Characteristics of coexisting localized scleroderma and inflammatory arthritis

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Abstract

Objective: Localized scleroderma (LS), including morphea and linear scleroderma, is an autoimmune disease where excessive subcutaneous collagen deposits lead to thickening, scarring, and fibrosis of the tissues. LS coexisting with inflammatory arthritis is less well-described but has been reported in as many as 20% of 53 LS patients in a recent cohort. Herein, we describe a cohort of 8 children with both LS and inflammatory arthritis. The objective of this study is to determine the characteristics of inflammatory arthritis in children with LS and their response to treatment regimens.

Methods: A retrospective chart review was completed on patients less than 19 years of age who were diagnosed with either morphea or linear scleroderma at the Children of Alabama center from 2004–2018. Patients were identified using ICD-9 and ICD-10 diagnostic codes. Records were reviewed for additional diagnostic codes, exams, and laboratory findings confirming coexisting inflammatory arthritis and LS.

Results: A total of 87 patients with a diagnosis of either morphea or linear scleroderma were identified. Eight (9%) had coexisting inflammatory arthritis according to the diagnostic codes with documented active arthritis. Median age of initial rheumatic disease diagnosis was 7.5 years. A majority of patients with both LS and inflammatory arthritis were female (62.5%). Half of the patients (n=4, 50%) had LS lesions over arthritic joints. All of the identified patients were diagnosed with a form of juvenile idiopathic arthritis (JIA). The JIA diagnoses varied widely in 3 (37.5%) patients with rheumatoid factor (RF) negative polyarticular JIA, 2 (25%) with oligoarticular JIA, 2 (25%) with psoriatic JIA, and 1 (12.5%) with enthesitis-related JIA. The timing of onset of LS and inflammatory arthritis varied widely. Three (37.5%) patients had LS lesions preceding clinical arthritis, and three (37.5%) had arthritis before the appearance of LS. Two (25%) patients had both LS and arthritis at the time of diagnosis. All patients received methotrexate (MTX) during their disease course with only 3 (37.5%) receiving systemic steroids during treatment. All 8 patients showed resolution of LS lesions. However, 6 of the 8 patients demonstrated active arthritis on combination MTX and TNFi therapy.

Conclusion: In this cohort of pediatric LS, 9% of patients had coexisting inflammatory arthritis. The characteristics of this cohort varied widely. All patients received MTX initially and showed a resolution of LS lesions. However, in the majority of patients, the arthritis failed to respond to MTX and TNFi combination therapy. These results suggest that inflammatory arthritis coexisting with LS may be less likely to respond to traditional inflammatory arthritis or JIA therapies.

Keywords: Localized scleroderma, juvenile idiopathic arthritis, morphea, linear scleroderma

Introduction

Localized scleroderma (LS) is an autoimmune disease where excessive collagen deposits underneath the skin lead to thickening, scarring, and fibrosis of the tissues. It can be further classified as morphea or linear scleroderma based on the pattern and layer of skin involvement (1). Morphea describes generally well-circumscribed areas of induration, thickening, and hyper- or hypo-pigmentation, and according to the areas of involvement it can be classified into multiple categories; (1) plaque: involving 1–2 anatomic sites, (2) generalized: individual plaques becoming confluent lesions, (3) deep: affecting the deep dermis, subcutaneous tissue, fascia, and the superficial muscle, and profunda: causing the entire skin to feel taut, thickened, and bound down (1, 2). Linear scleroderma, however, appears as one or more linear streaks on the body that can involve different layers of skin, muscle, and bone. Primarily involving the extremities, the complications include deformities, contractures, and disruption of growth. One specific type of linear scleroderma is coup de sabre, where the face and/or scalp is affected (2).

Localized scleroderma, including morphea and linear scleroderma, therefore, is often limited to the skin, subcutaneous tissues, and rarely, muscle and bone. This differs greatly from the diseases of systemic sclero-
rosis, including diffuse cutaneous scleroderma and limited cutaneous scleroderma [formerly calcifications, Raynaud’s phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia (CREST syndrome), as they are known to extensively involve the pulmonary, gastrointestinal, renal, and other organ systems, which is caused by diffuse inflammation throughout the body (3).

However, as research into localized scleroderma progresses, there is increasing evidence in the literature that this disease may be a manifestation of a diffuse systemic inflammatory process, as some studies have described neurologic, vascular, articular, and other affected organ systems (4). In a study of 750 patients with childhood localized scleroderma by Zulian F et al. (4), 22.4% of the patients showed one or more extracutaneous manifestations, the most common of which was articular involvement, including oligo- and poly-arthritis (4, 5).

Localized scleroderma coexisting with inflammatory arthritis and juvenile idiopathic arthritis (JIA) is not well-described. JIA defines a collection of inflammatory arthritides of childhood with onset prior to 16 years of age, a minimum duration of 6 weeks, and an unknown etiology. Dependent on the type of involved joint, the number of joints involved, positive or negative autoantibodies [i.e., presence or absence of rheumatoid factor (RF) and human leukocyte antigen B27 (HLA-B27)], and presence of extraarticular manifestations, JIA can be further classified into 7 mutually exclusive subcategories: systemic JIA, oligoarthritis, RF-positive or RF-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, or undifferentiated arthritis (6). In patients with localized scleroderma, co-existing inflammatory arthritis has been reported in as many as 20.8% in a recent cohort of 53 patients by Kashem et al. (7). In this study, the majority of patients were categorized as linear or generalized variants of morphea/scleroderma, and most were treated with methotrexate. Patients with arthritis had higher anti-nuclear antibody (ANA) titers and variable joint distributions (7).

Herein, we describe a cohort of 8 children with both LS and inflammatory arthritis. The objective of this study is to determine the association of inflammatory arthritis in children with LS with respect to site of disease involvement, timing of disease onset, presence of autoantibodies, and treatment regimens.

### Methods

A retrospective chart review was completed on patients younger than 19 years of age who were diagnosed with localized scleroderma at the Children’s of Alabama center from 2004 - 2018. Patients were identified from the electronic medical record using diagnostic codes for morphea (ICD-9 701.0 and ICD-10 L94.0) and linear scleroderma (ICD-9 701.0 and ICD-10 L94.1). Once the patients were identified, all their clinical notes were reviewed for documentation of confirmed coexisting diagnosis of inflammatory arthritis. The characteristics of interest included patient demographics, site of disease involvement, timing of disease onset, presence of autoantibodies.

### Main Points

- Chronic arthritis can be present in up to 9% of children with localized scleroderma without preference for juvenile idiopathic arthritis subtype.
- Arthritis, when present in children with localized scleroderma, can present in advance of, coincident with, or following diagnosis of the skin involvement.
- When chronic arthritis coexists with localized scleroderma, the arthritis component of disease is harder to control than the skin disease using DMARDs, including biologics.

### Table 1. Patient demographics (N=8).

| Variable                          | N (%)          |
|-----------------------------------|----------------|
| **Age of Onset (years)**          | Median 7.50    |
| **Gender**                        |                |
| Male                              | 3/8 (37.5%)    |
| Female                            | 5/8 (62.5%)    |
| **Scleroderma subtype**           |                |
| Circumscribed                     | 7/8 (87.5%)    |
| Linear                            | 1/8 (12.5%)    |
| **Morphea Crosses Arthritic Joint**|                |
| Yes                               | 4/8 (50%)      |
| No                                | 4/8 (50%)      |
| **Arthritis Distribution**        |                |
| Large Joints                      | 5/8 (62.5%)    |
| Small Joints                      | 8/8 (100%)     |
| **Previously Diagnosed Arthritis Subtype** |          |
| Oligo JIA                         | 2/8 (25%)      |
| Psoriatic Arthritis               | 2/8 (25%)      |
| RF-neg PolyJIA                    | 3/8 (37.5%)    |
| Enthesitis-related                | 1/8 (12.5%)    |
| **Timing of Diagnosis**           |                |
| Arthritis precedes morphea        | 3/8 (37.5%)    |
| Morphea precedes arthritis        | 3/8 (37.5%)    |
| Simultaneous presentation         | 2/8 (25%)      |
| **Antibodies**                    |                |
| ANA positive                      | 2/8 (50%)      |
| RF-positive                       | 1/4 (25%)      |
| HLA-B27 positive                  | 0/5 (0%)       |

ANA: anti-nuclear antibody; RF: rheumatoid factor; HLA-B27: human leukocyte antigen B27.
location of arthritis and joint count, arthritis subtype, laboratory data with ANA status and other autoantibodies, treatment modalities, and each individual’s response to treatment. Active arthritis was defined by clinical examination and imaging, including MRI and x-rays. Clinical findings included joint effusions, joint swelling, joint pain, and limitation in range of motion. LS was evaluated using non-standardized clinical examinations with findings of erythema, skin thickening, and atrophy. Treatment success was defined by improvement in symptoms or remission of arthritis documented per clinical examination findings, and resolution or stability of LS lesions via clinical exam and imaging. Means, standard deviations, frequencies, and proportions were computed for all demographic, clinical, and laboratory features using Microsoft Excel. This study was approved by the institutional review board at the University of Alabama, Birmingham on September 14, 2018 (Decision Number: IRB-300002129).

Results

A total of 87 patients with a diagnosis of LS were identified. Eight (9%) had coexisting inflammatory arthritis, as documented by a pediatric rheumatologist. The median age of initial rheumatic disease diagnosis was 7.5 years, with a mean age of 8.9 ± 4.2 years. Patients were followed for a mean of 7 years during the course of their illness. A majority of patients with both LS and inflammatory arthritis were female (62.5%). Four patients (50%) had LS lesions over arthritis joints. All of the identified patients were diagnosed with a form of juvenile idiopathic arthritis (JIA) in addition to LS. Some of these patients had diagnoses prior to onset of LS and some were given diagnoses of JIA despite prior LS findings, largely due to coding and insurance medication authorization purposes. These JIA subtypes, per ILAR criteria, varied widely in 3 (37.5%) patients with RF-negative polyarticular JIA, 2 (25%) patients with oligoarticular JIA, 2 (25%) patients with psoriatic JIA, and 1 (12.5%) with enthesitis-related JIA (Table 1). RF-negative polyarticular JIA was diagnosed if there was arthritis of 5 or more joints during the first 6 months of disease with negative rheumatoid factor. Patients with oligoarticular JIA were diagnosed with arthritis of 1-4 joints during the course of disease in the absence of psoriasis or RF positivity. The 2 patients with psoriatic JIA were diagnosed if there was presence of arthritis and a family history or personal history of psoriasis. The patient with enthesitis-related JIA was diagnosed on the basis of arthritis and enthesitis of the calcaneal attachment in the Achilles tendon and inflammatory back pain.

The distribution of arthritis varied; all patients had at least 1 small joint affected. Five patients (62.5%) had at least 1 large joint affected. The timing of onset of LS and inflammatory arthritis also varied widely. Three (37.5%) patients had LS lesions preceding the appearance of clinical arthritis on examination, and 3 (37.5%) patients had arthritis before the appearance of LS. Two (25%) patients had a simultaneous diagnosis of LS and arthritis. With respect to autoantibodies, 8 patients showed results for an extractable nuclear antibody panel and only 2 patients had positive ANA titers—one patient with a 1:320 titer and 1 patient with a 1:80 titer. Specific autoantibodies (i.e., anti-double stranded DNA, Scl-70, SS-A, SS-B, anti-Smith, and anti-RNP) were negative in all four patients with results available. None of the 5 patients tested for HLA-B27 were positive. One patient with a positive ANA titer also tested positive for RF (Table 2).

All patients received methotrexate (MTX) during their disease with only 3 (37.5%) receiving systemic steroids during treatment. There was a wide variety of second-line medication choices and dosages with varying clinical effects. Second-line medications included etanercept (ETN), adalimumab (ADA), infliximab (IFX), abatacept, leflunomide (LEF), sulfasalazine, mycophenolate mofetil (MMF), tocolizumab, hydroxychloroquine, and rituximab. Three patients (37.5%) achieved full remission of arthritis, one with MTX monotherapy and 2 using an additional second-line medication (one patient with MMF + ETN and one patient with LEF monotherapy). Three patients (37.5%) showed improvement in arthritis with second-line medication (one with MTX+ETN, one with MMF+IFX, and one with MTX+ADA). Two patients (25%) were either uncontrolled or lost to follow-up after failing several medications. All patients had stabilization or improvement in the localized scleroderma lesions, irrespective of the medication prescribed (Table 3, 4).

Discussion

In this single-center cohort of pediatric patients with LS, approximately 9% had coexisting inflammatory arthritis. This is lower than the 20.8% figure reported by Kashem et al. (7). Our cohort was similar to prior studies with respect to female predominance and age of onset (8, 9). However, the majority of our cohort

### Table 2. Patient characteristics (N=8).

| Patient | Age at Diagnosis | Sex | Crosses Arthritic Joint | Crosses LS Distribution | # of Small Joints | # of Large Joints | Time between LS and Arthritis Diagnoses | Diagnosed JIA Subtype | LS Subtype |
|---------|-----------------|-----|------------------------|-------------------------|------------------|------------------|-----------------------------------|----------------------|-----------|
| 1       | 13              | M   | N                      | N                       | 3                | 2                | Simultaneous diagnosis             | RF-negative Poly-JIA | Circumscribed |
| 2       | 15              | F   | N                      | N                       | 2                | 2                | Arthritis 9 months prior to LS      | Enthesitis-related Arthritis | Circumscribed |
| 3       | 13              | F   | Y                      | Y                       | 0                | 3                | Simultaneous diagnosis             | Oligo-JIA            | Circumscribed |
| 4       | 5               | M   | Y                      | Y                       | 1                | 3                | LS 2 years prior to arthritis       | Psoriatic Arthritis   | Circumscribed |
| 5       | 3               | M   | N                      | N                       | 4                | 4                | Arthritis 5 months prior to LS      | RF-negative Poly-JIA  | Circumscribed |
| 6       | 7               | F   | Y                      | Y                       | 1                | 3                | Arthritis 8 years prior to LS       | Psoriatic Arthritis   | Circumscribed |
| 7       | 7               | F   | N                      | N                       | 10               | 0                | LS 3 years prior to arthritis       | RF-negative Poly-JIA  | Circumscribed |
| 8       | 8               | F   | Y                      | Y                       | 2                | 0                | LS 9 months prior to arthritis      | Oligo-JIA            | Linear    |

LS: localized scleroderma; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor.
had circumscribed, plaque lesions rather than true linear scleroderma. Half of the patients in this cohort had active arthritis at the site of an LS lesion, suggesting a systemic inflammatory component with a possible shared immunopathology (10). Presence of autoantibodies was inconsistent with only 2 patients having a positive ANA titer and no patients with any identifiable extractable nuclear antigens, which was again a lower proportion than in previous studies (7-9). Presence of autoantibodies in combination with the type of LS lesion, suggesting a systemic inflammatory arthritis was inconsistent irrespective of second-line medications, including sulfasalazine, leflunomide, hydroxychloroquine, and biologic agents such as TNF inhibitors, abatacept, tocilizumab, and rituximab, which can be used alone or in combination to treat refractory JIA and inflammatory arthritis (16). Patients #5 and #6 were particularly difficult to treat and each failed multiple biologic courses throughout their illness. Patient #5 had persistent bilateral wrist and ankle arthritis during treatment and patient #6 suffered from persistent unilateral ankle and knee arthritis. Arthritis in both cases was assessed with clinical examination findings of pain, swelling, and effusion in addition to MRI imaging.

Current consensus recommends MTX with or without corticosteroid bridge therapy be used as first-line therapy in active LS. MMF is recommended as second-line therapy (10, 11, 17), which was also used in our cohort. From a population standpoint, as many as 30% of patients with LS have a reported family history of autoimmune disease, and about 10% of children with LS have concurrent autoimmune disease, commonly vitiligo, alopecia areata, or JIA (10, 18). Jacob et al. (19) found a strong association between HLA alleles and LS, suggesting that natural killer cells or CD-8 T cells may play a role in the immunopathogenesis of LS, which may explain the higher proportions of co-existing autoimmune disease. The results of our study suggest that patients with LS and coexisting inflammatory arthritis may have poorer response rates to traditional anti-arthritis medications, and this risk may in part be due to underlying genetic component. A better understanding of the immunopathogenesis and genetic association between LS and inflammatory arthritis is needed in order to better guide treatment plans in patients with LS.

### Table 3. Autoantibodies.

| Patient | ANA | dsDNA | Scl-70 | RF | SS-A | SS-B | Smith | RNP | Smooth Muscle | CCP | HLA-B27 |
|---------|-----|-------|--------|----|------|------|-------|-----|---------------|-----|---------|
| 1       | (-) | NT    | NT     | NT | NT   | NT   | NT    | NT  | NT            | (-) | (-)     |
| 2       | (-) | NT    | NT     | NT | NT   | NT   | NT    | NT  | NT            | NT  | (-)     |
| 3       | (-) | NT    | NT     | NT | NT   | NT   | NT    | NT  | NT            | NT  | NT      |
| 4       | (-) | NT    | NT     | NT | NT   | (-)  | (-)   | NT  | NT            | NT  | (-)     |
| 5       | (-) | (-)   | (-)    | (-) | (-)  | (-)  | (-)   | (-) | NT            | NT  | NT      |
| 6       | (+) | 1:320 - Homogeneous | NT | NT | (-) | NT | NT | NT | NT | (-) | (-) |
| 7       | (-) | (-)   | (-)    | (-) | (-)  | (-)  | (-)   | (-) | NT            | (-) | NT      |
| 8       | (+) | 1:80 - Homogeneous | (-) | (-) | (+) | (-) | (-) | (-) | NT | NT | NT   |

NT: not tested; ANA: anti-nuclear antibody; dsDNA: anti-double stranded DNA; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; HLA-B27: human leukocyte antigen B27.

### Table 4. Therapies and outcomes.

| Patient | Therapies | LS Resolved | Arthritis in Remission |
|---------|-----------|-------------|------------------------|
| 1       | CS, MTX, TNFi x3, LEF | Y | Y, on meds |
| 2       | MTX, TNFi x2 | Y | N |
| 3       | MTX | Y | N |
| 4       | MTX, TNFi, MMF | Y | Y, on meds |
| 5       | CS, MTX, TNFi x2, ABT | Y | N |
| 6       | CS, MTX, TNFi, ABT, SSZ, MMF, TCZ, HCQ, RTX | Y | N |
| 7       | CS, MTX, TNFi, MMF | Y | N |
| 8       | MTX, TNFi | Y | N |

S: corticosteroids; TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; MMF: mycophenolate; SSZ: sulfasalazine; TCZ: tocilizumab; HCQ: hydroxychloroquine; LEF: leflunomide; RTX: rituximab; ABT: abatacept.
and coexisting inflammatory arthritis who fail to respond to MTX and traditional second-line anti-arthritic medications.

This study had several limitations, most notably the small sample size and the retrospective nature. However, the clinical records for all patients with a diagnosis code consistent with LS were examined in detail. As this was a retrospective study spanning many years, laboratory testing was not standardized and was missing for several patients. Additionally, 2 patients—patient 5 and patient 8—were lost to follow-up during treatment, making the true treatment success or failure difficult to assess.

In a single pediatric rheumatology clinic over 14 years, inflammatory arthritis coexisted in 9% of children with LS. Patient characteristics varied widely in terms of disease involvement, timing of disease onset, presence of autoantibodies, and treatment response. All patients showed an improvement in the morphea lesions with the use of MTX, but the arthritis had variable responses. Although the comorbid presentation of LS and inflammatory arthritis suggests an underlying systemic inflammatory component and perhaps even a shared immunopathology and a genetic component, additional studies are needed to clearly understand the relationship between localized scleroderma and inflammatory arthritis, and subsequently design the most appropriate treatment plan.

Ethics Committee Approval: Ethics committee approval was received for this study from University of Alabama, Birmingham (Decision Number: IRB-300002129; Decision Date: September 14, 2018).

Informed Consent: Written informed consent was obtained from parents or legal guardians of the patients who participated in this study.

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