzole, with the use of riluzole ranging from a few days to 3 years. When BP occurred, the status of the ALS patients was paretic and/or bedridden in all cases. BP occurred throughout the body, and we confirmed that the bullous lesions were located not only at the compression site, but also at the anterior part of the chest, abdomen, and limbs. Treatment for BP was successful, as oral prednisone and/or local corticosteroids were effective in 8 cases.

Conclusion  These six new cases, in combination with previous cases, expand our knowledge of the relationship between dermatological lesions and ALS. The pathogenesis of BP-ALS is poorly understood, however, some immunological aberrance is likely.

Key words: amyotrophic lateral sclerosis (ALS), bullous pemphigoid (BP)

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Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating degenerative motor neuron disease that affects both the upper and lower body and is characterized by muscle weakness, atrophy, spasticity, and lethal respiratory failure. Furthermore, several studies have shown unique morphological and physiological alterations in the skin of patients with ALS (1-3).

Bullous pemphigoid (BP) is a chronic blistering disease most frequently observed in elderly patients. It occurs in an elderly population with a median age of 80 years and is known to have significantly increased mortality rates compared to the general population (4). Patients with BP typically have circulating autoantibodies against two skin antigens, BP 230 (BP antigen 1, BPAG1) and/or BP 180 (BP antigen 2, BPAG2). BPAG1 exists in the intracellular part of the hemidesmosomes, while BPAG2, or type XVII collagen, is a transmembrane protein. BPAG1 has specific isoforms, one of which is specific to the epithelium, while another is specific to the nervous system. Recent studies show that cross-reactivity between these isoforms could be pathogenic in BP (5). Exposure to the neuronal antigen could lead to an immune reaction against the epithelial isoform. BP has been reported in adult patients with various neurological disorders, suggesting a potential relationship with neurodegenerative diseases (6).
We herein present the cases of six Japanese patients with ALS who developed BP on their body trunk and extremities. We assessed the association between ALS and BP using the clinical and biological findings of these six cases. In addition, we also present a detailed systematic review of the literature to enhance the current knowledge regarding the clinical manifestations in patients with ALS with BP.

**Materials and Methods**

We encountered six new cases of BP in patients with ALS (BP-ALS) and collated the anonymized clinical data as well as laboratory and histopathological results related to BP. A detailed systematic review of the literature was also performed to look for published cases of BP in ALS. The Google Scholar and PubMed databases were searched to identify relevant peer-reviewed manuscripts using the following search terms: amyotrophic lateral sclerosis, motor neuron disease, neurodegenerative disease/disorder, neurological disorder, and bullous pemphigoid. Only manuscripts written in English were reviewed. The reference lists found in the relevant articles and textbooks were hand searched. Specified data were extracted and tabulated. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

**Results**

**Case 1**

A 71-year-old man, affected by ALS for at least 17 years, had been using tracheostomy positive pressure ventilation (TPPV) for the past 14 years. The patient had severe functional disabilities with complete paralysis of the limbs and swallowing difficulties. He was not receiving any medication for ALS. When he was hospitalized at 65 years of age, he complained of cutaneous lesions located in the anterior chest, palms, and forearms. The lesions had spread to the body trunk. He presented with tense blisters, mainly located over the urticarial plaques (Figure a). She had hypereosinophilia (11.8%) and hyper-IgE-emia (2,003.5 mg/dL), and BP was confirmed by the presence of subepidermal blisters associated with inflammatory cell (eosinophils, neutrophils, and lymphocytes) infiltration around the blood vessels (Figure b). A relapse occurred 6 years later, and he had BP in the anterior part of the trunk at 71 years of age. Enzyme-linked immunosorbent assays (ELISAs) for anti-BPAG2 antibodies were negative at 65 and 71 years of age. Treatment, including antiseptic care and topical corticosteroid therapy, was initiated at both 62 and 64 years of age. The outcome was favorable (Figure c), and treatment with the corticosteroids was discontinued after 4 months.

**Case 2**

A 65-year-old man, affected by ALS for at least 9 years, had been using TPPV for the past 6 years. The patient had severe functional disabilities with complete paralysis of the upper and lower limbs and swallowing difficulties. He was not receiving any medication for ALS. He complained of cutaneous lesions on his bilateral lower extremities and left foot at 62 years of age. After a week, he had extensive crusted and bullous lesions on all of his limbs. BP was confirmed by the presence of subepidermal blisters associated with inflammatory cell (eosinophils, neutrophils, and lymphocytes) infiltration around the blood vessels (Figure e). However, an ELISA for anti-BPAG2 antibodies was negative, and hypereosinophilia was not reported. When he was hospitalized at 64 years of age, his BP had returned. Laboratory investigations disclosed the presence of anti-BPAG2 antibodies and hypereosinophilia (14.9%). Treatment, including antiseptic care and topical corticosteroid therapy, was initiated at both 62 and 64 years of age. The outcome was favorable (Figure c), and treatment with the corticosteroids was discontinued after 4 months.

**Case 3**

A 61-year-old woman, affected by ALS for at least 3 years, had functional disabilities with muscle weakness in the lower limbs. She had started treatment with riluzole (100 mg/day) prior to the onset of BP. After a few days, she complained of cutaneous lesions on her hands and forearms. The lesions had spread to the buttocks and lower limbs after the patient discontinuing riluzole treatment and were associated with tense blisters, mainly located over the urticarial plaques (Figure a). She had hypereosinophilia (11.8%) and hyper-IgE-emia (2,003.5 mg/dL), and BP was confirmed by the presence of subepidermal blisters associated with inflammatory cell infiltration and linear deposits of C3 and immunoglobulin G (IgG) along the basal membrane zone. An ELISA for anti-BPAG2 was positive. Treatment, including the oral administration of prednisone and antiseptic care, was initiated. The outcome was favorable, and treatment with the corticosteroid was discontinued.

**Case 4**

A 76-year-old man, affected by ALS for at least 4 years, had functional disabilities with muscle weakness of the lower limbs. We identified a hexanucleotide repeat expansion in C9orf72 (7). He had been treated with riluzole for the past 3 years (100 mg/day). Additionally, he had dystrophic lesions on the palms (Figure b), and soon thereafter the lesions spread to the body trunk. He presented with bullous lesions of the palms and forearms, and had infected dermatitis localized to the anterior chest, palms, and forearms. The patient had hypereosinophilia (12.0%) and hyper-IgE-emia (1,646.2 mg/dL), and BP was confirmed by the presence of subepidermal blisters associated with the infiltration of eosinophils and linear deposits of C3 and IgG along the basal membrane zone (Figure f and g). ELISAs disclosed positivity for anti-BPAG2 antibodies. Treatment, including the oral administration of prednisone and antiseptic care, was initiated. The outcome was favorable, and treatment with the corticosteroid was discontinued.
tic care, was initiated, and the outcome was favorable. However, the patient died of respiratory failure 3 months after the onset of BP.

**Case 5**

A 72-year-old woman, affected by ALS for at least 3 years, had functional disabilities with muscle weakness of the lower limbs. She had been treated for 1 year with riluzole (100 mg/day), and eczema and pseudo-urticarial lesions occurred. The lesions were localized to the anterior part of the trunk and had spread to the foot and proximal part of the lower limbs. The diagnosis of BP was made clinically, although no skin biopsies or autoantibody measurements were performed. Treatment using local betamethasone 17-valerate was initiated. Following the discontinuation of riluzole, the dermatological lesions disappeared. After 1 month, the patient began to suffer from fasciculation, and she hoped to restart the riluzole treatment. After we restarted riluzole treatment, she developed extensive bullous lesions on the bilateral lower limbs.

**Case 6**

A 71-year-old woman, affected by ALS for at least 8 years, had been using TPPV for the past 1 year. The patient had severe functional disabilities with complete paralysis of the limbs and swallowing difficulties. She was not receiving any medication for ALS. The skin lesions were localized on the bilateral palms and had spread to the foot and proximal part of the lower limbs. She had hypereosinophilia (15.5%), and BP was confirmed by the presence of subepidermal blisters associated with the infiltration of neutrophils and eosinophils around the blood vessels. ELISAs for anti-BPAG 2 were positive. Treatment, including the oral administration of prednisone, antiseptic care, and local betamethasone 17-valerate, was initiated. The outcome was favorable, and treatment with the corticosteroid was continued for 7 months.

**Systematic literature review**

Three cases of BP-ALS with sufficient clinical details
Table 1. Demographic and Clinical Features in Published Cases and Six New Patients of ALS with BP Described in this Report.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Onset Age (yrs)</th>
<th>Disease duration (yrs)</th>
<th>Site of onset</th>
<th>Riluzole treatment</th>
<th>Pathology*</th>
<th>Eosinophilia</th>
<th>autoantibody†</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>44</td>
<td>3</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Severe functional disability with complete paralysis of the forelimbs</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>38</td>
<td>9</td>
<td>limb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Severe functional disability with complete paralysis of the forelimbs</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>65</td>
<td>3</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N.D.</td>
</tr>
<tr>
<td>Our Case (Patient 1)</td>
<td>71</td>
<td>M</td>
<td>54</td>
<td>11</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N.D.</td>
</tr>
<tr>
<td>Our Case (Patient 2)</td>
<td>65</td>
<td>M</td>
<td>56</td>
<td>6</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N.D.</td>
</tr>
<tr>
<td>Our Case (Patient 3)</td>
<td>61</td>
<td>F</td>
<td>58</td>
<td>3</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bedridden with TPPV</td>
</tr>
<tr>
<td>Our Case (Patient 4)</td>
<td>76</td>
<td>M</td>
<td>72</td>
<td>4</td>
<td>limb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bedridden</td>
</tr>
<tr>
<td>Our Case (Patient 5)</td>
<td>72</td>
<td>F</td>
<td>69</td>
<td>3</td>
<td>limb</td>
<td>+</td>
<td>N.D.</td>
<td>-</td>
<td>N.D.</td>
<td>Bedridden</td>
</tr>
<tr>
<td>Our Case (Patient 6)</td>
<td>71</td>
<td>F</td>
<td>63</td>
<td>8</td>
<td>limb</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Bedridden with TPPV</td>
</tr>
</tbody>
</table>

† ALS onset age
‡ From ALS onset to the occurrence of BP
# Bullous pemphigoid was confirmed by the presence of subepidermal blisters associated with linear deposits of C3 and IgG along the basal membrane zone.
† Circulating antiepidermal antibodies against two skin antigens, BP 230 (BP antigen 1, BPAG1) and BP 180 (BP antigen 2, BPAG2), were measured.
N.D.: not done, TPPV: tracheostomy positive pressure ventilation

Table 2. Location of BP and Outcome in 9 Patients of ALS with BP.

<table>
<thead>
<tr>
<th>Reference</th>
<th>location of BP (onset)</th>
<th>location of BP (spread)</th>
<th>Treatment for BP</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>forearms lower limbs</td>
<td>palms</td>
<td>prednisone (1 mg/kg per day) antiseptic care classic adjuvant corticosteroid therapy</td>
<td>favorable</td>
</tr>
<tr>
<td>1</td>
<td>elbows axills flexor forearms</td>
<td>anterior chest pubis proximal part of lower limbs</td>
<td>prednisone (1 mg/kg per day) antiseptic care classic adjuvant corticosteroid therapy</td>
<td>favorable</td>
</tr>
<tr>
<td>1</td>
<td>anterior part of trunk proximal part of lower limbs</td>
<td>(−)</td>
<td>prednisone (20 mg/d) local betamethasone-17 valerate terfenadine (120 mg/d)</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 1)</td>
<td>(1st: 65yrs) anterior chest lower part of abdomen</td>
<td>forearms lower limbs</td>
<td>topical corticosteroid therapy antiseptic care</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 2)</td>
<td>all limbs</td>
<td>(−)</td>
<td>topical corticosteroid therapy antiseptic care</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 3)</td>
<td>hand forearms</td>
<td>buttoks lower limbs</td>
<td>prednisone (1 mg/kg per day) antiseptic care</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 4)</td>
<td>palms</td>
<td>body trunk forearms</td>
<td>prednisone (1 mg/kg per day) antiseptic care</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 5)</td>
<td>anterior part of trunk foot proximal part of lower limbs</td>
<td></td>
<td>local betamethasone-17 valerate</td>
<td>favorable</td>
</tr>
<tr>
<td>Our Case (Patient 6)</td>
<td>palms</td>
<td>forearms lower limbs</td>
<td>prednisone (1 mg/kg per day) antiseptic care local betamethasone-17 valerate</td>
<td>favorable</td>
</tr>
</tbody>
</table>

were identified in the relevant literature. The data from all 9 cases (the 3 published cases and our 6 new cases) were collated (Table 1, 2). The mean disease duration (from ALS onset to the occurrence of BP) was 5.6±3.1 years. All patients had limb-onset ALS. Four of the 9 patients received riluzole, and the use of riluzole in these patients ranged from a few days to 3 years. BP was confirmed histopathologically in all cases (except for case 5 among our cases), and hypereosinophilia was observed with an increased frequency (77.8%). Autoantibodies to skin antigens were detected in 5 of 7 (71.4%) patients (we could not test autoantibodies in two of our cases). The histopathological findings and the frequency of hypereosinophilia and autoantibodies to skin antigens in BP-ALS cases closely resemble the characteristics of purely BP (8, 9). When BP occurred, the status of the patients with ALS was paretic and/or bedridden in all cases. As shown in Table 2, BP occurred throughout the body, and we confirmed that the bullous lesions were present not only at the compression site, but also at the anterior part of the chest, abdomen, and limbs. Treatment for BP was successful, as oral prednisone and/or local corticosteroids were effective in all cases. With regard to neurological disorders in patients with BP, a prospective case-control study from France assessed the
independent risk factors for BP, which included neurological disorders, particularly dementia and Parkinson’s disease, psychiatric disorders (unipolar and bipolar disorders), bedridden condition, and chronic use of neuroleptics or spironolactone (6). Neurological disorders such as dementia occur frequently in the elderly, and unexpected cases of BP occurring in adult patients with various neurological disorders have been consistently reported (10). Peramiquel et al. reported two patients with longstanding multiple sclerosis (MS) who developed vesicles and bullae consistent with the diagnosis of BP (11). Langan et al. performed a matched case-control analysis based on a large population-based UK general practice database (4). They reported that significant associations were only observed when neurological disease was diagnosed before the onset of pemphigoid. The study findings, except the association with epilepsy, were robust to sensitivity analyses. Strong associations were observed between specific neurological diseases and the later development of BP, supporting possible causal associations. The mechanisms for disease occurrence according to these findings include immobility or age-related autoimmunity.

Discussion

In this study, the clinical course, laboratory, and histopathological data of six new patients with ALS and BP were described and collated with the data from 3 additional cases of ALS cases with BP that had been published previously. The clinical course, results of laboratory data including anti-BPAG2 antibodies and histopathological analyses, and prompt response to oral corticosteroids of all patients were consistent with BP. An association between ALS and BP was first published by Chosidow et al. in 2000, where three cases in a randomized clinical trial were used to compare the anti-glutamate agent riluzole with a placebo (1). Previous studies showed a potential association between neurological diseases and BP, most of which were reported by dermatologists (4, 6). A prospective case-control study assessing the potential risk factors for BP was also reported by dermatologists in 2011; this study found that the risk factors for BP included neurological disorders, particularly dementia and Parkinson’s disease, psychiatric disorders (unipolar and bipolar disorders), bedridden conditions, and the chronic use of several drugs (6).

In the present study, all of the patients showed the typical clinical course of ALS, and they were in a paretic and/or bedridden state. All six cases had no family history, but we identified a hexanucleotide repeat expansion in C9orf72 in case 4. Additionally, no patient developed bedsore formation. The proportion of ALS patients on TPPV is relatively higher in Japan than in other countries. By following the course of the patients with ALS with a longer follow-up, BP-ALS may be identified by the neurologists. Several study groups have reported that the bedridden and/or paretic state could be a high risk factor for BP in these chronic neurological disorders (6, 12). The occurrence of BP on only the affected side of a hemiplegic patient would appear to support this clinical hypothesis. In our patients and published cases, however, bullous lesions actually had a broader distribution rather than being observed only on the paretic limbs and compression site. Our six new cases and the 3 published cases had a clinical course greater than 3 years and all patients were bedridden or in a severe paretic state. Physical compression in the advanced stage of ALS may be the cause of BP in the bedridden state. However, we speculate that there may be a specific relationship between ALS and BP other than just the result of physical compression. Moreover, the clinical findings of four patients taking riluzole may indicate an association between the occurrence of BP and riluzole therapy. Especially in case 5, the administration of riluzole may have played a role in the development of bullous lesions, although the pathogenic relevance of riluzole remains unclear. Riluzole was not found to be a risk factor of BP in a multicenter, prospective, randomized clinical trial compared to a placebo. Further observations are necessary to confirm the incidence and the relationship between ALS with BP and riluzole treatment.

What mechanisms underlie the biological link between ALS and skin disorders? The importance of glial cell activation and pro-inflammatory cytokines in the pathogenesis of ALS has been confirmed by numerous studies. Some immunologically aberrant perpetuations induced by such cytokines may occur in the pathogenesis of ALS (13). Autoantibodies against skin antigens were confirmed in cases 2, 3, and 4. BPAG1, one of the target antigens in BP, is a member of the plakin family. There are at least three major forms of BPAG1, which have some epitopes in common but also have different tissue-specific actions. The epithelial isoform BPAG1-e links hemidesmosomes to keratin filaments, while BPAG1-a is detected in the nervous system and maintains the organization of the microtubule network in neurons; BPAG1-b expression is more restricted to striated muscles (14). The similarity between the epithelial and neural isoforms of BPAG1 suggests that immunological cross-reactions may play a role in the association of ALS with BP. Li et al. demonstrated that antibody in the serum of patients with BP and neurological diseases recognizes BPAG1 in both the epidermis and the brain (5). These observations raise the possibility that the neuronal isoform of BPAG1 acts as a shared autoantigen in both neurological diseases and BP. Because patients with ALS were not included in the previous study, it is necessary to validate these findings in patients with ALS in the future.

Light and electron microscope alterations in skin connective tissue were previously described in patients with ALS (15, 16). BP in ALS may be under-recognized; however, more importantly, it is treatable with steroid therapy. The pathogenesis of ALS with BP is poorly understood, but most likely involves immunological aberrance. In addition, from the viewpoint of care, treating BP with corticosteroids is beneficial in most cases and should be considered to prevent the progression and promote the recovery of BP.
The authors state that they have no Conflict of Interest (COI).

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References