Mucosal Morbidity in Patients With Epidermolysis Bullosa Acquisita

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Background: Epidermolysis bullosa acquisita is an acquired inflammatory and/or dermolytic subepidermal blistering disease characterized by IgG autoantibodies to type VII collagen. Four patients with documented epidermolysis bullosa acquisita were evaluated by a multidisciplinary team of care providers (4 dermatologists, an ophthalmologist, a radiologist, a voice and speech specialist, and an otolaryngologist) for 1 to 5 years to characterize mucosal involvement and its complications and response to treatment. Patients were evaluated clinically and by slitlamp examinations, endoscopies, computed tomographic scans, and videofluorographic swallowing studies. Spiral computed tomographic scans for virtual endoscopy were used for the nontraumatic evaluation of airways in 2 patients with respiratory tract compromise.

Observations: Involvement of 5 or more mucosal sites—mouth, nose, conjunctiva, pharynx, and larynx—was documented in all patients. Complications included ankyloglossia, periodontal disease, scarring and crusting of nasal mucosa, symblepharon formation, obstruction of nasolacrimal ducts, deformation of the epiglottis, impaired phonation, dysphagia, esophageal strictures, and supraglottic stenosis requiring emergency tracheostomy.

Conclusions: Epidermolysis bullosa acquisita may extensively (or predominantly) affect mucosal epithelia in a manner resembling cicatricial pemphigoid. Mucosal disease in these patients is often subclinical, can lead to serious complications, and is best managed using a multidisciplinary approach.

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PATIENTS AND METHODS

PATIENTS

Four patients (aged 32-43 years) with EBA (duration, 3-14 years) were studied; 1 patient has been previously described16,17 in part. All patients had some degree of inflammatory or dermolytic skin lesions at presentation. Additional criteria for the diagnosis of EBA were the presence of deposits of IgG and C3 in epidermal basement membrane and either circulating IgG autoantibodies that bound the dermal side of 1-mol/L sodium chloride split skin in indirect immunofluorescence microscopic studies and type VII collagen by immunoblotting, or in situ deposits of IgG on anchoring fibrils as determined by direct immunoelectron microscopy.

LABORATORY STUDIES

Direct and indirect immunofluorescence microscopy studies were performed as described previously.20,21 Normal-appearing perillesional skin of patients with undetectable circulating anti-type VII collagen autoantibodies was studied by direct immunoelectron microscopy to locate in situ deposits of IgG.20,21 Extracts of lamina densa-dermis from normal human skin were studied by immunoblotting to detect the presence of IgG autoantibodies to type VII collagen, as described.22

IMAGING STUDIES

A flexible nasopharyngoscope (Precision Instrument Division, Olympus Corp, Melville, NY) or a straight nasal endoscope was used to visualize the nasal mucosa, epiglottis, pharynx, larynx, and proximal esophagus. Swallowing function was evaluated by a modified barium swallow study recorded videofluoroscopically. The oropharyngeal and esophageal phases of swallowing were assessed with 3 textures—liquid (10 mL), puree (5 mL), and graham cracker (one quarter piece)—in both lateral and posterior planes. Videotapes were studied to assess oropharyngeal function, the duration of swallowing phases, and the movement of bolus materials from the oral cavity to the esophagus.

Spiral computed tomographic (CT) studies of the supraglottic and subglottic regions were used as a noninvasive imaging technique in 2 patients in whom airway compromise developed. The CT scans were done helically (High-Speed Advantage; General Electric Medical Systems, Milwaukeee, Wis) during slow inspiration or expiration using a 3- or a 5-mm-section thickness and a helical pitch of 1.0 or 1.3.23-25 The CT scans were processed using a surface-rendering technique (virtual endoscopy) that sculpts away all soft tissues of the neck and produces a 3-dimensional model of the airway contour.26 Data were displayed on a specialized computer workstation (Indigo 2 Maximum Impact; Silicon Graphics, Mountain View, Calif) capable of interactive manipulation and “fly-through visualization” (ie, simulated endoscopy) of the 3-dimensional models.27 Results of these studies were compared with the findings of endoscopy.

REPORT OF A CASE

Patient 4, a 36-year-old man from Guyana, was referred for the evaluation of oral and nasopharyngeal blisters and erosions. The patient reported that similar lesions had developed on his skin between 1985 and 1993; subsequently, lesions had been confined to his mucous membranes. His history referable to this involvement included chronic sinusitis requiring intermittent antibiotic therapy, gastroesophageal reflux, hoarseness, and an esophageal stricture treated successfully with bougienage in 1995. Despite intermittent treatment with dapsone and prednisone (the former of partial and the latter of minimal benefit), the disease persists.

In contrast, patient 2 had severe oral involvement characterized by blisters, erosions, and scarring that resulted in ankyloglossia, mandibular contracture, and a notably restricted oral aperture. All patients had gingivitis; patients 2 and 4 had severe involvement resulting in marked periodontal disease, substantial alveolar bone loss, and freely mobile teeth.

NASAL CAVITY

In addition to oral lesions, chronic, erosive, and crusted lesions developed in the nasal mucosa of all patients. Three patients reported bouts of recurrent, yet mild, epistaxis. Patients 2 and 4 had severe involvement that resulted in scarring and obliteration of the turbinate. Patient 4 also had synechiae between his nasal septum and the remnant of the right inferior turbinate, occlusion of the nasolacrimal duct in the right inferior meatus, and episodes of acute and chronic sinusitis.

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forearms, elbows, thighs, knees, legs, and trunk; body hair density within scars was decreased. Fingernails and toenails were normal; there were no milia or blisters on the patient’s skin. The oral mucosa showed sites of erythema and erosion. The tongue was depapillated and scarred, and the buccal mucosa was also scarred. The gingivae were recessed and bled on touch. Multiple teeth in all 4 quadrants were mobile; radiographs identified severe generalized alveolar bone loss. Otolaryngological consultation and nasopharyngoscopy revealed extensive crusts overlying denuded sites on the nasal mucosa, the obliteration of nasal turbinates, the loss of other intranasal anatomic landmarks, a globular epiglottis, eroded mucosa covering the supraglottic region and the true and false vocal cords, and a 2- to 3-mm synchia between the left arytenoid and the posterior hypopharyngeal wall.

As summarized in Table 1, laboratory test results substantiated the diagnosis of EBA. The patient was initially treated with cyclosporine (2.5 mg/kg of body weight per day), dexamethasone elixir in a “swish-and-spit” regimen 3 times each day, and twice-a-day nasal irrigations with isotonic sodium chloride solution, followed by nasal lubricant (Ponaris). Cyclosporine therapy was discontinued after 6 weeks because of sustained elevations in serum creatinine levels. Subsequent stepwise and beneficial additions to the patient’s treatment regimen included omeprazole, 20 mg a day; olsalazine, 2 g two times each day (in place of dexamethasone); frequent dental cleanings; and beclomethasone nasal spray twice each day.

Nine months after his initial presentation, the patient reported difficulty swallowing and a 4.5-kg weight loss. A barium swallow study revealed narrowing of the cervical esophagus at the level of the pyriform sinuses and aspiration of barium into the trachea. Upper gastrointestinal tract endoscopy showed notable dilation of the pyriform sinuses and a broad adhesion between the interarytenoid region and the posterior hypopharyngeal wall that had not been seen on previous examinations (Figure 1). Videofluoroscopic swallowing studies verified the esophageal inlet stenosis and identified the pooling of food in dilated pyriform sinuses, aspiration during swallowing, and the use of multiple swallows to empty material pooled in the pyriform sinuses. Spinal CT scanning for virtual endoscopy confirmed the epiglottic and laryngeal deformities (Figure 2) but indicated that there was no evidence of subglottic stenosis.

Under general anesthesia, the patient underwent direct laryngoscopy and carbon dioxide laser excision of cricopharyngeal scars and the most proximal aspects of the large adhesion between the postcricoid mucosa and the posterior hypopharyngeal wall. Although the esophageal inlet was significantly expanded, it was not possible to ablate the large adhesion because its longitudinal dimension was too extensive (ie, it represented a vertically oriented esophageal stricture). Immediately following laser surgery and while the patient was still subject to general anesthesia, the cricopharyngeal area was injected with triamcinolone acetonide (30 mg at a concentration of 40 g/L). The patient had an uncomplicated postoperative course, no complications from endotracheal intubation, and immediately improved swallowing function. He regained his lost weight during the ensuing months; serial endoscopy found no recurrent strictures in the proximal esophagus up to 18 months after the operation.

In mid-1998, the patient noted intermittent irritation of the right eye associated with episodes of epiphora and discharge. Slitlamp examination revealed conjunctival scarring and medial and lateral symblepharon of both eyes. Of note, there was partial occlusion of the superior punctum of the right eye and stenosis of the superior punctum of the left eye. Compression of the right lacrimal sac resulted in the regurgitation of mucoid discharge from the inferior punctum, indicating stasis in the lacrimal outflow system. Obstruction of the right nasolacrimal duct ostium beneath the inferior meatus was noted by nasal endoscopy. Treatment with prednisolone acetate, 0.12% ophthalmic solution; bacitracin ophthalmic ointment; and massage of the lacrimal sac resolved associated symptoms.

PHARYNX OR LARYNX

Although symptoms referable to the pharyngolaryngeal area were sometimes minimal, all patients showed disease activity in this relatively inaccessible anatomic region. Patient 1 had a slightly globular and minimally thickened epiglottis, several pharyngeal and laryngeal erosions, and erythema of the arytenoids. Patient 2 had a bulbous, thickened, and U-shaped epiglottis that was displaced posteriorly due to interarytenoid and aryepiglottic fold fusions (Figure 2). The latter resulted in progressive supraglottic stenosis and eventually acute airway compromise requiring tracheotomy in 1996. Despite daily treatment with cyclosporine (2.5-4.0 mg/kg each day) and prednisone (10-20 mg/d) for the past several years, the patient’s current maximal glottic “chink” (ie, space between the vocal cords) is about 2 mm. Endoscopy of patient 3 revealed erythema of the arytenoids and true vocal cords—findings thought to be directly related to her gastroesophageal reflux. Alterations in patient 4 were described earlier. The pharynx, larynx, and trachea were also evaluated by spiral CT with computer-aided 3-dimensional reconstruction in patients 2 and 4. This virtual-endoscopy technique provided images that were comparable to those obtained by direct visualization (Figure 2) and allowed the supraglottic and subglottic regions to be evaluated noninvasively.

SWALLOWING

Patients 1, 3, and 4 underwent noninvasive, functional swallowing studies of barium contrast–impregnated solid, semisolid, and liquid materials. Videofluoroscopy revealed that all patients had difficulty during the pharyngeal phase of swallowing. During patient 4’s most pronounced esophageal impairment, he had extensive swallowing difficulties, with pharyngeal bolus retention of food and bouts of aspiration. As observed by videofluoroscopy, liquids were more consistently aspirated than solid or semisolid foods. Furthermore, many instances of aspiration were completely subclinical, eliciting no coughing or foreign body sensations.

VOICE

All patients reported changes in their voice quality as a consequence of EBA. Patients 1 and 3—patients with active but
less severe manifestations of disease—reported occasions when they temporarily (ie, for 12-36 hours) lost their voice following loud singing or shouting. Patient 2 experienced a progressive decline in phonation over many years. Following his tracheotomy in 1996, the volume and tonal consistency of his voice declined even further. Although his most recent endoscopy studies revealed a minimal airway diameter, he remains capable of speaking with the assistance of a Passy-Muir valve fitted onto his tracheostomy tube. Since the time of his first presentation to dermatologic services

Table 1. Cutaneous and Laboratory Findings in Patients With Epidermolysis Bullosa Acquisita

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Duration, y</th>
<th>Major Cutaneous Findings</th>
<th>Immunofluorescence</th>
<th>Immunoelectron Microscopy</th>
<th>Immunoblot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/32</td>
<td>3</td>
<td>Initial widespread inflammatory blisters, gradually evolving into dermolytic lesions primarily on the dorsum of hands and posterior thighs</td>
<td>IgG, C3c 640</td>
<td>ND</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>2/M/43</td>
<td>14</td>
<td>Chronic, severe, widespread dermolytic mutilating disease with scarring alopecia, loss of nails, digital fusion, and contractures</td>
<td>IgG, C3c, IgE, IgA, IgM 2560</td>
<td>ND</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>3/F/36</td>
<td>4</td>
<td>Dermolytic lesions confined to areas of trauma, including hands, elbows, knees, and feet</td>
<td>IgG, C3c, Negative</td>
<td>Sublamina densa</td>
<td>Negative</td>
</tr>
<tr>
<td>4/M/36</td>
<td>12</td>
<td>Initial widespread inflammatory blisters evolving into dermolytic skin disease primarily affecting lower legs</td>
<td>IgG, C3c†, Negative</td>
<td>Sublamina densa</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*All immunoreactants were present in a continuous, linear pattern in epidermal basement membrane. Results of indirect immunofluorescence (IF) studies correspond to titers of IgG anti–basement membrane autoantibodies directed exclusively to the dermal side of the test substrate. Immunelectron microscopy of patients’ skin showed in situ deposits of IgG in the sublamina densa region overlying anchoring fibrils. Immunoblot studies were performed on extracts of lamina densa and densus as described previously. ND indicates not done.

†Findings of direct IF testing were positive only on the patient’s split-skin specimen; all in situ deposits of IgG and C3c were confined to the dermal side of the patient’s split skin.

Figure 1. Preoperative view of stenosis of esophageal inlet in patient 4. The inlet is the small opening just left of the broad adhesion between the arytenoids, postcricoid mucosa, and the posterior hypopharyngeal wall. The broad adhesion was reduced with carbon dioxide laser surgery.

Figure 2. Spiral computed tomographic (CT) imaging with 3-dimensional computer reconstruction (ie, virtual endoscopy) is comparable to flexible endoscopy for visualizing structures in the hypopharyngeal and laryngeal regions of patients with epidermolysis bullosa acquisita. Spiral CT images (A, C, and E) are compared with results of laryngoscopy (B, D, and F); the anterior plane is at the top of each panel. Displayed are the vocal cords of patient 4 (A and B), the bulbous and globular-appearing epiglottis of patient 4 (G and D), and the markedly thickened and U-shaped epiglottis of patient 2 (E and F). Although virtual endoscopy allowed noninvasive imaging of morphologic alterations, endoscopy was essential for the identification of superficial lesions (eg, blisters and erosions) and their extent of involvement.
In 1996, patient 4 had a raspy, hoarse voice. Laryngeal involvement (exacerbated or initiated by gastroesophageal reflux) was deemed responsible.

**ESOPHAGUS**

In addition to the mucosal disease described earlier, patients 2 and 4 had esophageal erosions and strictures. In patient 2, these lesions were successfully treated by balloon dilation under direct visualization as described. Patient 4's lesions were summarized earlier.

**COMMENT**

In most patients with EBA, chronic dermolytic lesions develop either initially or following a phase of disease characterized by inflammatory subepidermal blisters. With prolonged dermolytic disease, scarring becomes notable and can obliterate normal structures such as hair and nails. As shown in this study, EBA can affect mucous membranes in an analogous, progressive manner. Such lesions cause particular morbidity to mucosal epithelia that are typically juxtaposed and subject to bridging scars, strictures, wound contraction, and tissue loss. Furthermore, as demonstrated by many of our patients, mucosal involvement can be subclinical, chronic, and prone to life-threatening complications before symptoms referable to the erosive lesions themselves are identified. Laryngeal and pharyngeal mucosal involvement appears to be particularly susceptible to such silent complications, as demonstrated by 2 patients in this series in whom marked airway deformity developed before major symptoms arose.

In this study, evaluation of the nasal cavity, pharynx, and larynx by endoscopy and of the eyes by slitlamp ex-
amination provided particularly important information. Both procedures were quickly performed on an outpatient basis with minimal discomfort and no complications. In addition, noninvasive videofluoroscopy swallowing studies provided important data about the structure and function of our patients’ oropharyngeal and proximal esophageal regions. The results of these studies exceeded information provided by traditional barium swallow studies (which, in our experience, evaluated middle to lower esophageal and gastroesophageal regions more critically). In patients with substantial pharyngeal and laryngeal involvement, CT scans and virtual endoscopy also provided meaningful information about airway diameter and integrity both above and below the true vocal cords. By excluding the existence of subglottic stenosis, these studies were helpful in preoperative decisions regarding the treatment of patient 4 and also guided the management of patient 2’s airway compromise. Because of its noninvasive nature, virtual endoscopy has the potential to play an increasing role in the evaluation of airways in patients with diseases characterized by epithelial fragility (eg, epidermolysis bullosa). This technique appears to hold particular promise for the evaluation of the subglottic region of adults and all airways of children (ie, sites and subjects, respectively, often difficult to evaluate nontraumatically by endoscopy).

The management of patients with EBA in this series was guided substantially by the extent of their mucosal disease. Local measures of particular importance included the use of topical corticosteroids under occlusion for gingival and oral mucosal disease, regular irrigations with isotonic saline solution and intranasal lubricant (Ponarix) for nasal involvement, and topical corticosteroids for ocular disease. Symptoms of gastroesophageal reflux in all patients responded to treatment with antacids, histamine 2-receptor antagonists, or proton pump inhibitors. Because gastroesophageal reflux can cause substantial laryngeal injury and voice impairment, aggressive treatment of this disorder is warranted in patients with EBA who are already at risk for mucosal disease. As reflected by patients in this series and by previous reports,1,7 EBA remains largely a disease resistant to treatment with parenteral agents. Although the inflammatory disease in patient 1 remitted following treatment with tapering daily doses of dapsone and prednisone, the other patients in this series had chronic, active dermolytic disease. The use of cyclosporine (alone and in combination with prednisone) proved of partial benefit in 1 patient but had to be discontinued in another because of sustained elevations of serum creatine levels. Recently, 2 patients in this series were treated with daclizumab (a humanized monoclonal antibody directed against the interleukin 2 receptor); to date, no significant responses or complications from the use of this agent have been observed.

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