High Frequency of Genital Lichen Sclerosus in a Prospective Series of 76 Patients With Morphea

Toward a Better Understanding of the Spectrum of Morphea

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Objective: To compare the frequency of genital lichen sclerosus (LS) in patients with morphea with that of control patients.

Design: A prospective multicenter study.

Setting: Four French academic dermatology departments: Strasbourg, Montpellier, Tenon Hospital Paris, and Henri Mondor Hospital Créteil.

Patients: Patients were recruited from November 1, 2008, through June 30, 2010. Seventy-six patients with morphea and 101 age- and sex-matched controls, who underwent complete clinical examination, were enrolled.

Interventions: A complete clinical examination and, if deemed necessary, a cutaneous biopsy.

Main Outcome Measure: The frequency of genital LS.

Results: There were 58 women and 18 men (a 3:1 ratio) with a median age of 59 years. Mean (range) age at diagnosis was 54 (13-87) years. Forty-nine patients had plaque morphea, 9 had generalized morphea, and 18 had linear morphea. Three patients (3%) in the control group and 29 patients (38%) with morphea had LS (odds ratio, 19.8; 95% CI, 5.7-106.9; \( P < .001 \)). Twenty-two patients with plaque morphea (45%) and only 1 patient with linear morphea (6%) had associated genital LS.

Conclusions: Genital LS is significantly more frequent in patients with morphea than in unaffected individuals. Forty-five percent of patients with plaque morphea have associated LS. Complete clinical examination, including careful inspection of genital mucosa, should therefore be mandatory in patients with morphea because genital LS bears a risk of evolution into squamous cell carcinoma and thus needs treatment with topical corticosteroids.


ORPHEA AND LICHEN SCLEROSUS (LS) ARE 2 ENTITIES THAT ARE CHARACTERIZED CLINICALLY BY PLAQUES OF INDURATED, SCLEROTIC, AND DYSCHROMIC SKIN AND PATHOLOGICALLY BY AN INFLAMMATORY DERMAL INFILTRATE AND DERMAL FIBROSIS. THEIR CAUSE IS LARGELY UNKNOWN, ALTHOUGH BOTH GENETIC AND ENVIRONMENTAL FACTORS, SUCH AS PREDISPOSING HLA ALLELES, HAVE BEEN DESCRIBED. \(^2^1\) MORPHEA INVOLVES THE SKIN, BUT THE EXTREMITIES, THE FACE, AND THE AREOLAR AREA ARE USUALLY SPARED, WHILE LS USUALLY INVOLVES THE GENITAL MUCOSA. SKIN INVOLVEMENT CAN OCCUR IN LS BUT IS RARE.

Although there are some similarities between morphea and LS, their exact relationship remains debated. Some authors\(^2^2\) consider that LS is a superficial variant of morphea occurring mostly in the genital area, whereas others\(^2^3-2^5\) consider that they are 2 unrelated entities. In some cases involving the skin, referred to as “white spot disease,” the differential diagnoses between morphea and LS can be impossible. However, lesions occurring on genital mucosa are usually considered synonymous with LS. Yet, to our knowl-

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edge, no study has evaluated the frequency of LS in patients with typical morphea. Furthermore, in clinical practice, genital examination is not systematically performed in patients with morphea. Neither is it recommended in most dermatology textbooks. However, it is important to diagnose genital LS if present, because this entity bears a significant risk of squamous cell carcinoma. This risk can probably be reduced by early and sustained treatment with topical corticosteroids. Thus, the aim of this study was to evaluate the frequency of genital LS in patients with morphea.

METHODS

This is a prospective multicenter study. Patients were recruited from November 1, 2008, through June 30, 2010, in the departments of dermatology from 4 French universities: Strasbourg, Montpellier, Tenon Hospital Paris, and Henri Mondor Hospital Créteil. Patients were included if the diagnosis of morphea was confirmed clinically by an experienced dermatologist or after a skin biopsy. Data were collected on a standardized questionnaire and included age and sex. For this purpose, a comparison test was conducted between the expected difference in prevalence would be 10%, would be 50 to 80 patients with a power of 95%.

Statistical analyses were performed in collaboration with the Statistiques et Methodologies at the Université de Strasbourg. Before starting the study, we estimated that the number of patients to be included, assuming that the incidence of LS in the general population is 1 in 300 to 1 in 1000 and that the expected difference in prevalence would be 10%, would be 50 to 80 patients with a power of 95%.

The main objective was to compare the frequency of genital LS in patients with morphea with that of the control group. For this purpose, a comparison test was conducted between the frequency of genital LS in these 2 groups. The odds ratio was calculated by the Fisher exact test. We compared the age and sex between case patients and the control group by the chi-square method. Under French law, this type of study, which does not involve any invasive investigation but relies on a questionnaire performed during a regular consultation, does not need the approval of the institutional review board.

RESULTS

EPIDEMIOLOGY

We included 76 patients with morphea. This group consisted of 18 men (24%) and 58 women (76%). The mean (range) age was 54 (13-87) years. The mean (range) duration of morphea was estimated to be 7.9 years (6 months–36 years), but it was not specified in 46 cases. The diagnosis was made on typical clinical findings in 50 patients and was confirmed by a biopsy in 26.

One hundred one controls were included (68 women and 33 men). The mean (range) age was 57 (1-87) years. There was no significant statistical difference between the patients and the control group for age (P = .44) and sex (P = .30).

Forty-nine patients had plaque morphea, 18 had linear morphea, and 9 had generalized morphea. In only 1 patient, the clinicopathologic findings were typically those of extragenital LS. This patient had pathologically confirmed plaques of both morphea and extragenital LS. The clinical characteristics in these patients are summarized in Table 2.

FREQUENCY OF GENITAL LS

Three patients (3%) in the control group and 29 patients (38%) with morphea had LS. Thus, compared with the frequency in the control group, genital LS is significantly more frequent in patients with morphea, with an odds ratio of 19.8 (95% CI, 5.7-106.9; P < .001).

The frequency of LS according to type of morphea is illustrated in Figure 1. Forty-five percent of patients with plaque morphea and only 6% of patients with linear morphea had genital LS (P < .001).

Twenty percent of patients had genital pruritus. Interestingly, none of the patients spontaneously complained about this symptom, which was always revealed through specific questioning.

INCIDENT CASES

Twenty-seven patients were incident cases of morphea who did not see a dermatologist before this study and in whom diagnosis of morphea was previously not established. Their mean (range) age was 50.8 (13-84) years, and the female to male ratio was 21:6. The mean (range) duration of morphea was estimated as 4.6 years (6 months–33 years). Of these 27 patients, 13 (48%) had genital LS. The mean (range) age of the 13 patients with genital LS was 64.9 (14-
84) years. Ten of the 13 patients had plaque morphea (Figure 2) and 3 had generalized morphea.

**Table 2. Clinical Characteristics of Patients With Morphea**

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Female/Male Sex</th>
<th>Mean Age, y (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque morphea (n=49)</td>
<td>Common variant</td>
<td>32</td>
<td>27/5</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>Atrophoderma of Pasini and Pierini</td>
<td>10</td>
<td>9/1</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td>Keloid morphea</td>
<td>1</td>
<td>1/0</td>
<td>62.0</td>
</tr>
<tr>
<td></td>
<td>Guttate morphea</td>
<td>1</td>
<td>1/0</td>
<td>62.0</td>
</tr>
<tr>
<td></td>
<td>Deep morphea</td>
<td>3</td>
<td>2/1</td>
<td>68.0</td>
</tr>
<tr>
<td></td>
<td>Schulman’s fasciitis</td>
<td>2</td>
<td>1/1</td>
<td>64.5</td>
</tr>
<tr>
<td>Linear morphea (n=18)</td>
<td>Band</td>
<td></td>
<td>6/2</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper and lower limbs</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhoidal</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>En coup de sabre</td>
<td>6</td>
<td>5/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parry Romberg syndrome</td>
<td>4</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>Generalized morphea</td>
<td>. . .</td>
<td>9</td>
<td>4/5</td>
<td>62.6</td>
</tr>
</tbody>
</table>

\(^a\) At inclusion.

This study shows that genital LS is significantly more frequent in patients with morphea than in controls and that LS is found with an unexpected high frequency of 38% in patients with morphea. The prevalence of LS in the population is difficult to evaluate, but it is estimated from 1 in 300 to 1 in 1000.

Thus, the frequency of LS in the controls of this study is ten times higher than the frequency usually estimated to occur in the general population. This can be explained by a selection bias in our control group of patients mainly recruited in a dermatology department and examined by experienced dermatologists. However, it should also raise some doubt about the usually published data regarding prevalence rates of LS in the general population. It might be that the exact prevalence of LS in the general population is largely underestimated. Indeed, evaluation of prevalence is difficult because the manifestation may be asymptomatic, patients do not consult for discomfort because of the genital location of the lesions, and many physicians are not familiar with this entity and are thus unable to correctly diagnose it. Only a systematic genital examination by an experienced practitioner will provide valuable prevalence rates. In any case, this unusually high frequency of LS in the control group could have harmed this study by lowering our ability to demonstrate a difference in the frequency of genital LS between controls and patients with morphea. This was not the case because there is still a large and significant difference.

Genital LS was significantly more frequent in patients with plaque morphea than in patients with linear morphea. This observation further supports the fact that those 2 entities might result from different pathomechanisms. Only 1 patient with linear morphea had associated LS. There were, however, too few patients with lin-
ear morphea included in this study to draw any definitive conclusion about a possible association. Patients with plaque morphea are those with the highest risk of associated genital LS, with occurrences in about 45% of patients. Furthermore, when we restrict our analysis to patients with incident morphea, that is, those who were not diagnosed with morphea before entering this study, we find a comparatively high frequency of LS of 48%. This fact could suggest that LS usually precedes morphea. The association between morphea and LS has been reported previously, mainly in patients with plaque morphea. But it was reported only once in a case of linear monoclonal morphea in a young boy. In most cases, however, the LS was extragenital. Only 1 study reported 7 cases of patients with morphea and genital LS. The fact that 38% of patients with morphea have associated genital LS strongly supports the fact that these 2 diseases share common pathogenetic pathways, and possibly a common genetic background, if they are not one and the same disease. Indeed, both entities are chronic inflammatory skin diseases characterized by dermal fibrosis. Lichen sclerosus could be the genital manifestation of morphea.

In conclusion, this study clearly shows that LS is significantly more frequent in patients with morphea. This finding should definitely affect our clinical practice. Indeed, it is not the standard of care to completely undress patients with morphea, and this practice is not recommended in the major dermatology textbooks. The results of this study, however, show that it is mandatory to perform a complete examination, including the genital mucosa. That will allow us to diagnose a substantial number of cases of LS and eventually to prevent or at least to provide early diagnosis of the genital carcinomas that will arise on them.

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REFERENCES

Missing Genital Lichen Sclerosus in Patients With Morphea

Don’t Ask? Don’t Tell?

Lichen sclerosus (LS) is an autoimmune inflammatory dermatosis that most commonly affects the female genitalia, with an estimated prevalence of 1 in 300 to 1 in 1000. An increased frequency of autoimmune disorders, including thyroid disease, vitiligo, alopecia areata, and pernicious anemia, occurs in patients with vulvar LS compared with controls. A diagnosis of LS should prompt evaluation for other autoimmune diseases, including thyroid disease, vitiligo, alopecia areata, and pernicious anemia, occurs in patients with vulvar LS compared with controls.

A diagnosis of LS should prompt evaluation for other autoimmune diseases, but what conditions should prompt physicians to investigate for genital LS?

The article by Lutz et al2 demonstrates an increased frequency of genital LS in males and females with plaque, linear, or generalized morphea. More than 40% of patients with plaque morphea and two-thirds of patients with generalized morphea were found to have genital LS. Morphea and LS may exhibit overlapping clinical and histopathologic features. Whether morphea and LS represent a disease continuum remains debatable, but the presence of morphea as a marker for genital LS should no longer be overlooked.

The practice gap of failing to diagnose genital LS in patients with morphea likely begins with an incomplete history. Dermatologists may be reluctant to inquire about genital symptoms out of fear of “opening Pandora’s box.” Patients may not consider their genital symptoms to be relevant to their dermatologic evaluation. Finally, patients may be reluctant to report genital symptoms. Lutz et al found that 20% of their patients with genital LS had genital pruritus when questioned, but none spontaneously disclosed this symptom. A brief discussion between patient and physician regarding the rationale for questioning about genital symptoms will ease the anxiety of those involved and facilitate a focused interview.

Patients with genital LS most commonly present with genital pruritus. Dysuria, dyspareunia, painful defecation, and constipation also occur. Genital LS may, however, be asymptomatic even in the setting of advanced disease. Therefore, thorough examination is paramount to making the diagnosis. Dermatologists should become com-