Clinical Features and Efficacy of Antimalarial Treatment for Reticular Erythematous Mucinosis

A Case Series of 11 Patients

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Background: Reticular erythematous mucinosis (REM syndrome) is a rare cutaneous disease that predominantly affects the chest and upper back area of middle-aged women. Although antimalarial treatment is generally considered the most effective approach, only a few case reports exist on its use in REM syndrome.

Observations: A total of 11 patients with REM syndrome (10 women and 1 man), mean age, 44 years (age range, 37-54 years), were included in this retrospective analysis. Ten of the 11 patients were cigarette smokers (91%), and 6 had concomitant autoimmune diseases (55%). Since no clinical score exists for REM syndrome, we used the validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) to evaluate the efficacy of antimalarial treatment. Overall, a significant decrease in the clinical score was observed from a median of 4 (range, 2-8) before initiation of treatment to 0 (range, 0-4) after 3 months of antimalarial therapy and to 0 (range, 0-4) after 12 months of therapy (P < .001). Two patients withdrew from the study owing to adverse gastrointestinal tract effects (nausea and vomiting); 2 relapsed after finishing their antimalarial regimens; 3 patients were free of disease 2 years after the end of treatment; and 4 patients were lost to follow-up.

Conclusion: Antimalarial agents significantly improve or completely clear the skin lesions of patients with REM syndrome and should be considered as a first-line therapy for this rare disease.

Reticular erythematous mucinosis (REM syndrome) is a rare cutaneous disease first described by Steigleder et al more than 30 years ago. Predominantly affecting middle-aged women, REM syndrome skin lesions are typically located on the central area of the chest or on the upper back but may also spread to the upper abdomen. Clinically, REM syndrome presents as persistent erythema in a reticular pattern and/or confluent erythematous papules and plaques that lack scale or other surface changes (Figure 1).

Histopathologic features of REM syndrome include superficial and mid-dermal perivascular lymphocytic infiltrates as well as dermal mucin deposition (Figure 2). The cause of the disease is largely unclear, but several factors such as UV light, immunologic disturbances, and viral infections have been postulated to be associated with the induction of REM syndrome.2-7 Owing to its clinical and histopathologic characteristics, REM syndrome has been considered by some authors to belong to a spectrum of cutaneous lupus erythematosus (CLE)-like skin changes.5,6

Numerous treatments have been reported for REM syndrome, including topical and systemic corticosteroids, topical tacrolimus, phototherapy (eg, UV-B and UV-A1 irradiation), laser therapy, and immunosuppressive agents such as cyclosporine.5,7-10 Antimalarial treatment is generally considered the most effective approach in patients with REM syndrome. However, to our knowledge, few case reports exist on the use of chloroquine or hydroxychloroquine in REM syndrome, with varying degree of response.11-13 We therefore initiated the present retrospective study using a clinical scoring system to evaluate the clinical characteristics and the efficacy of antimalarial therapy in a series of German patients with REM syndrome.

Methods

Patients

A retrospective review of patients with REM syndrome treated at the outpatient clinic for connective tissue diseases at the dermatology department...
at Ruhr University, Bochum was performed following approval by the institutional review board. We only included patients who had received a monotherapy with chloroquine or hydroxychloroquine for at least 3 months. Consequently, patients who had undergone additional systemic corticosteroid or immunosuppressive therapy or any concomitant topical therapy (eg, with topical corticosteroids or topical calcineurin inhibitors) were excluded from this analysis. Additional topical therapy was restricted to the use of emollients.

A standard workup for CLE used in our department was performed in all patients, including a detailed medical history (current medications, autoimmune diseases, smoking status, and comorbidities), physical examination, phototesting with UV-A and UV-B irradiation, chest radiography, echocardiography, ultrasonography of the abdomen, and urinalysis. Serologic analysis included routine blood chemical analysis, a complete blood cell count, and screening for antinuclear antibodies, extractable nuclear antibodies (including anti-Ro and anti-La antibodies, anti-Jo-1 antibodies, anti-U1-ribonucleoprotein antibodies, antihistone antibodies, and anti-Smith antibodies), anti-double-stranded deoxyribonucleic antibodies, rheumatoid factor, antibodies against citrullinated proteins, circulating immune complexes, complement components (C3 and C4), C-reactive protein, and immunoglobulin levels (IgA, IgM, and IgG).

ANTIMALARIAL TREATMENT

Patients were treated with either chloroquine or hydroxychloroquine, depending on the personal preference of the treating physician. Patients treated with hydroxychloroquine received a maximum daily dose of 5 to 6 mg/kg of body weight (total dose, 400 mg of hydroxychloroquine sulfate). Patients treated with chloroquine received a maximum daily dose of 3 to 4 mg/kg of body weight (total dose, 250 mg of chloroquine phosphate). In case of gastrointestinal tract (GI) (eg, nausea and vomiting) or neurologic (eg, headache, dizziness, insomnia) adverse effects, the daily dose of both antimalarial drugs was halved. Every 4 weeks for the first 3 months of treatment, and every 3 months thereafter, all patients underwent urinalysis and blood tests, including a complete blood cell count and serum chemical analysis for evaluation of glucose and electrolyte levels. This testing is standard in our department for patients undergoing antimalarial treatment. Yearly ophthalmologic evaluations were also performed in all treated patients.

CLINICAL EVALUATION

To our knowledge, a clinical score for REM syndrome does not exist. We therefore decided to use a validated clinical score for the severity of skin manifestation in CLE, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). We only used the activity score of the CLASI because REM syndrome does not result in skin damage (eg, scarring, atrophy, hyperpigmentation, hypopigmentation). All of the patients' skin lesions had been photographed at each presentation in our department, and these pictures were retrospectively used to apply the CLASI. In each patient, the same investigator who initiated antimalarial treatment also performed the CLASI evaluation at baseline and after 3 and 12 months of antimalarial treatment.

STATISTICAL ANALYSIS

Data analysis was performed using a commercially available statistical software package (MedCalc; MedCalc Software, Mariakerke, Belgium). The distribution of data was graphically assessed. Nonnormally distributed data were expressed as medians with ranges. Pretherapeutic and posttherapeutic comparisons were performed using the Kruskal-Wallis analysis of variance, including post hoc comparisons. Moreover, the Fisher exact test was used. The Spearman coefficient of rank correlation was evaluated for the clinical score and the duration of disease. \( P < .05 \) was considered significant.
Table 1. Characteristics of Patients With REM Syndrome Treated With Chloroquine or Hydroxychloroquine

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Duration of Disease From First Onset of Symptoms</th>
<th>Location of Skin Lesions</th>
<th>Pretreatment</th>
<th>History of Photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/33</td>
<td>10 y</td>
<td>Central chest, upper back</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2/F/43</td>
<td>15 y</td>
<td>Central chest, left shoulder</td>
<td>Topical steroids</td>
<td>Yes</td>
</tr>
<tr>
<td>3/F/43</td>
<td>1 y</td>
<td>Central chest, upper abdomen</td>
<td>Topical steroids</td>
<td>No</td>
</tr>
<tr>
<td>4/F/52</td>
<td>18 y</td>
<td>Central chest, upper back</td>
<td>Topical steroids</td>
<td>No</td>
</tr>
<tr>
<td>5/F/54</td>
<td>10 y</td>
<td>Central chest, upper back, neck</td>
<td>Topical and systemic steroids, azathioprine</td>
<td>Yes</td>
</tr>
<tr>
<td>6/F/48</td>
<td>10 y</td>
<td>Central chest, upper back, upper abdomen</td>
<td>Topical steroids, PUVA</td>
<td>Yes</td>
</tr>
<tr>
<td>7/F/37</td>
<td>6 y</td>
<td>Central chest, upper back</td>
<td>Topical steroids</td>
<td>No</td>
</tr>
<tr>
<td>8/M/41</td>
<td>15 y</td>
<td>Central chest, upper back</td>
<td>Topical steroids</td>
<td>No</td>
</tr>
<tr>
<td>9/F/50</td>
<td>5 y</td>
<td>Central chest</td>
<td>Topical steroids</td>
<td>No</td>
</tr>
<tr>
<td>10/F/43</td>
<td>26 y</td>
<td>Central chest, upper back, neck</td>
<td>Topical steroids</td>
<td>Yes</td>
</tr>
<tr>
<td>11/F/40</td>
<td>1 mo</td>
<td>Central chest, upper back</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: PUVA, psoralen plus UV-A; REM, reticular erythematous mucinosis.

RESULTS

PATIENT CHARACTERISTICS

A total of 11 patients with REM syndrome (10 women and 1 man), mean age, 44 years (age range, 37-54 years), were diagnosed and treated with antimalarial agents at our institution from January 1, 2006, to January 1, 2010. Three other patients with REM syndrome but naive to antimalarial therapy (2 treated with systemic steroids only, and 1 with systemic steroids and azathioprine) were excluded from this retrospective analysis. All patients were transferred from primary care dermatologists. Suspected diagnoses included cutaneous T-cell lymphoma (1 patient), pseudolymphoma (1 patient), CLE (3 patients), and seborrheic eczema (2 patients). Four patients were transferred without any suspected diagnosis.

All patients’ relevant clinical characteristics are listed in Table 1. Mean disease duration was 10.5 years (range, 1 month to 26 years). Seven of the 11 patients had Fitzpatrick skin type I (65%). Six patients reported photosensitivity (exacerbation of skin lesions after UV irradiation), but none of the patients had abnormal findings in the phototesting with UV-A and UV-B irradiation. Direct immunofluorescence analysis for IgA and IgG, fibrinogen, and complement C3 was performed in 6 patients, and all results were negative. There were no relevant abnormal findings in the 11 patients’ routine laboratory testing or in their antibody profiles.

Ten of the 11 patients were active cigarette smokers at the time of REM syndrome diagnosis (91%). Six of the 11 patients had a history of autoimmune diseases (55%) (Hashimoto thyroiditis in 3 patients and diabetes mellitus, psoriasis arthritis, and rheumatoid arthritis in 1 patient each). None of the 11 patients had evidence for concomitant malignant disease at the time of REM syndrome diagnosis. Nine of the 11 patients had received pretreatment that was not effective (82%) with topical (n=9) or systemic corticosteroids (n=1), azathioprine (n=1), or psoralen plus UV-A phototherapy (n=1). These treatments had been finished at least 4 weeks before beginning monotherapy with the antimalarial agent.

RESPONSE TO ANTIMALARIAL THERAPY

The CLASI scores found before and during antimalarial treatment are listed in Table 2. Five patients were treated with chloroquine, and 6 patients were treated with hydroxychloroquine, respectively. In 9 patients, antimalarial agents were given for at least 12 months. Two patients (patients 5 and 6, both undergoing chloroquine treatment) decided to stop treatment after 4 months owing to GI adverse effects (vomiting and nausea). The chloroquine dose in these 2 patients had been halved to 250 mg every other day, but this did not reduce the severity of the adverse effects. Dose reductions were not performed in any of the other 9 patients.

Overall, a significant decrease of the CLASI score was observed from a median of 4 (range, 2-8) before initiation of treatment to 0 (range, 0-4) after 3 months of antimalarial therapy and to 0 (range, 0-4) after 12 months of therapy (P < .001). The mean CLASI scores before treatment and after 3 and 12 months of antimalarial therapy were 4.6 (range, 2-8), 0.8 (range, 0-4), and 0.7 (range, 0-4), respectively. Representative clinical pictures of the response of antimalarial agents in REM syndrome are provided in Figure 3 and Figure 4. In most patients, the first signs of improvement were seen after the first 2 months of antimalarial treatment. There was no significant correlation between the baseline CLASI score and the duration of disease (r=0.12; P = .68) or between disease duration and treatment response (r=0.2; P = .36). Moreover, there was no significant difference in efficacy (as measured by CLASI score reduction) between chloroquine and hydroxychloroquine (P = .43).

FOLLOW-UP

Two patients, patients 5 and 6, had a relapse of their skin lesions 14 and 20 months after finishing their respective antimalarial regimens. Both of them refused a second course of antimalarial treatment owing to GI adverse effects. Two patients (patients 8 and 11) decided to continue antimalarial treatment, and 3 patients (patients 1, 2, and 3) were still free of disease 2 years after
the end of the 12-month treatment period. Four of the patients (patients 4, 7, 9, and 10) were lost to follow-up.

COMMENT

This study largely confirms the characteristic clinical findings of REM syndrome previously published in the literature: REM syndrome predominantly affects middle-aged women and mainly affects the chest and upper back area. Reticular erythematous mucinosis is a rare disease: only 14 patients could be identified for this analysis at our institution within a 5-year observation period. Only 11 of them had been treated with antimalarial monotherapy and were finally included in this study. In line with previous reports, we found that a high proportion of our patients had concomitant autoimmune disorders, especially thyroid disease.17 We could not confirm the sporadically reported association of REM syndrome with malignant neoplasms (lung, breast, and colon carcinoma).18 Some of our patients reported on an exacerbation of their skin disease following sun exposure. Interestingly, none of them developed reproducible lesions in the UV-A and UV-B phototests. In line with this, phototesting results were negative for 3 previously reported patients with REM syndrome, but they nonetheless showed exacerbation of skin lesions following whole-body UV-A irradiation, which suggests that other trigger factors besides UV light (eg, heat, perspiration) might play a role in REM syndrome.14 We did not find any abnormalities in the results of direct immunofluorescence analysis performed for 6 of our patients, whereas positive results have previously been observed in about 20% of REM syndrome cases.15 Nevertheless, it should be taken into account that a similar proportion of healthy individuals show positive immunofluorescence findings on healthy UV-exposed skin.19

Antimalarial treatment is the mainstay of systemic therapy for CLE.20 The present study demonstrated that antimalarial agents are highly effective in treating REM syndrome as well. It has been hypothesized that REM syndrome may belong to a spectrum of CLE-like skin changes.3 6 Comparing the characteristic clinical and histopathologic features of REM syndrome with the respective subtypes of CLE, we find that REM syndrome shares most similarities with lupus erythematosus tumidus (LET).21 There has been some debate lately about whether LET is a separate own CLE subtype or a nonspecific manifestation within the lupus erythematosus classification system.22,23 Both conditions histologi-

### Table 2. CLASI Scores Before and After 3 and 12 Months of Antimalarial Therapy

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Type of Antimalarial Drug</th>
<th>CLASI Score</th>
<th>Pretreatment</th>
<th>Month 3</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/33</td>
<td>Hydroxychloroquine</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2/F/43</td>
<td>Hydroxychloroquine</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3/F/43</td>
<td>Hydroxychloroquine</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4/F/52</td>
<td>Chloroquine</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5/F/54</td>
<td>Chloroquine</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6/F/48</td>
<td>Chloroquine</td>
<td>6</td>
<td>1</td>
<td>1(^a)</td>
<td></td>
</tr>
<tr>
<td>7/F/37</td>
<td>Chloroquine</td>
<td>6</td>
<td>1</td>
<td>1(^a)</td>
<td></td>
</tr>
<tr>
<td>8/M/41</td>
<td>Hydroxychloroquine</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9/F/50</td>
<td>Hydroxychloroquine</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10/F/43</td>
<td>Hydroxychloroquine</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11/F/40</td>
<td>Chloroquine</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CLASI, mean</td>
<td>NA</td>
<td>4.6</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>CLASI, median</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index\(^a\); NA, not applicable.

\(^a\) These patients discontinued antimalarial therapy after 4 months owing to gastrointestinal tract adverse effects.

![Patient 3. A. Clinical presentation of patient 3 with reticular erythematosus mucinosis before the initiation of antimalarial therapy. B. Almost complete clearance of former skin lesions after 3 months of treatment with hydroxychloroquine. The Cutaneous Lupus Erythematosus Disease Area and Severity Index decreased from 4 to 1 after 3 months of therapy.](https://archderm.jamanetwork.com/)
cally show perivascular lymphocytic infiltrates, absence of interface dermatitis, negative direct immunofluorescence findings, and dermal mucin deposition. Moreover, both REM syndrome and LET usually lack serologic abnormalities, usually do not show systemic involvement, resolve without residual lesions, and respond well to antimalarial agents.

Interestingly, most patients with REM syndrome in this study were smokers (91%; n=10). To our knowledge, smoking habits have so far not been evaluated in REM syndrome. Accumulating evidence indicates that smoking is significantly associated with CLE and with cutaneous damage and active lupus eruption in systemic lupus erythematosus. However, based on the small number of patients evaluated in the present study, no conclusions can be drawn on the pathogenetic role of smoking in REM syndrome.

This study has several limitations. With the help of clinical photographs, we performed an unblinded, uncontrolled retrospective analysis of a relatively small number of patients with REM syndrome using a clinical score for CLE. Moreover, secondary outcome measures (eg, pretreatment and posttreatment colorimetry, ultrasonographic scanning, histopathologic scores) are lacking. Further investigations on REM syndrome, done under more rigorous, prospective conditions with the aid of a standardized instrument to measure treatment outcome, would be important. However, such conditions are almost impossible to create, given the rarity of this particular disease.

In conclusion, the present retrospective analysis demonstrated that patients with REM syndrome experience significant improvement or even complete clearing of their skin lesions with antimalarial treatment. Given their high efficacy and good tolerability, antimalarials should be considered as a first-line treatment for this rare disease.

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Author Contributions: Dr Kreuter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kreuter, Tigges, Altmeyer, and Gambichler. Acquisition of data: Kreuter, Scola, Tigges, and Gambichler. Analysis and interpretation of data: Kreuter, Tigges, and Gambichler. Drafting of the manuscript: Kreuter. Critical revision of the manuscript for important intellectual content: Scola, Tigges, Altmeyer, and Gambichler. Statistical analysis: Gambichler. Administrative, technical, and material support: Kreuter, Scola, Tigges, and Altmeyer.

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REFERENCES

Recognizing and Managing Reticular Erythematous Mucinosis

The study by Kreuter et al identifies several practice and knowledge gaps regarding the diagnosis and management of reticular erythematous mucinosis (REM). The authors diagnosed REM in only 14 patients over 5 years in their referral dermatology center, and all of these patients had been referred by primary dermatologists for alternative diagnoses. Because of its rarity, many dermatologists may not recognize the characteristic features of REM. The authors discuss the substantial clinical and histologic similarities between REM and lupus erythematosus, thereby identifying another gap in our understanding of the relationship between these 2 entities and calling into question whether they are in fact distinct entities. The authors highlight the clinical similarities by using the Cutaneous Lupus Erythematosus Disease Area and Severity Index to assess REM activity and response to treatment.

Practice gaps related to dermatologists’ knowledge about systemic diseases associated with REM are also addressed in the study. The association of autoimmune diseases with REM has been described in case reports and series. Kreuter et al also demonstrate a marked prevalence of autoimmune conditions among patients with REM, autoimmune thyroiditis being the most common. The authors report no associated malignant neoplasms in their patients, an association that has been anecdotally reported previously. To my knowledge, this is the largest series of patients with REM reported to date, and while larger studies are needed to address the possible association of REM with malignant neoplasms, aggressive malignancy screening is likely unnecessary.

Dermatologists must be aware of the use of antimalarial agents as first-line therapy for REM. The authors confirm previously published anecdotal reports of the efficacy of antimalarial agents in REM. Because of reports of reduced efficacy of antimalarial drugs in tobacco smokers with lupus erythematosus, dermatologists might avoid the use of these drugs in patients with REM who smoke. Interestingly, 10 of the 11 patients evaluated in this study were smokers, yet all improved or cleared with antimalarial treatment. No conclusion can be drawn as to the potential etiologic role of tobacco abuse in REM, and further study to address this possibility seems warranted; nonetheless, antimalarial agents should not be withheld from patients because of tobacco use.

Closing these gaps requires a combination of educational and research efforts. Studies such as this add to the knowledge and competence of dermatologists. Continuing medical education programs can also enhance dermatologists’ ability to recognize and treat REM effectively. Collaborative multicenter studies or the creation of patient registries would enable the study of larger numbers of patients with REM to answer questions about its relationship to lupus erythematosus tumidus, the possible etiologic role of tobacco use, and its association with autoimmune conditions.