Successful Long-term Use of Oral Isotretinoin for the Management of Morbihan Disease

A Case Series Report and Review of the Literature

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Background: Morbihan disease (MD) is characterized by persistent erythema and solid edema of the upper two-thirds of the face. It is generally regarded as a late-stage complication of rosacea, although its etiology is poorly understood. The standard therapeutic management includes systemic anti-inflammatory medications; however, the clinical response, if any, is often unsatisfactory. We review the current challenges and a promising new option for the treatment of MD.

Observations: Five cases of MD were treated with long-term (>6 months; mean, 16 months) oral isotretinoin, with documented nonrecurrence. The mean sustained daily dose was 60 mg/d (range, 40-80 mg/d), and the mean cumulative dose was approximately 285 mg/kg (range, 170-491 mg/kg). The total treatment period ranged from 10 to 24 months, with a mean disease-free follow-up period of 9 months (range, 1-24 months). A substantial clinical improvement was not noted until 6 months of treatment in all 5 cases.

Conclusions: We report 5 cases of MD that were successfully treated with long-term oral isotretinoin, with lasting results. Further research is required to better understand the pathogenesis of MD and isotretinoin’s mechanism of action in this condition.


Since its first description by French dermatologist Robert Degos in 1957, Morbihan disease (MD) has remained an ambiguous entity with respect to its etiology and clinical manifestations. The word Morbihan references the French district where the condition was first reported; however, MD has gone by several other names, including rosaceous lymphedema, solid persistent facial edema, and morbus Morbihan.1,3 We report 5 cases of MD that were successfully treated with long-term oral isotretinoin therapy along with a literature review of current options for the treatment of MD.

CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS, AND HISTOPATHOLOGIC FINDINGS

Morbihan disease is characterized by persistent erythema and solid edema of the upper two-thirds of the face.1-12 Clinical examination typically reveals firm, nonpitting edema and erythema, particularly of the forehead, glabella, eyelids, nose, and cheeks.1-12 Facial erythema has been described as ill-defined or discrete patches or as solitary plaques.2,3,5-7 Pitting edema may be evident in its early stages; however, it is believed that fibrotic induration due to recurrent inflammation gives way to the solid edema that is typical of MD.1,3 Subjective symptoms are normally minimal; however, patients with severe periorbital edema may develop disfigurement of facial contours, with subsequent visual field narrowing.1,3,4 Morbihan disease is generally regarded as a late-stage complication of rosacea; however, documented reports of MD as an initial presentation of rosacea complicates its classification as a distinct entity or adverse outcome.3,10,13-16 Nevertheless, MD remains a diagnosis of exclusion and necessitates the omission of other conditions with a similar clinical presentation.3 The differential diagnosis is varied and includes congenital, inflammatory, infectious, and neoplastic diseases.13,15 Melkersson-Rosenthal syndrome, systemic lupus erythematosus, dermatomyositis, sarcoidosis, chronic actinic dermatitis, and...
chronic contact dermatitis are most frequently considered in the differential diagnosis.3

Unfortunately, skin biopsies are not routinely performed in these cases, and biopsy specimens are usually obtained when other possible diagnoses are being considered. As a result, our knowledge of MD's histopathologic findings is limited, and the findings reported in the literature are rather vague. Features include dilated blood vessels, perifollicular fibrosis, perivascular and perifollicular infiltration of lymphocytes, and, rarely, an increased number of mast cells.1,3,4,13 Also, Nagasaka et al1 reported dilated and damaged lymphatic vessels with adjacent epithelioid cell granulomas and lymphatic obstruction via histiocytic infiltration.

PATHOGENESIS

The clinical manifestations of MD appear to result from an imbalance between lymphatic production and drainage. Although the exact pathogenesis of MD remains poorly understood, there is a strong suggestion of an association between MD and rosacea in the existing literature.6-8,10,12

Morbihan disease is likely a manifestation of downstream effects from rosacea’s recurrent episodes of vascular dilation and inflammation.17 In this setting, byproducts of acute and chronic inflammation eventually give rise to tissue remodeling and structural damage of both blood and lymphatic vessels.1-4 This vessel damage is of particular concern among individuals with frequent rosacea exacerbations, who may be susceptible to subsequent lymphatic pooling and impaired drainage.1,3,4,18 The mechanisms for lymphatic vessel destruction may vary by inflammatory trigger, which likely accounts for the variation in histologic findings.2

The stark contrast in incidence between rosacea and MD raises questions regarding the underlying factors promoting the development of MD. Wohlrab et al3 reported a preexisting lymphatic drainage defect in the affected skin of patients with MD through ultrasonography and laser Doppler flowmetry. While their findings suggest a possible cause, there is no way to ascertain whether this insufficiency preceded the diagnosis of rosacea.

TREATMENT

Reported systemic therapy for the treatment of MD includes anti-inflammatory drugs such as systemic corticosteroids, oral antibiotics, thalidomide, and antihista-

![Table. Patient Characteristics](http://archderm.jamanetwork.com/)

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Weight, kg</th>
<th>Sustained Daily Dose of Oral Isotretinoin, mg/d</th>
<th>Total Dose of Oral Isotretinoin, mg/kg</th>
<th>Treatment Period, mo</th>
<th>Disease-Free Follow-up, mo</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/60</td>
<td>76</td>
<td>80</td>
<td>316</td>
<td>20</td>
<td>24</td>
<td>Dry lips and joint pain³</td>
</tr>
<tr>
<td>2/F/81</td>
<td>54</td>
<td>40</td>
<td>258</td>
<td>14</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>3/F/46</td>
<td>57</td>
<td>60</td>
<td>170</td>
<td>10</td>
<td>4</td>
<td>Dry skin</td>
</tr>
<tr>
<td>4/M/54</td>
<td>97</td>
<td>80</td>
<td>190</td>
<td>13</td>
<td>1</td>
<td>Hyperlipidemia⁴ and dry skin</td>
</tr>
<tr>
<td>5/F/21</td>
<td>60</td>
<td>40</td>
<td>491</td>
<td>24</td>
<td>8</td>
<td>None</td>
</tr>
</tbody>
</table>

³Resolved with temporary discontinuation of treatment, decrease in dose, or treatment intervention.

A total of 5 patients (3 women, 2 men) with MD were treated with long-term (>6 months; mean, 16 months) oral isotretinoin at our institution, with documented nonrecurrence. All patients’ relevant clinical characteristics are listed in the Table. The mean sustained daily dose was 60 mg/d (range, 40-80 mg/d), and the mean cumulative dose was approximately 285 mg/kg (range, 170-491 mg/kg). The total treatment period ranged from 10 to 24 months, with a mean disease-free follow-up period of 9 months (range, 1-24 months). A substantial clinical improvement was not noted until 6 months of treatment in all 5 cases. Representative clinical pictures of the response to oral isotretinoin therapy are shown in the Figure.

To date, pharmacological treatment options mostly involve systemic immunomodulators such as corticoste-
roids, antibiotics, and antihistamines; however, the clinical response with these therapies has largely been inadequate. There have been reports of more invasive interventions, including surgical reduction, carbon dioxide laser blepharoplasty, and radiography, with unpredictable outcomes. To our knowledge, this is the first case series to report the effective use of long-term oral isotretinoin for the treatment of MD with complete and lasting results.

Insight into isotretinoin's mechanism of action is limited by the undefined pathogenesis of MD. Conceivably, MD may respond to the same immunomodulatory and anti-inflammatory properties that make oral isotretinoin useful for the management of rosacea. There is also evidence to support isotretinoin's role in the repair of structural tissue damage via alterations in cellular metabolism and its ability to inhibit fibroblast proliferation as well as the migration and proliferation of connective tissue constituents. As a result, isotretinoin therapy may alter the downstream effects of chronic inflammation that would otherwise result in damage to the dermal matrix.

We treated patients with a daily dose ranging from 40 to 80 mg/d for up to 24 months (range, 9-24 months). In contrast, previous reports documenting the use of oral isotretinoin for the treatment of MD recommend doses ranging from 10 to 50 mg/d for 4 to 6 weeks, both of which are substantially lower than those that were found to be effective in our patients. The effective treatment dose in our sample appeared to be somewhat dependent on body weight, with patients who weighed more than 70 kg requiring a daily dose of 80 mg and those who weighed between 50 and 60 kg requiring 40 to 60 mg/d. All 5 patients were given a starting dose of 20 mg/d, which was titrated up until a clinical response was observed. Adverse effects, which were limited to dry lips, joint pain, and hyperlipidemia, were mild and easily managed. Clinical improvements in facial erythema and edema were noted within 4 to 6 weeks of treatment initiation, as documented in the existing literature; however, the most substantial effects were observed after 6 months of therapy. Isotretinoin therapy was continued until facial erythema and edema had completely resolved (10 to 24 months). All 5 patients described in our case series have completed therapy, with no documented disease recurrence.

Morbihan disease has long been considered a refractory condition with discouraging treatment options. The use of long-term oral isotretinoin, a treatment regimen not previously described (to our knowledge), is a promising alternative. Adverse events were minimal and easily managed; however, patients should be closely monitored given the safety profile of oral isotretinoin. Further research is required to better understand the pathogenesis of MD and isotretinoin's mechanism of action in this condition.
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REFERENCES