Onychomycosis in Systemic Lupus Erythematosus: A Case Control Study

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ABSTRACT. Objective. Immunosuppressed patients are prone to develop onychomycosis. In systemic lupus erythematosus (SLE) there are no previous studies. We aimed to establish the prevalence, clinical characteristics, and organisms causing onychomycosis in SLE patients compared with controls.

Methods. Fifty consecutive patients with SLE seen on an outpatient basis and 50 sex and age matched controls. Samples were obtained when abnormal nails were found: distal and lateral subungual onychomycosis (DLSO), white superficial, proximal subungual (PSO), endonyx, and total dystrophic (TDO). The nail specimens were evaluated in a blinded fashion, by mycologic examination and culture.

Results. Of the SLE patients, there were 12 (24%) with onychomycosis confirmed. The distribution of the clinical forms were TDO 6/12 (50%), DLSO 4/12 (33%), and PSO 2/12 (17%). The causative organisms were isolated in 6 cases: Trichophyton rubrum 3/6 (50%), Trichophyton mentagrophytes 2/6 (33%), Microsporum canis 1/6 (17%). Direct microscopy examination revealed fungal elements in the other 6 cases. Of the 50 controls, 4 (8%) presented onychomycosis [p = 0.029; OR 3.63 (95% CI 1.04–14.68)]; DLSO 2/4 (50%), and TDO 2/4 (50%). Trichophyton rubrum was isolated in 1 and Trichophyton mentagrophytes in 1 (50%).

Conclusion. These data suggest a higher prevalence of onychomycosis in SLE versus controls, the predominant organism was Trichophyton rubrum, an anthropophilic dermatophyte. Toenails were more frequently affected and the most common clinical presentation was TDO. PSO, a rare pattern in immunocompetent subjects, was exclusively found in the lupus group. (J Rheumatol 2003;30:1491–4)

Key Indexing Terms:
ONYCHOMYCOsis
DERMATOPHYtOSIS

Onychomycosis, a mycotic infection of the nail unit, may be the commonest nail disorder in adults. It is estimated that 50% of all nail disorders are caused by fungal infection. It occurs worldwide, and accounts for 30% of all superficial fungal infection. Onychomycosis is caused by 3 groups of fungi, namely dermatophytes, nondermatophyte, molds, and yeast; dermatophytes make up 80% of the cases, at least in temperate zones. It occurs as primary onychomycosis caused by nail pathogens that invade the healthy nail plate, or represents a secondary invasion of the nail with pre-existing cutaneous disease. The prevalence has been estimated between 2.8–6.5%. It is apparent that onychomycosis is not an uncommon disease, and its prevalence is increasing.

Recently, Baran, et al classified fungal nail infection in 5 clinical patterns: distal and lateral subungual onychomycosis (DLSO), superficial onychomycosis, proximal subungual onychomycosis (PSO), endonyx onychomycosis, and total dystrophic onychomycosis (TDO). With regard to localization, the prevalence of toenail onychomycosis is higher than fingernail onychomycosis or concurrent infection of both sites. It is generally accepted that the vast majority of cases are caused by anthropophilic dermatophytes (82%); Trichophyton rubrum is the commonest, followed by T. mentagrophytes. Immunosuppressed patients are prone to development of onychomycosis, as are
organ transplant recipients and patients with acquired immunodeficiency syndrome.

The literature concerning nail alterations in SLE is scarce. Urowitz, et al. detected nail changes in 42 of 165 SLE patients (25%); the most common abnormality found was onycholysis. Vaughn, et al. observed diffuse dyschromia in about 52% of black SLE patients; however, no systematized study has investigated fungal infection. The aim of our study was to determine the prevalence, clinical characteristics, and organisms causing onychomycosis in patients with SLE versus controls without lupus.

MATERIAL AND METHODS
Over a period of 12 weeks, 50 consecutive SLE patients seen at the rheumatologic outpatient clinic were included. They were examined by a dermatologist for nail lesions and compared with 50 consecutive sex and age matched control patients without SLE attending a dermatologic outpatient hospital. Patients were informed about the protocol. In order to avoid referral bias, we excluded patients referred to the dermatologist for the management of any problem involving the nail, including onychomycosis; also excluded were: those receiving topical or systemic treatment for mycosis at any time during the previous 3 months and those who declined to have their nails examined. All patients enrolled in the study provided informed consent before any procedures related to the study were carried out. The study protocol was approved by the ethics committee of the hospital.

Evaluation of nails in hands and feet was performed by the same dermatologist. When any abnormality was found, sampling of nails for mycologic examination was done by experienced personnel trained specifically in the procedures. Separate samples were obtained if more than one nail was suggestive of onychomycosis. Demographic data were obtained in each case and nail scrapings were sent to the regional mycology laboratory, where they were tested in a blinded manner. Mycologic examination included: microscopic examination of a 30% potassium hydroxide (KOH) preparation of nail scrapings, investigations for hyphae, and mycological culture on Saboraud dextrose agar with chloramphenicol (0.05 mg/ml) using both cycloheximide-free and supplemented media (0.5 mg/ml), incubated at 25°C for at least 2 to 3 weeks. The identification of the isolated agents on culture was based on their morphologic characteristics both macroscopically and microscopically.

According to previous reports, onychomycosis was considered positive if: (1) mycologic examination of nail scrapings revealed fungal elements (fungi filaments or yeast pseudomycelia seen on KOH preparation); or (2) culture for dermatophytes, nondermatophyte molds, or yeast was positive on growth media; or (3) both procedures were positive (KOH and culture).

Results were evaluated by descriptive statistics. Differences were considered significant at p < 0.05. Onychomycosis prevalence was tested with chi-square test. Risk odds ratios (OR) and 95% confidence intervals (CI) were determined.

RESULTS
From the 50 patients, there were 46 (92%) women with a mean age 32 ± 12 years (range 15–73) and a female-to-male ratio of 11:1. The overall time of evolution of disease in the SLE group was 6.56 ± 4.62 years (range 1–20); in all cases nail changes appeared after diagnosis of SLE; the time between the diagnosis of SLE and the beginning of the onychomycosis was 6 years (range 1.5–11); and none of the patients had received prior antifungal therapy. At the time of sampling all patients were receiving oral prednisone 16.25 ± 13.75 mg/day (range 2.5–60).

From the 50 lupus patients, abnormal-appearing nails were observed in 16 (32%) cases; there were 12 (24%) patients with confirmed onychomycosis [p = 0.029; OR 3.63 (95% CI 1.04–14.68)], i.e., positive culture in 6 (50%) patients and fungal elements on nail scrapings with negative culture in 6 (50%). Onychomycosis of the toenails was present in 12 (100%) patients, and toenails plus fingernail involvement in only 3 (25%). In the remaining 34 (68%) patients, we found no nail abnormalities on physical examination. Table 1 shows the results of KOH examination and culture.

Considering only those cases in which an organism was grown (6 patients), the isolated organisms were a dermatophyte in all cases (100%). The causative organism was Trichophyton rubrum in 3/6 (50%), T. mentagrophytes 2/6 (33%), and Microsporum canis 1/6 (17%). The distribution of the clinical forms were as follows: TDO 6 (50%), DLSO 4 (33%), and PSO 2 (17%) (Figure 1). We were unable to find any relationship between time of evolution of the SLE, the amount of corticosteroids, and the beginning of the onychomycosis.

Of the 50 matched controls with dermatologic illness not involving the nail, abnormal-appearing nails were observed in 6/50 (12%) of the cases; there were 4 patients (8%) with confirmed onychomycosis; but in the remaining 46 (92%) we could not detect nail abnormalities on physical examination. The distribution of the clinical forms were DLSO in 2/4 (50%); in the other 2 cases (50%) we observed the TDO form. Fungal elements on nail scrapings were seen in 2/4 patients (50%), and positive cultures were obtained in the other 2 patients (50%). The organisms isolated corresponded to the dermatophyte group in both cases (100%), T. rubrum in one case (50%) and T. mentagrophytes in the other. Involvement of the toenails was present in all patients. No patient in the control group was receiving corticosteroids.

In both groups onychomycosis involved the feet essentially in a symmetric form, in foot onychomycosis the DLSO and TDO patterns involved the great toenails in the majority of instances. In both fingernails and toenails the most common organism was a dermatophyte. The PSO pattern was found exclusively in the lupus group, and the third and fourth toenails were more likely to be infected.

DISCUSSION
Our data suggest that onychomycosis in Mexican SLE patients is not an uncommon disease [12 out of 50 (24%) patients], the frequency compares to results found in the HIV-positive population (23.2%)14, but was higher compared with the control group; prevalence in the latter group corresponds to studies in general populations from different countries.
In our study, the prevalence of toenail onychomycosis was higher than onychomycosis in the fingernail or concurrent infection at both sites, but not significantly different versus the general population worldwide. In SLE, *Trichophyton rubrum* was the most frequent agent isolated, not different from previous communications from the general population; however, it is remarkable that zoophilic dermatophyte species like *Microsporum canis* was isolated from nails: this species causes less than 1% of total nail infections. A similar trend toward a slight increase in infections with *M. canis* has been seen in Slovenia and Italy.

The clinical pattern most frequently found was TDO in both groups, in contrast to previous reports where the DLSO pattern predominated, possibly reflecting the long period of time between the beginning of nail infection and diagnosis. Surprisingly, the PSO pattern was found in 2/12 (17%) of our lupus patients and in no control subjects: this rare form of mycotic leukonychia occurs almost exclusively in immunodeficient patients. Because PSO is unusual in healthy persons, its presence has been suggested to be associated with an immunodeficient state; however we must recognize that our sample size is small and larger studies in lupus patients are required.

The probable factors responsible for this major prevalence in our SLE patients could be: (1) toenails are not systematically reviewed, so onychomycosis remains undetected in a majority of patients; (2) patients do not report nail changes because they are not usually cause for complaint, and (3) immunosuppressive drugs are frequently used.

For onychomycosis many effective topical antifungals are available including ciclopirox, naftifine, and terbinafine; however, topical treatment of nails is significantly less effective than oral therapy. Systemic therapy includes: pulse itraconazole 400 mg daily for one week per month for 3 months; this was found to be equally effective as continuous

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**Table 1. Clinical patterns and organisms causing onychomycosis isolated by mycological examination or culture in the lupus group.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Pattern</th>
<th>Light Microscopic Examination</th>
<th>Culture</th>
<th>Microorganism</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TDO</td>
<td>+</td>
<td>+</td>
<td><em>Trichophyton rubrum</em></td>
<td>Toenail/fingernail</td>
</tr>
<tr>
<td>2</td>
<td>TDO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail</td>
</tr>
<tr>
<td>3</td>
<td>TDO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail</td>
</tr>
<tr>
<td>4</td>
<td>PSO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail</td>
</tr>
<tr>
<td>5</td>
<td>DLSO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail/fingernail</td>
</tr>
<tr>
<td>6</td>
<td>TDO</td>
<td>+</td>
<td>+</td>
<td><em>T. rubrum</em></td>
<td>Toenail</td>
</tr>
<tr>
<td>7</td>
<td>DLSO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail</td>
</tr>
<tr>
<td>8</td>
<td>TDO</td>
<td>+</td>
<td>–</td>
<td>No growth</td>
<td>Toenail</td>
</tr>
<tr>
<td>9</td>
<td>TDO</td>
<td>+</td>
<td>+</td>
<td><em>T. mentagrophytes</em></td>
<td>Toenail/fingernail</td>
</tr>
<tr>
<td>10</td>
<td>PSO</td>
<td>+</td>
<td>+</td>
<td><em>Microsporum canis</em></td>
<td>Toenail</td>
</tr>
<tr>
<td>11</td>
<td>DLSO</td>
<td>–</td>
<td>+</td>
<td><em>T. rubrum</em></td>
<td>Toenail</td>
</tr>
<tr>
<td>12</td>
<td>DLSO</td>
<td>–</td>
<td>+</td>
<td><em>T. mentagrophytes</em></td>
<td>Toenail</td>
</tr>
</tbody>
</table>

TDO: Total dystrophic onychomycosis; DLSO: distal and lateral subungual onychomycosis; PSO: proximal subungual onychomycosis. T:Trichophyton.

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**Figure 1. Clinical appearance of the different patterns of infection observed in the patients with SLE: (A) distal and lateral subungual onychomycosis, (B) proximal subungual onychomycosis, and (C) total dystrophic onychomycosis.**
therapy with 200 mg daily for the same period of treatment\textsuperscript{26}. Fluconazole, is recommended at doses between 150 mg to 450 mg every week for 3 months for fingernails and 6 months for toenails\textsuperscript{27}. Terbinafine, which was approved by the US Food and Drug Administration for the treatment of onychomycosis in 1996, may be more efficacious than either pulse dosing or continuous dosing with itraconazole. An evidence-based analysis of published studies cited the production of disease-free nails in 35% to 50% of patients treated with terbinafine versus 25% to 40% of patients treated with itraconazole\textsuperscript{28}. However, there have been reports of serious cutaneous side effects, including cases of terbinafine-induced or exacerbated SLE\textsuperscript{29-31}. This suggests that terbinafine must be used with caution in patients with SLE.

An advantage of our study is that the clinical evaluation, mycologic sampling, and laboratory analysis were performed by a small number of persons, all highly skilled in these techniques; however, in order to minimize false-negative results, histological examination is desirable because hyphal invasion provides definitive proof of a fungal etiology.

Onychomycosis is not merely a cosmetic problem. Additional studies with more patients from different geographical locations are needed to establish the real prevalence of onychomycosis and to validate our results.

REFERENCES