A New Method for Measuring Progression in Patients With Ocular Cicatricial Pemphigoid

J. James Rowsey, MD; Yolanda Macias-Rodriguez, MD; Chris Cukrowski, DO

Objectives: To describe a method to measure the progression of ocular cicatricial pemphigoid and to compare its facility with traditional methods used to measure the progression of the disease.

Methods: The proposed method consists of measuring (in millimeters) the total relative inferior conjunctival surface available in 3 gaze positions. This method was used to monitor 7 eyes of 4 patients with ocular cicatricial pemphigoid over 2 years. The changes in the conjunctival measurements from baseline were compared with the changes documented by traditional methods.

Results: During the study, 2 eyes remained stable (changes, < 3 mm), 2 had a decrease of 10 mm or more, and 3 had a change in measurements between 4 and 9 mm. With the proposed method, we demonstrated the detection of more subtle changes in the conjunctiva of all patients. Patients who had changes between 4 and 9 mm easily underwent staging by the traditional systems when the new technique was used as a reference.

Conclusion: The proposed method offers an objective variable that can be used in consecutive visits to detect subtle progression or disease control in patients with ocular cicatricial pemphigoid.


Ocular cicatricial pemphigoid (OCP) is an acquired autoimmune mucous membrane pemphigoid, type II hypersensitivity reaction, in which the antigen-antibody-complement interaction occurs at the level of the conjunctival epithelial basement membrane zone.1-3 Bullous pemphigoid 180, laminin 5, and β4 integrin are the purported antigens located in the transmembrane hemidesmosomal area in the lamina lucida.3-11

Clinically, OCP is a bilateral disease that is characterized by acute inflammation of the conjunctiva, with redness, blisters, and ulceration of the conjunctiva. Chronic inflammation is associated with subepithelial scarring that leads to fornix shortening.12-14 More recently, the combined influences of connective tissue growth factor and transforming growth factor β3 in the cascade of scarring have been demonstrated.15 This scarring induces eyelid distortion, keratinization of the ocular surface, and eventual ocular fixation causing blindness.13-16 The progression of pemphigoid may be subtle and variable, despite aggressive immunosuppressive therapy. Minimal changes in the conjunctiva, especially conjunctival shrinkage, fornix shortening, and progressive symblepharon, may elude documentation. Algorithms may not categorize the progressive loss of the conjunctival surface and may miss valuable intervention time.

The proved methods for monitoring changes in patients with OCP are the staging systems described by Tauber and coworkers,17 Foster,18 and Mondino and Brown.19 These methods are invaluable for staging the disease, but do not provide sufficient discriminate information for detecting subtle changes in the conjunctival fornix. The disease can progress undocumented within the same stage in either system. We have developed a method to document nuances of progression that has been helpful for providing earlier intervention whenever the disease becomes more active. This article describes this method and compares its facility with traditional methods used to measure the progression of the disease.

Methods

A clinical method to measure the amount of conjunctival shrinkage was designed to detect progressive cicatricial changes in the conjunctiva of patients with OCP. It was used in
the regular appointments of 4 patients for 2 years. Each patient was informed of the measurement technique being used and the purpose of the measurement. No observer was masked. This method was compared with 2 of the standard methods of staging the disease, described by Tauber et al17 and Mondino and Brown.19 The comparison was made to see which methods could document minute changes in the conjunctiva of the patients with OCP between appointments.

PATIENTS

We made the comparison in 4 patients with confirmed OCP. The 4 patients were women, ranging in age from 69 to 77 years. Table 1 shows the clinical summaries of the patients.

Measurements and staging were performed at each appointment of these 4 patients, and the changes between each appointment were documented.

NEW METHOD TO MEASURE THE CONJUNCTIVA

The new method consists of measuring (in millimeters) the distance between the lower limbus and the posterior edge of the retracted lower eyelid margin in 3 different gaze positions: looking up, looking up to the right, and looking up to the left. These gaze positions place the examined conjunctiva on stretch at the 5-, 6-, and 7-o’clock positions. Measurements are taken in millimeters of the stretched conjunctiva. The subconjunctival cicatrix allows eyelid traction to pull the eye inferiorly. As the patient looks up, the eyelid is pulled down until the globe first moves due to the traction on the eyelid. A measurement is taken along each direction of gaze (Figure, A-D).

The result of the sum of the 3 measurements is noted in the medical record at each appointment beside a simple line diagram (Figure, E). The normal conjunctiva measurement is approximately 15 mm in each area of the inspection (sum, 45 mm). This is the total “available” conjunctiva.

We compared the apparent conjunctival shrinkage in millimeters with the staging system of Mondino and Brown.15

THE STAGING SYSTEM OF MONDINO AND BROWN

This method is based on the percentage of conjunctival shrinkage. Stage I of cicatricial pemphigoid shows 25% or less shrinkage of the conjunctival fornices. Stage II of cicatricial pemphigoid shows 25% to 50% conjunctival shrinkage. Stage III of cicatricial pemphigoid shows conjunctival shrinkage of about 75%. The inferior fornix is nearly obliterated; the shallow superior fornix is still present. Stage IV or the end stage of cicatricial pemphigoid shows obliteration of the conjunctival fornices.

THE STAGING SYSTEM OF TAUBER ET AL

This method describes conjunctival destruction and the presence of symblepharon: stage I, chronic conjunctivitis and subepithelial fibrosis; stage II, fornix foreshortening by any degree; stage III, symblepharon by any degree; and stage IV, ankyloblepharon and a frozen globe.

To describe degrees within stages II and III, a indicates 0% to 25%; b, 25% to 50%; c, 50% to 75%; and d, 75% to 100%

For stage II, a through d describe percentage loss of inferior fornix depth. For stage III, a through d describe percentage of horizontal involvement by symblephara, and describe the number of symblephara counted in each patient.

RESULTS

The results of these 4 patients are congruent with the extant staging systems of Mondino and Brown15 and Tauber et al.17

These methods were compared at each appointment. We compared date of service, conjunctival measurement, stages of Tauber et al17 and Mondino and Brown,15 time between visits, changes from baseline, and interventions.

We calculated the stage of Tauber et al17 and Mondino and Brown15 based on the difference in millimeters measured at the slitlamp examination. If 100% of the available conjunctiva measures 45 mm in a healthy eye, then 32 mm represents 25% of conjunctival loss; 22 mm, 50% loss; and 11 mm, 75% loss.

In patient 1, minimal shortening was noted at the first visit in each eye. After surgical procedures on the eyelid in both eyes, the right eye showed a shortening of 1.2 mm in 6 months, and the left eye fornix was reduced after the surgery from 42 to 30 mm (loss of 12 mm). These changes represent progression from stage IaIIia(1) to IIBIIia(1) by Tauber et al17 or from stage I to IIb by Mondino and Brown15 for the right eye, and from stage Ia to IIb by Tauber et al or from stage 1 to II by Mondino and Brown for the left eye. The treatment with methotrexate was increased to 20 mg/wk, and then reduced to 15 mg/wk (Table 2).

In patient 2, the right eye demonstrated no progression in 9 months, but the left eye demonstrated a minute progression of 2 mm. This 2 mm is within the variation of the measurement technique. By measuring the staging change, the left eye demonstrated progression from

### Table 1. Clinical Summaries of the Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Time of Disease Diagnosis, y</th>
<th>Systemic Diseases</th>
<th>Immunosuppressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>0</td>
<td>High blood pressure, arthritis, and clausathrophia</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>0</td>
<td>Thyroid</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>30</td>
<td>Thyroid</td>
<td>Methotrexate, 25 mg/wk</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>6</td>
<td>High blood pressure, thyroid, arthritis, and clausathrophia</td>
<td>Methotrexate, 7.5 mg/wk</td>
</tr>
</tbody>
</table>

*All patients were women.†Time before the first appointment.
stage IIa to IIb (Tauber et al\textsuperscript{17}) and from stage I to II (Mondino and Brown\textsuperscript{19}). The eye remained stable throughout the follow-up (Table 3).

In patient 3, the right eye progressed from 36 to 32 mm. When the patient was treated with methotrexate, 25 mg/wk, only 4 mm of conjunctival surface was subsequently lost in the follow-up period. This corresponds to a change from stage II\textsuperscript{1a}IIb\textsuperscript{(1)} to IIb\textsuperscript{IIb}(1) (Tauber et al\textsuperscript{17}) and from stage I to II (Mondino and Brown\textsuperscript{19}) (Table 3).

The left eye progressed from 34 to 30 mm in 17 months, or a decrease from stage II\textsuperscript{1a}IIb\textsuperscript{(1)} to IIb\textsuperscript{IIb}(1) (Tauber et al\textsuperscript{17}) and from stage I to II (Mondino and Brown\textsuperscript{19}). Immunosuppressive initial treatment was methotrexate, 25 mg/wk; then, cyclosporine, 100 mg/d, was added (Table 3).

Patient 4 demonstrated 30 mm of conjunctiva at the first visit, and after 6 months of treatment with prednisone, in doses from 30 to 40 mg/d, and methotrexate, 10 mg/wk, had an expansion of the conjunctiva to 36 mm.
This relaxation of the conjunctiva with treatment is consistent with a regression of scarring from stage IIbIIIa(1) to IlaIIa(1) by Tauber et al.17 and from stage II to I by Mondino and Brown19 (Table 3).

Two major therapeutic frustrations confront the clinician treating OCP: the early diagnosis and the determination of progression when the diagnosis is established.16-22 This potentially blinding disease may be missed in the early stages because of nonspecific patient complaints of redness and irritation and the subtle conjunctival changes of subepithelial fibrosis.12,23 These patient complaints may be treated as different common conjunctival entities for years before the true nature of the problem surfaces with the earliest signs of conjunctival shrinkage.20,23

The most common mimics of pemphigoid are old acute or current chronic conjunctivitis, chemical injuries, drug toxicities, Sjögren syndrome, and sarcoid.13,24

A history of severe prior conjunctivitis, corneal scars of old adenovirus, cultures of the conjunctiva, a history

**Table 2. Measurements and Changes During the Study in Patient 1**

<table>
<thead>
<tr>
<th>Date</th>
<th>Present Study Conjunctiva, mm</th>
<th>Staging System</th>
<th>Changes From Baseline</th>
<th>Systemic Immunosuppressants and Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tauber et al17</td>
<td>Mondino and Brown19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Eye</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/19/01</td>
<td>15 + 14 + 15 = 44</td>
<td>IaIIa(1)</td>
<td>I</td>
<td>NA</td>
</tr>
<tr>
<td>6/6/02</td>
<td>11 + 10 + 11 = 32</td>
<td>IaIIa(1)</td>
<td>II</td>
<td>3½</td>
</tr>
<tr>
<td>8/29/02</td>
<td>12 + 10 + 11 = 33</td>
<td>IaIIa(1)</td>
<td>I</td>
<td>10</td>
</tr>
<tr>
<td>10/3/02</td>
<td>13 + 9 + 8 = 30</td>
<td>IaIIa(1)</td>
<td>II</td>
<td>11</td>
</tr>
<tr>
<td>10/25/02</td>
<td>12 + 10 + 11 = 33</td>
<td>IaIIa(1)</td>
<td>I</td>
<td>12</td>
</tr>
<tr>
<td>11/21/02</td>
<td>12 + 10 + 11 = 33</td>
<td>IaIIa(1)</td>
<td>I</td>
<td>13</td>
</tr>
<tr>
<td>10/19/01</td>
<td>13 + 15 + 14 = 42</td>
<td>Ila</td>
<td>I</td>
<td>NA</td>
</tr>
<tr>
<td>6/6/02</td>
<td>14 + 13 + 13 = 40</td>
<td>Ila</td>
<td>I</td>
<td>8</td>
</tr>
<tr>
<td>8/29/02</td>
<td>11 + 9 + 11 = 31</td>
<td>Ilb</td>
<td>II</td>
<td>10</td>
</tr>
<tr>
<td>10/3/02</td>
<td>9 + 9 + 11 = 29</td>
<td>Ilb</td>
<td>II</td>
<td>11</td>
</tr>
<tr>
<td>10/25/02</td>
<td>10 + 8 + 12 = 30</td>
<td>Ilb</td>
<td>II</td>
<td>12</td>
</tr>
<tr>
<td>11/21/02</td>
<td>10 + 9 + 11 = 30</td>
<td>Ilb</td>
<td>II</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 3. Measurements and Changes During the Study in Patients 2 Through 4**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye</th>
<th>Date</th>
<th>Present Study Conjunctiva, mm</th>
<th>Staging System</th>
<th>Changes From Baseline</th>
<th>Systemic Immunosuppressants and Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tauber et al17</td>
<td>Mondino and Brown19</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>4/19/02</td>
<td>8 + 7 + 7 = 22</td>
<td>IlaIIa(1)</td>
<td>III</td>
<td>NA</td>
</tr>
<tr>
<td>1/15/03</td>
<td>Left</td>
<td>8 + 7 + 7 = 22</td>
<td>IlaIIa(1)</td>
<td>III</td>
<td>9</td>
<td>0 + 1 + 0 = 1 = 0</td>
</tr>
<tr>
<td>1/15/03</td>
<td>Left</td>
<td>11 + 10 + 13 = 34</td>
<td>IlaIIa(1)</td>
<td>I</td>
<td>NA</td>
<td>1 + 0 + 1 = 2</td>
</tr>
<tr>
<td>8/15/01</td>
<td>Right</td>
<td>15 + 11 + 10 = 36</td>
<td>IlbIIa(1)</td>
<td>II</td>
<td>9</td>
<td>1 + 0 + 1 = 2</td>
</tr>
<tr>
<td>2/11/02</td>
<td>Left</td>
<td>12 + 9 + 9 = 30</td>
<td>IlbIIa(1)</td>
<td>I</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>1/13/03</td>
<td>Left</td>
<td>13 + 10 + 9 = 32</td>
<td>IlbIIa(1)</td>
<td>I</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>8/15/01</td>
<td>Left</td>
<td>10 + 10 + 14 = 34</td>
<td>IlbIIa(1)</td>
<td>I</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>2/11/02</td>
<td>Left</td>
<td>10 + 9 + 12 = 31</td>
<td>IlbIIa(1)</td>
<td>II</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>1/13/03</td>
<td>Left</td>
<td>9 + 8 + 13 = 30</td>
<td>IlbIIa(1)</td>
<td>II</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>5/17/02</td>
<td>Left</td>
<td>10 + 9 + 11 = 30</td>
<td>IlbIIa(1)</td>
<td>II</td>
<td>17</td>
<td>2 + 1 + 1 = 4</td>
</tr>
<tr>
<td>11/14/02</td>
<td>Left</td>
<td>12 + 10 + 14 = 36</td>
<td>IlbIIa(1)</td>
<td>I</td>
<td>8</td>
<td>−3 + −2 + −2 = −7</td>
</tr>
<tr>
<td>1/20/03</td>
<td>Left</td>
<td>13 + 11 + 13 = 37</td>
<td>IlbIIa(1)</td>
<td>I</td>
<td>8</td>
<td>−3 + −2 + −2 = −7</td>
</tr>
</tbody>
</table>

**Abbreviation:** NA, data not applicable.

This relaxation of the conjunctiva with treatment is consistent with a regression of scarring from stage IIbIIIa(1) to IlaIIa(1) by Tauber et al17 and from stage II to I by Mondino and Brown19 (Table 3).
of fluids splashed in the eye, and prior drug use, especially for glaucoma, may all help in delineating the cause of conjunctival scarring. Treatment modalities, such as oral dapsone, topical or systemic corticosteroids, elimination of toxic drugs, immunosuppressive agents, conjunctival reconstruction, all hinge on the periodicity of the clinician in determining progression.

Acute disease activity may lead to rapid progression, whereas slow progression may be associated with minimal conjunctival erythema. Mondino and Brown noted that 9 (30%) of 18 patients with stage 1 disease demonstrated progression during a 22-month follow-up period. Unfortunately, the more severe the disease, the greater the tendency to progression. Patients with stage II disease demonstrated a 75% progression rate, and those with stage III disease, a 78% progression rate. This study suggests that the later stages of the disease may progress without careful monitoring and intervention. The advanced staging system of Tauber et al defines more readily the presence of symblephara in addition to fornix depth loss.

We propose a method of measurement that one of us (J.J.R.) has used for the past 6 years to determine if disease progression or stability can be ascertained in the face of a reasonable therapeutic intervention. We have noted that the normal measurement of the inferior conjunctiva is approximately 15 mm in each observed area, for a cumulative total of 45 mm. Patients are first diagnosed as having the disease, however, after conjunctival shrinkage has already occurred. No patient demonstrated a full 45 mm of residual conjunctiva when diagnosed as having pemphigoid.

The proposed technique is useful for comparing the same patient data against previous examination results. A cumulative measurement decrease of more than 3 mm is reasonably consistent with disease progression. The instruction to retract the lower eyelid while the patient is in an upward gaze provides comparable results between observers. Intraobserver and interobserver variations have not been addressed in this analysis. Measurement errors between examinations may occur if the different retraction pressure is applied to the lower eyelid. The end point of first globe movement on eyelid retraction is the best standardized technique for providing consistent measurements. It is reasonably easy to stage the disease by the published methods, once the progression (in millimeters) is documented. The millimeter measurement is more readily compared than even a serial photographic comparison. It is easy to document a linear 45-mm cicatization to 33 mm, all in stage IIa of the disease (0%-25% loss). Similarly, cumulative loss of the conjunctival total from 32 to 22 mm is more readily appreciated than determining if any progression has occurred within stage IIb (25%-50% loss). We have documented the independent addition of symblephara at each visit on the medical record, but have noted that this progressive shortening is normally documented as an extension of the subepithelial fibrosis already being measured. Horizontal shortening of the eyelid seems to be reflected in the simultaneous vertical conjunctival fibrosis being measured. We were intrigued that some disease regression appeared with heavy treatment, as in patient 4. Previous observers have not suggested disease regression with exacerbation of the conjunctival surface with aggressive intervention. We are unable to determine if this is truly relaxation and expansion of the conjunctiva or decreased orbicularis spasm with eyelid retraction when the disease remits. By using this technique, we were able to classify our patients more readily than by the system of either Tauber et al or Mondino and Brown, and were able to ascertain subtle progression between stages. Validation of the technique with a larger series of patients with OCP is warranted. We submit this proposed simplified technique for others to consider in these difficult therapeutic decisions.

In conclusion, a new method of measuring conjunctival progressive fibrosis in patients with OCP is proposed. Four patients demonstrated changes in conjunctival cicatization during a 2-year period. Use of this method demonstrates subtle progression of pemphigoid.

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15. Razzaque MS, Foster CS, Ahmed AR. Role of connective tissue growth factor in...
At the beginning of last year, the report by an outstanding expert of the judicial court of St Petersburg that they had identified a murderer in Saratow by means of an Optogram, which they had succeeded in obtaining from the eye of the slain, created a great commotion in the Russian press.

In my article, “About Optography and its Medicolegal Aspects,” printed in the “Journal of Hygiene, Medicolegal and Practical Medicine” of January, published by the Ministry of the Interior, I refuted not only the fact of the discovery of the murderer—which had turned out to be untrue—but also the possibility that such Optograms could preserve themselves on the retina of slain person and then be photographed. I concluded my article by attaching the following letter of Professor W.

Esteemed Doctor!

Since the visual purple is bleached by light to a visible degree, and therefore should be unsuitable for still photography, since furthermore the eye has the tendency not to remain fixed for any time, or—if it were to remain fixed—in most instances the objects before it would be moving and not rest, therefore, like in the case which you have cited, one should not count on finding a picture in the post mortem eye. Since the very first paper about Optography were published, no additional ones have appeared about this subject.

Heidelberg, Institute of Physiology,
29/X 1891
Respectfully,
Professor W. Kuehne


Notes From Our Ophthalmic Heritage

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