Bullous Pemphigoid with Esophageal Involvement Presenting as Exfoliative Esophagitis and Acute Upper Gastrointestinal Bleeding: Reports of Two Cases and Review of the Literature

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Bullous pemphigoid is the most common autoimmune blistering skin disease usually occurs in the elderly. The characteristic skin lesions present large and tense blisters arising on normal, erythematous, or urticarial bases and most commonly involve lower abdomen, inner thighs and flexural areas. The mucous membrane lesions occur in about 10 to 35 percent of patients and are almost limited to the oral mucous membrane. Esophageal involvement is a rare condition which may be completely asymptomatic or complicates with dysphagia and even life-threatening massive upper gastrointestinal bleeding. We present two cases of elderly patients with newly onset extensive bullous pemphigoid confirmed by pathological and immunofluorescence studies. One patient developed severe dysphagia. Endoscopy revealed diffuse exfoliative esophagitis and upper gastrointestinal hemorrhage; the other patient developed poor feeding and hematemesis aspirated from nasogastric tube and endoscopy showed multiple ulcers occurred on mid and lower esophagus. Both patients showed much improvement after systemic corticosteroid use. (Dermatol Sinica 26: 171-179, 2008)

Key words: Bullous pemphigoid, Esophagus, Exfoliative esophagitis, Upper gastrointestinal bleeding

INTRODUCTION
Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease usually occurs in the elderly. The characteristic skin lesions present large and tense blisters arising on normal, erythematous, or urticarial bases and most commonly involve lower abdomen, inner thighs and flexural areas. The principle histological findings are subepidermal blister without epidermal necrosis and a superficial dermal infiltrate consisting characteristically of lymphocytes, histiocytes, and eosinophils. Direct immunofluorescence (DIF) study demonstrates linear C3 and IgG depositions at the epidermal basement membrane zone (BMZ). Indirect immunofluorescence (IIF) shows positive for BMZ antibody. The diagnosis depends on the collective interpretation of the clinical, histological and immunofluorescence findings. The mucous membrane lesions occur in about 10 to 35 percent of patients and are almost limited to the oral mucous membrane. Esophageal involvement is a rare condition
which may be completely asymptomatic or complicated with dysphagia and even life-threatening massive upper gastrointestinal bleeding (UGIB).\(^2\) Herein, we present two cases of elderly patients with newly onset extensive BP and complicated with esophageal involvement and UGIB.

**CASE REPORT**

**CASE 1**

A 60-year-old man, who is a hepatitis B carrier, has been diagnosed as having advanced hepatocellular carcinoma with peritoneal seeding and colon involvement. He had been treated by left lobectomy and S6 segmental hepatectomy, transcatheter arterial chemoembolism, recurrence tumor excision and left hemicolectomy. Tense blisters developed on bilateral upper extremities in 2006 June, and spread to the trunk and face including oral mucosa. He visited our clinic and was then admitted to our dermatology ward in 2006 July. On physical examination, there were numerous variously sized erosions and tense bullae, on either erythematous or normal bases, over the face, trunk and four extremities (Fig. 1A). There were numerous oral ulcers but no corneal or rectal involvement. A skin biopsy was done from an intact blister on the back and the histopathology showed subepidermal vesicles and collection of eosinophils in the vesicle. The serum IIF study demonstrated positive anti-BMZ antibody and negative anti-intercellular substance (ICS) antibody. The serum immunoblotting revealed the presence of antibodies

**Fig. 1**

(A) Skin lesions of case 1 showed tense blisters and erosions on the trunk and upper limbs.
(B) Immunoblotting revealed the presence of antibodies against the 230 kDa and 180 kDa proteins (arrow) and absence of antibodies against the 130 kDa (arrowhead).
(C) Endoscopy revealed diffuse exfoliative esophagitis with hemorrhage.
(D) Eighteen days after the first endoscopy, follow-up endoscopy showed resolution of previous esophageal erosions.
against the 230 kDa and 180 kDa proteins (Fig. 1B). According to the clinical presentation, pathology and immunology studies, bullous pemphigoid was diagnosed.

During admission, low dose prednisolone (20 mg/day) was given initially due to comorbidity. Persistent positive stool occult blood was noted and sudden onset of dysphagia was complained after one week of oral prednisolone therapy. Concurrently, the skin activity of BP also increased significantly. Around 15~30 new blisters developed even under systemic prednisolone therapy. Endoscopy showed diffuse exfoliative esophagitis and easily contact bleeding from esophagocardial (EC) junction extended to 20 cm below the incisors (Fig. 1C). Gastric erosion at antrum and plenty of blood clots were also noted at stomach. An endoscopic biopsy from esophagus showed no residual esophageal epithelium and free of microorganism or evidence of malignancy. Thus esophageal involvement of BP was suspected. We increased systemic prednisolone to 80 mg per day and the skin ulcers healed gradually accompanied with the improvement of dysphagia. Eighteen days after the first endoscopy, a follow-up endoscopy showed resolution of previous esophageal erosions (Fig. 1D). The prednisolone dose was tapered smoothly. Four months later, he was maintained on prednisolone 25 mg/day.

**CASE 2**

A 62-year-old man had 3 episodes of ischemic stroke and complicated with left ischemic stroke. Fig. 2

(A) Skin lesions of case 2 showed tense blisters and wheals on the trunk.
(B) Some target-like, edematous lesions were noted on the left thigh.
(C) Several ulcers were found at the lower and middle esophagus.
(D) The esophageal DIF study demonstrated linear C3 deposition at basement membrane zone. (original magnification, x400)
hemiplegia and right hemiparesis. He was on long-term nasogastric (NG) tube feeding due to debilitated status. Numerous erythematous wheals on the hands and the soles were noted by his family members in 2006 September. Tense vesicles and bullae developed from the erythematous bases thereafter. He was brought to one local hospital and was referred to our hospital in 2006 October. On physical examination, there were numerous tense bullae and vesicles on the hands, soles, auricles, trunk, and some wheal-like, edematous, erythematous plaques on the thighs (Fig. 2A, 2B). The pathology of the skin biopsies revealed subepidermal blisters as well as eosinophilic and lymphocytic infiltrates in the papillary dermis. The serum IIF study demonstrated positive anti-BMZ antibody. DIF study demonstrated linear C3 and IgG deposits at BMZ. BP was diagnosed according to the clinical presentation, pathology and immunology studies. Topical clobetasol propionate ointment for the whole body was administered initially.

However, hematemesis from the NG tube and poor feeding were noted. We held NG feeding and intravenous omeprazole was administered, but hematemesis was still noted on consecutive days. Endoscopy disclosed superficial gastritis at the antrum and five ulcers at lower and middle esophagus (Fig. 2C). No active bleeding or blood clot was noted in the stomach. Under the suspicion of esophageal involvement of BP, oral prednisolone 30 mg per day was given. Fourteen days after the first endoscopy, a second endoscopy revealed the size of ulcers decreased compared to the last finding. An esophageal biopsy was done and the pathology revealed squamous hyperplasia with petechial hemorrhage. The esophageal DIF study demonstrated linear C3 deposition at BMZ (Fig. 2D). The prednisolone dose was tapered smoothly. Six months later, he was maintained on prednisolone 10 mg/day.

**DISCUSSION**

Bullous pemphigoid (BP) with esophageal involvement is a rare condition, and it can be suspected when clinically esophageal blisters, erosions and desquamation with concurrent BP skin lesions are noted. Esophageal biopsies, DIF study, or serum IIF study can further confirm the diagnosis. However, esophageal biopsy may be precluded from poor operative endoscopic field due to UGIB or comorbidity. Besides, the specimens acquired by endoscope may not be suitable for delicate DIF examinations. So the diagnosis of BP with esophageal involvement may be done clinically and the rapid clinical response to the administration of systemic corticosteroids.

In our cases, both patients had active BP skin lesions and concurrent esophageal lesions with UGIB. Systemic corticosteroid use increases the risk of peptic ulcers and gastrointestinal hemorrhage, which would not manifest as esophageal ulcers. Our cases also had gastric lesions with concurrent corticosteroid use (case 1: gastric erosion; case 2: superficial gastritis). Case 1 had both esophageal and gastric erosions and hemorrhage demonstrated by endoscopy and esophagus healed faster than stomach. We consider that UGIB in case 2 is from esophagus due to the severity of endoscopic findings (esophageal ulcer v.s. gastric hyperemic patches). The cutaneous and esophageal lesions improved rapidly by systemic corticosteroid treatment. All these features make a clinical diagnosis of corticosteroid-induced esophageal ulcers unlikely. Other etiologies such as viral infection, candidal infection and gastroesophageal reflux could be excluded by the endoscopic findings and the rapid response to prednisolone therapy. Linear C3 deposition at BMZ was noted in the esophageal DIF study of case 2, and this further confirmed the diagnosis.
### Table 1 Reported Cases of Bullous Pemphigoid with Esophageal Involvement

<table>
<thead>
<tr>
<th>Report Year</th>
<th>Age/Sex</th>
<th>Duration of BP</th>
<th>Underlying disorder/ concurrent medications</th>
<th>Pathology/immunology studies</th>
<th>Oral mucosa involvement</th>
<th>Esophageal symptoms</th>
<th>Endoscopic findings</th>
<th>Esophageal biopsy</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parviz et al. (1967)</td>
<td>71/M</td>
<td>9 weeks</td>
<td>None/ NM</td>
<td>Subepidermal bullae/ NM</td>
<td>(+)</td>
<td>Sore throat, dysphagia, substernal burning, foreign body sensation, vomiting a cast</td>
<td>NM</td>
<td>Devoid of epithelium, regeneration at 4 weeks</td>
<td>Systemic corticosteroid</td>
<td>Completely healed</td>
</tr>
<tr>
<td>Eng et al. (1978)</td>
<td>84/F</td>
<td>2 weeks</td>
<td>Hypertension, diabetes mellitus/ NM</td>
<td>Subepidermal vesicles/ DIF: Linear C3 at BMZ, IIF: (-)</td>
<td>(+)</td>
<td>Throat pain and dysphagia, massive hematochezia, syncope</td>
<td>Several bullous lesions of various sizes at proximal and distal esophagus, fresh blood in the distal esophagus</td>
<td>NM</td>
<td>Systemic corticosteroid</td>
<td>Follow-up esophagram showed improvement, expired due to sepsis</td>
</tr>
<tr>
<td>Sharon et al. (1978)</td>
<td>65/M</td>
<td>1 year</td>
<td>NM/ NM</td>
<td>Subepidermal vesicles/ IIF: 1:20 (+)</td>
<td>Candidiasis, no ulceration, no bullae</td>
<td>Upper abdominal pain, may be unrelated</td>
<td>Numerous bullae, scattered throughout the esophageal mucosa</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Nagashima et al. (2000)</td>
<td>73/M</td>
<td>18 days</td>
<td>Atrial fibrillation/ Warfarin</td>
<td>NM/NM</td>
<td>(+)</td>
<td>Odynophagia, massive bleeding</td>
<td>Numerous superficial, circular erosions, fresh blood and clot in esophagus</td>
<td>Normal</td>
<td>Systemic corticosteroid, endoscopic APC x III</td>
<td>Completely healed</td>
</tr>
<tr>
<td>Hwang et al. (2004)</td>
<td>48/F</td>
<td>4 months</td>
<td>End stage renal disease/ NM</td>
<td>Subepidermal blisters/ NM</td>
<td>(+)</td>
<td>Hematemesis</td>
<td>Diffuse desquamation of esophagus with hemorrhage</td>
<td>Separation of mucosal layer which is consisted with the intact entire mucosa</td>
<td>Systemic corticosteroid, azathioprine, endoscopic hemostasis</td>
<td>Completely healed</td>
</tr>
<tr>
<td>Chong et al. (2006)</td>
<td>70/M</td>
<td>NM</td>
<td>Cerebrovascular disease, dementia/ NM</td>
<td>Subepidermal blisters/ DIF: Linear C3, IgG at BMZ</td>
<td>NM</td>
<td>Hematemesis, hypotension</td>
<td>Raw patches in the mid esophagus, blood filled bullae, NG tube (+)</td>
<td>NM</td>
<td>Omeprazole, sucralfate, antiemetic, topical steroid, PEG insertion</td>
<td>Completely healed</td>
</tr>
<tr>
<td>Wu et al. (This report)</td>
<td>60/M</td>
<td>6 weeks</td>
<td>Hepatitis B, hepatocellular carcinoma/ Chinese herbal medicine</td>
<td>Subepidermal blisters/ IIF: 1:20 (+)</td>
<td>(+)</td>
<td>Dysphagia</td>
<td>Diffuse linear slough-off and easily contact bleeding from mid esophagus to EC junction</td>
<td>Devoid of epithelium, regeneration at 3 weeks</td>
<td>Systemic corticosteroid, omeprazole</td>
<td>Completely healed</td>
</tr>
<tr>
<td>Wu et al. (This report)</td>
<td>62/M</td>
<td>2 weeks</td>
<td>Hypertension, cerebral vascular disease, pneumoconiosis, depression/ Enalapril, amiodipine, aspirin, amitriptyline, trazodone</td>
<td>Subepidermal blisters/ DIF: Linear C3, IgG at BMZ, IIF: 1:20 (+)</td>
<td>(+)</td>
<td>Poor feeding and hematemesis from NG tube</td>
<td>Five ulcers at lower and middle esophagus, NG tube (+)</td>
<td>Squamous hyperplasia, linear C3 at esophageal BMZ</td>
<td>Systemic corticosteroid, omeprazole</td>
<td>Completely healed</td>
</tr>
</tbody>
</table>

F, female; M, male; BP, bullous pemphigoid; NM, not mentioned; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; BMZ, basement membrane zone; NG, nasogastric; EC, esophagocardial; PEG, percutaneous endoscopic gastrostomy; APC, argon plasma coagulation; +,detected; -, not detect
A review of the literature on BP with esophageal involvement was summarized in Table 1. Among these 8 cases, six of them had new-onset BP and also oral mucosal lesions. Six patients had UGIB and four of them had significant morbidity as shock or severe anemia. During endoscopy, fresh blood or clot was found in esophagus in five patients. One patient who receiving warfarin due to atrial fibrillation, showed active bleeding and required endoscopic hemostasis with argon plasma coagulation (APC). Two patients were on long-term NG tube feeding due to previous stroke. One patient noted substernal burning following food intake, and a sensation of a foreign body deep in his pharynx, followed by vomiting a long, thin membranous cast. One patient received percutaneous endoscopic gastrostomy for long-term enteral access to avoid repeated esophageal trauma from NG tube. One patient had malignancy (hepatocellular carcinoma), one patient had end stage renal disease on hemodialysis. Due to the rarity of the cases, no obvious relationship between BP with esophageal involvement and underlying systemic disease was found. All patients who received systemic corticosteroids showed significant symptomatic relief and objective improvement from further endoscopy or esophagram. One patient died of sepsis after systemic corticosteroid (dose not mentioned) treatment for two weeks.

BP with esophageal involvement should be differentiated from cicatricial pemphigoid (CP), which most commonly affects the eyes and mouth, but nasal, genital and skin lesions are not infrequently found. Ocular involvement most commonly presents as conjunctivitis and can progress to entropion, trichiasis, symblepharon formation, corneal ulceration and blindness in severe case. Esophageal lesions occasionally occur and may result in recurrent strictures. The major differences

### Table 2 Comparison of Bullous Pemphigoid and Cicatricial Pemphigoid

<table>
<thead>
<tr>
<th></th>
<th>Bullous pemphigoid</th>
<th>Cicatricial pemphigoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin involvement</td>
<td>All, large and tense bullae,</td>
<td>25~35%, small vesicles, transient,</td>
</tr>
<tr>
<td></td>
<td>scarring rare</td>
<td>may or may not scarring</td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td>10~35% (mainly on oral mucosa)</td>
<td>Oral: all</td>
</tr>
<tr>
<td></td>
<td>Esophageal: rare</td>
<td>Ocular: 75%</td>
</tr>
<tr>
<td>Autoantigens</td>
<td>BPAG1, BPAG2</td>
<td>BPAG2, Laminin-5, integrin subunit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β4, M168, type VII collagen</td>
</tr>
<tr>
<td>DIF</td>
<td>Linear C3 and IgG depositions</td>
<td>Linear C3 and IgG depositions</td>
</tr>
<tr>
<td>1M NaCl split</td>
<td>Roof (epidermis)</td>
<td>Roof (epidermis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Roof and base (combined)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Base (dermis)</td>
</tr>
</tbody>
</table>

BPAG, bullous pemphigoid antigen; DIF, direct immunofluorescence
between BP and CP are summarized in Table 2.

The esophageal mucosa is lined by a nonkeratinized, stratified squamous epithelium. Their basal plasmalemmata have numerous extensions projecting into the underlying connective tissue forming hemidesmosomes. The squamous lineage of the esophagus forms a stratified epithelium which has an average turnover time of about 7.5 days, which is more rapid than human skin turnover time. In human skin, the normal transit time for a basal cell, from the time it detaches from the basal layer to the time it enters the stratum corneum, is at least 14 days. This may partially explained the less symptomatic esophageal involvement in autoimmune bullous disease due to a rather rapid turnover rate.

Foroozan et al. had reported one patient had BP with extensive esophageal involvement and vomited a membranous cast which histologically showed the full thickness of the stratified squamous esophageal epithelium. Loss of the esophageal mucosa with resultant sloughing an intact epithelial cast is extremely rare. Esophageal cast was also described as esophagitis dissecans superficia lis, which may result from ingestion of corrosive liquids or autoimmune bullous diseases, but most are without an identified etiology. This phenomenon usually lacks significant bleeding and late complications. Most patients can be managed with conservative approach.

One of our patients had impaired esophageal motor function presented as dysphagia. Decreased gastroesophageal pressure difference, low sphincter tone, and less secondary peristalsis were observed in a previous study. The reason for esophageal motility function impairment is not completely known. Secondary inflammation and edema of the esophageal motor units is suspected. The improvement of esophageal motor function following regeneration of esophageal mucosa was observed.

In treating BP with esophageal involvement, systemic corticosteroid has been shown to be a highly effective therapy for the lesions in the esophagus, as well as those in the skins. UGI endoscopy is recommended for symptomatic patients and is helpful to differentiate esophageal involvement of BP from corticosteroid-related gastric hemorrhage. Although esophageal involvement of BP rarely occurs, acute UGIB may develop and is associated with significant morbidity or mortality, especially in patients who have bleeding tendency, hepatic insufficiency, renal insufficiency, or who are on anticoagulant therapy, on long-term NG tube feeding and debilitated status. Emergent endoscopic hemostasis and blood transfusion can be life saving.

In conclusion, BP with esophageal involvement is a rare condition. Some patients may be complicated with dysphagia and UGIB, especially in patients with comorbidity. Endoscopy is recommended for any suspicious patients for both diagnosis and emergent treatment. Systemic corticosteroid is the treatment of choice in most patients and the lesions usually improve rapidly.

REFERENCES


Bullous Pemphigoid with Esophageal Involvement

類天疱瘡合併以剝落性食道炎及急性上消化道出血為表現之食道侵犯：兩個病例報告及文獻回顧

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類天疱瘡是最常見好發於老年人的自體免疫水泡皮膚病。皮膚典型病灶呈現大而緊繃的水泡，水泡底部呈膚色、紅色或蕁麻疹樣，好發於下腹部、大腿內側及肢端曲側。百分之十到三十五的病患會有黏膜的病灶，多半僅侷限於口腔黏膜。食道侵犯在臨床上相當罕見，表現可全無症狀，或併發吞咽困難及可能有危及生命的大量上消化道出血。我們在此報告兩位老年病患罹患新發之廣泛性類天疱瘡，經病理切片和免疫螢光染色確定診斷。其一病患發生嚴重吞咽困難，而內視鏡發現廣泛性剝落性食道炎及上消化道出血；另一病患發生灌食不佳及鼻胃管反抽發現消化道出血，內視鏡顯示數個位於中段及下段食道的潰瘍。兩位病患在全身性類固醇治療下迅速改善。（中華皮誌：26: 171-179, 2008）