Skin disease is more recalcitrant than muscle disease: A long-term prospective study of 184 children with juvenile dermatomyositis

Andi Wang, BA,[a] Gabrielle A. Morgan, MA,[b] Amy S. Paller, MD,[c] and Lauren M. Pachman, MD[a,b]
Chicago, Illinois

Background: Persistent skin manifestations, especially calcinoses, contribute to morbidity in children with juvenile dermatomyositis.

Objective: To compare the course of skin and muscle involvement and document frequency of calcinosis in juvenile dermatomyositis.

Methods: Prospective cohort study of 184 untreated children with juvenile dermatomyositis (July 1971 to May 2019) at a single children's hospital.

Results: Disease Activity Scores (DASs) were persistently higher for skin versus muscle at all points; clinical inactivity (DAS ≤2) occurred earlier for muscle than skin. Among vascular features for DAS for skin, eyelid margin capillary dilatation was most frequent (54.3%) and persisted longest. Intravenous methylprednisolone reduced DAS for skin more than oral prednisone at 12 months (P = .04). Overall, 16.8% of patients (n = 31) had calcifications, with 4.9% at enrollment. Despite therapy, 25.0% of calcifications recurred and 22.6% failed to resolve; of the latter, 71.4% (n = 5) were present at enrollment. Children with persistent calcifications had longer duration of untreated disease than those whose calcifications resolved (mean 12.5 months) (P < .001). Hydroxychloroquine did not improve DAS for skin (P = .89).

Limitations: DAS does not quantify nailfold capillary dropout.

Conclusions: In juvenile dermatomyositis, skin disease presents with greater activity and is more recalcitrant to therapies than muscle disease. Early and aggressive treatment can limit the severity and persistence of calcifications identified later in the disease course. (J Am Acad Dermatol 2021;84:1610-8.)

Key words: calcinosis; IV methylprednisolone; juvenile dermatomyositis; oral prednisone; pediatric dermatology; vasculitis.

From the Division of Pediatric Rheumatology, Department of Pediatrics,[a] and Departments of Dermatology and Pediatrics,[c] Northwestern University Feinberg School of Medicine, Chicago; Cure JM Center of Excellence in Juvenile Dermatomyositis Care and Research, Stanley Manne Children's Research Institute[b]; and The Ann and Robert H. Lurie Children's Hospital of Chicago Research Center, Cure JM Myositis Center, Chicago.

Funding sources: Supported by the Vivian Allison and Daniel J. Pachman Fund (Pachman), the Cure JM Foundation (Morgan, Pachman), and R-21 AR077565 from the National Institute of Arthritis, Metabolic and Skin Diseases (Pachman). Research Electronic Data Capture is supported at Feinberg School of Medicine by the Northwestern University Clinical and Translational Science (NUCATS) Institute. NUCATS is funded in part by a Clinical and Translational Science Award grant from the National Institutes of Health UL1TR001422.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

IRB approval status: Reviewed and approved by the Lurie Children's Institutional Review Board (IRB 2019-2734).

Accepted for publication December 13, 2020.

Reprints not available from the authors.

Correspondence to: Lauren M. Pachman, MD, Division of Pediatric Rheumatology, The Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Chicago, IL 60611. E-mail: pachman@northwestern.edu.

Published online December 25, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.12.032

INTRODUCTION

Juvenile dermatomyositis, a rare autoimmune disease, affects 2.3 to 4.1 US children per million per year.[1-3] Defining features are symmetric proximal muscle weakness and a characteristic skin eruption, most often localized to the face and overlying joints.[4] Juvenile dermatomyositis may lead to severe sequelae, including dystrophic calcifications, persistent cutaneous inflammation, and organ involvement with functional limitations.[5-7]

Validated in 2003,[8] the Disease Activity Score (DAS) continues to be a widely used measure for quantifying skin and muscle activity in juvenile dermatomyositis.[9-13] The 20-point scale uses 11 possible points for muscle and 9 points for skin manifestations. Scored skin features include severity of skin erythema and Gottron papules, distribution, and the presence of erythema and telangiectasia at specific locations (eyelid, periungual region, and palate). The DAS monitors disease severity and response to treatment, and has been shown to predict juvenile dermatomyositis functional outcomes, such as cardiac dysfunction with high early Disease Activity Score—Skin (DAS-S) scores.[14] The DAS-S has the strongest correlation with the physician's visual analog scale.[15]

Prompt initiation of appropriate therapy is linked to optimal outcomes and reduction of long-term disability.[16-18] Although skin features often precede muscle complaints, calcinoses are a later complication. Calcinosis is a poorly understood and feared complication of juvenile dermatomyositis, contributing to significant morbidity. Reported to be present in 30% to 50% of juvenile dermatomyositis patients,[19-21] calcinoses often involve the extremities[22] and soft tissues, may be related to repeated local trauma, and are associated with longer disease duration before therapy.[23,24] Risk of calcification has been linked to delayed or suboptimal treatment[5,25] and the *TNFA*-308 GA or AA genotype.[26]

Using long-term tracking of DAS-S and Disease Activity Score—Muscle (DAS-M) scores,[8,9] this study compared skin and muscle activity, as well as patterns of calcifications, during the juvenile dermatomyositis disease course in 485 children at a single center.

CAPSULE SUMMARY

- Juvenile dermatomyositis skin signs are significantly more severe and persistent than muscle signs, despite therapy; eyelid margin capillary dilatation is a prominent, persistent vascular feature. Intravenous methylprednisolone controls skin disease more rapidly than oral prednisone.
- Clinicians should consider both the activity of skin manifestations and muscle dysfunction in therapeutic decision making.

METHODS

Patient selection and study design

Data from this single-center cohort study were extracted from the Juvenile Myositis Registry, currently a Research Electronic Data Capture database (hosted by Northwestern University Feinberg School of Medicine),[27] begun in July 1971 that includes all juvenile dermatomyositis patients treated at The Ann and Robert H. Lurie Children's Hospital of Chicago through May 2019. Clinical and laboratory data were captured for 184 children and adolescents who met inclusion criteria of diagnosis of juvenile dermatomyositis (using criteria at enrollment, such as those provided by Bohan and Peter[28] and later American College of Rheumatology criteria[29-31]) and untreated disease. The study was approved by the Lurie Children's Institutional Review Board; written informed consent and assent were obtained from legal guardians and patients aged 12 years or older, respectively.

Outcome measures and treatments

Duration of untreated disease was collected at the start of medical therapy. At enrollment and each visit, patients were assessed with the validated 20-point DAS,[8] which sums scores for skin activity (0-9 points) and muscle activity (0-11 points). The DAS-S evaluates the distribution and extent of involvement of cutaneous features, including mucocutaneous vasculature and Gottron sign/papules. DAS-M assesses muscle weakness and physical function. Disease severity is classified as absent (DAS-S 0; DAS-M 0), mild (DAS-S 1-3; DAS-M 0.5-3), moderate (DAS-S 4-5; DAS-M 4-5), moderate to severe (DAS-S 6; DAS-M 6-8), and severe (DAS-S 7-9; DAS-M 9-11). Therefore, classifications based on severity for DAS-M and DAS-S are comparable. A total DAS of 0 to 2 is considered clinically inactive, but may also reflect damage. Although validation of the DAS was not published until 2003,[8] our study used DAS data collected from 1971 by a single physician (L.M.P.), who generated and later validated the DAS. *TNFA* (TNFα)-308 polymorphisms were determined[32] and routine laboratory testing, muscle enzyme levels (creatinine phosphokinase, aldolase, lactate dehydrogenase, and serum glutamic-oxaloacetic transaminase)[33] and immune indicators of inflammation, was performed. At each visit,

Abbreviations used:

DAS: Disease Activity Score
DAS-M: Disease Activity Score—Muscle
DAS-S: Disease Activity Score—Skin
SD: standard deviation

medication use and the presence of calcifications on clinical examination were recorded. Regular use of intravenous methylprednisolone began in 1990,[34,35] supplementing the previous standard of treatment of oral prednisone.

Statistical analysis

Demographic characteristics, including age, sex, and duration of untreated disease, were recorded for all patients at enrollment (baseline), independent of the availability of DASs. Mean DASs were calculated for skin and muscle (and summed to total disease activity) at baseline and 6, 12, 24, 36, 48, and 60 months after medication initiation. Reduction in DAS (ΔDAS) quantified the percentage of change in DASs from baseline to various periods with treatment. A paired *t* test analyzed significant differences between mean DAS-S and DAS-M scores, as well as differences in ΔDAS-S between intravenous methylprednisolone and oral prednisone at each point. The percentage of participants reaching clinically inactive total DASs of 0, less than or equal to 1, and less than or equal to 2 was calculated for skin and muscle activity. A χ^2 test analyzed the proportion of participants who obtained clinically inactive skin disease, muscle disease, or both. Mean months since initiation of medication to reach clinical inactivity for total, skin, and muscle activity was also calculated, defined as the first time that patients achieved a DAS of less than or equal to 2, irrespective of whether the score was maintained. The frequency of the 5 abnormal vascular elements was calculated at baseline, 12 months, and patients' last visit. Participants were excluded if more than 24 months had elapsed between consecutive visits or they had fewer than 3 visits. Significance of differences in resolution of abnormal vascular elements used 1-way analysis of variance. χ^2 Testing was performed to determine the significance of differences in the development of calcification based on genotype (*TNFA* GG vs *TNFA* GA + *TNFA* AA). These analyses used SPSS, with significance defined as $P < .05$.

RESULTS

The 184 untreated juvenile dermatomyositis patients (Table I) were predominantly female individuals (75%), non-Hispanic White (72.2%), and of the *TNFA*-308 GG genotype (69%). The mean duration of untreated disease at enrollment was 10.4 months (standard deviation [SD] 17.5 months).

Table I. Demographic and baseline characteristics of 184 untreated juvenile dermatomyositis patients

Characteristic	Participants (N = 184)*
Age at first visit, mean (SD), y	7.1 (3.9)
Median (range)	6.3 (1.5—17.1)
Sex, no. (%)	
Male patient	46 (25)
Female patient	138 (75)
Race, no. (%)	
Non-Hispanic White	133 (72.2)
Hispanic	34 (18.4)
Black	7 (3.8)
Asian	7 (3.8)
Other	3 (1.6)
DUD, mean (SD), mo†	10.4 (17.5)
Follow-up time, mean (SD), y	6.7 (5.5)
DAS, mean (SD) (n = 166)	
DAS-total (range 0—20)	10.7 (3.6)
DAS-muscle (range 0—11)	4.9 (1.4)
DAS-skin (range 0—9)	5.8 (3.0)
Skin involvement type (n = 177), no. (%)	
Erythema, mild	80 (45.2)
Erythema, moderate	80 (45.2)
Erythema, severe	16 (9.0)
Atrophic changes only	0 (0)
Gottron papules only	1 (0.6)
Skin distribution (n = 176)‡	
Focal	104 (59.1)
Diffuse	55 (31.2)
Generalized	17 (9.7)
TNFA-308 genotype, no. (%) (n = 147)	
GG	102 (69.4)
GA	41 (27.9)
AA	4 (2.7)
Time to reach clinical skin inactivity (DAS-skin 0—2), mean (SD), mo	
0	18.4 (20.4)
≤1	12.8 (11.8)
≤2	11.3 (10.7)
Time to reach clinical muscle inactivity (DAS-muscle 0—2), mean (SD), mo	
0	9.5 (9.9)
≤1	6.2 (6.5)
≤2	4.0 (4.6)

DAS, Disease Activity Score; *DUD*, duration of untreated disease; *SD*, standard deviation.

*Patients with missing data are reflected in the modified N values listed.

†Defined as the interval between first symptoms and the beginning of treatment.

‡Focal distribution involves the area of joint-related skin. Diffuse includes extensor surfaces of limbs and shawl area. Generalized includes trunk involvement.

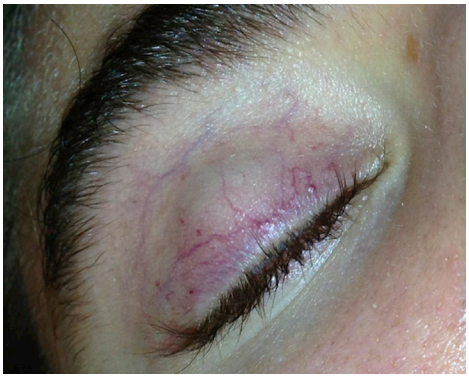

Fig 1. Juvenile dermatomyositis. Representative image of eyelid margin capillary dilatation.[8,54]

At entry, skin involvement was classified as minimal (Gottron papules only, 0.6%), mild (45.2%), moderate (45.2%), or severe (9.0%). Skin distribution was described as focal (59.1%; limited to joint regions), diffuse (31.2%; including extensor surfaces of limbs and shawl area), or generalized (9.7%; including truncal involvement). Some form of vascular involvement was observed in greater than 99% of patients. Fig 1 shows microvascular involvement with eyelid margin vessel dilatation. Other vascular findings included eyelid erythema, periungual (nailfold) capillary telangiectasia or erythema, palatal vessel dilatation, or all 3. Gottron papules were described in 82.3% (n = 135); of these, 64.4% were mild (mild erythema and slight thickening) and 36.5% persisted at 12-month follow-up.

At enrollment, patients presented with higher mean DAS-S (mean 5.7; SD 3.0) compared with mean DAS-M (mean 4.9; SD 1.4) (P = .002) (Fig 2, *A*). After initiation of therapy, total DASs decreased progressively at 6, 12, and 24 months from a mean at baseline of 10.7 (SD 3.6) to 2.7 (SD 2.4) at 24 months, but DAS-S was consistently more severe than DAS-M throughout the 60 months of evaluation while the patient received medication (all $P < .001$). By 36 months after enrollment and at subsequent points, the mean DAS-S was approximately 2.5-fold greater than the DAS-M (Fig 2, *A*).

The percentage of participants who achieved clinical inactivity by the last data point (DAS-M $\leq$ 2) for muscle (97.5%; n = 153) was higher than for skin (92.4%; n = 146) (P = .04). Only 81.6% of patients (n = 129) reached a DAS-S of 0, whereas 96.8% (n = 152) reached a DAS-M of 0 ($P < .001$). Of patients who reached DAS-S less than or equal to 2, only 17.8% (n = 26) maintained clinical inactivity throughout the observation period versus maintenance of DAS-M less than or equal to 2 in 49.0% (n = 152) ($P < .001$).

The duration of treatment before reaching DAS less than or equal to 2 was also longer for skin (mean 11.3 months [SD 10.7]) versus muscle (mean 4.0 months [SD 4.6]) ($P < .001$), as was time receiving medication before full clearance of the skin signs (DAS-S 0) in a mean of 18.4 months (SD 20.4) versus DAS-M of 0 in a mean of 9.5 months (SD 9.9) ($P < .001$) (Table I). The mean times to achieve clinical inactivity and clearance of total DAS were 15.1 months (SD 14.6) and 26.6 months (SD 26.4) while patients received medication, respectively.

Of the 164 patients with vascular data at baseline, 145 were included for analysis in accordance with inclusion criteria of less than 24 months having elapsed between consecutive visits and more than 3 visits in total. Eyelid margin capillary dilatation was the most frequently observed vascular feature at enrollment (n = 89) (Table II) and persisted (mean 7.8 months) longer than periungual (nailfold) telangiectasia (mean 3.5 months; P = .03) or palatal vessel dilatation (mean 3.3 months; P = .05), but not longer than periungual erythema (Table II).

Of the 184 patients, 9 (4.9%) had calcifications at enrollment; an additional 22 children developed calcifications (overall 16.8%). Of these calcifications, 87.0% (n = 27) were mild and 77.4% (n = 24) resolved. Calcifications developed in 24 patients with juvenile dermatomyositis after a mean of 65.6 months (SD 73.1) of receiving medication (median 41.4 months; range 3.2 to 139.3 months) and took an average of 5.6 months (SD 7.0) to resolve (Table II). Among patients whose calcifications resolved, the calcification recurred at the original site in 25.0%, with a mean time to recurrence of 62.1 months (SD 58.2). Calcifications never resolved in 7 patients (22.6%), 5 of whom had calcifications at enrollment and who had a longer duration of untreated disease than children whose calcifications resolved (60.3 months [SD 44.5] vs 12.5 [SD 14.8], respectively; $P < .001$). Recurrence of calcifications was associated with a longer duration of untreated disease than juvenile dermatomyositis without recurrences (23.1 months [SD 25.1] vs 8.8 [SD 6.9], respectively; P = .04). Based on *TNFA* genotype, the calcification risk was higher in the AA + AG genotypes, but did not reach significance (P = .06). Calcinosis also tended to occur more often in patients with higher initial DAS-S but again did not reach significance (P = .06).

Initial treatment options included oral prednisone (89%; n = 164), intravenous methylprednisolone (70%; n = 129), methotrexate (68%; n = 125), hydroxychloroquine (35%; n = 64), mycophenolate mofetil (29%; n = 53), cyclosporine (15%; n = 27), and intravenous immunoglobulin (1%; n = 2)

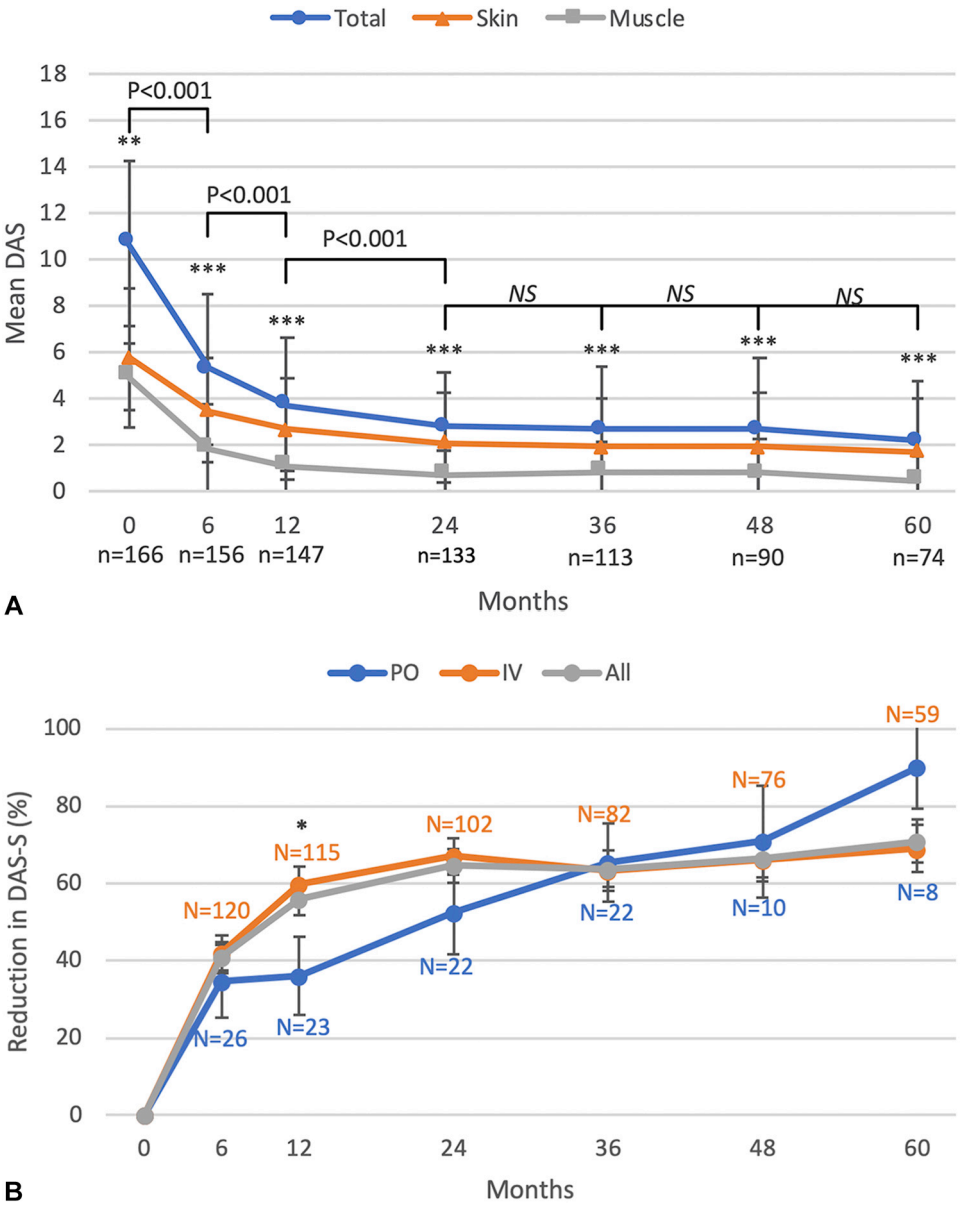

Fig 2. Changes in Disease Activity Scores during the juvenile dermatomyositis course. **A**, Mean Disease Activity Scores at serial visits. The asterisks above each set of data show the *P* value comparing scores for skin and for muscle at that point. Brackets between times indicate *P* values comparing the total Disease Activity Score between the 2 points. **P* < .05; ***P* < .01; ****P* < .001. **B**, Percentage of reduction in Disease Activity Score for skin. The asterisk shows the *P* value, if significant, comparing oral prednisone and intravenous methylprednisolone at that point. **P* < .05. *DAS*, Disease Activity Score; *DAS-S*, Disease Activity Score—Skin; *NS*, not significant.

(mycophenolate mofetil, cyclosporine, and intravenous immunoglobulin use started in the 2000s). Patients who had intravenous methylprednisolone at diagnosis had a significantly higher percentage of reduction in DAS-S (ΔDAS-S) at 12 months with treatment (but not other points) compared with those who only had oral prednisone available (pre-1990s) (*P* = .04) (Fig 2, *B*).

At 1 year, 76% of patients (n = 140) were being treated with oral prednisone, 26% (n = 48) with intravenous methylprednisolone, 48% (n = 89) with methotrexate, 27% (n = 50) with hydroxychloroquine, 13% (n = 24) with mycophenolate mofetil, 3% (n = 5) with cyclosporine, and 4% (n = 8) with intravenous immunoglobulin. Vitamin D3 or calcifediol/25-hydroxyvitamin D3 was prescribed for 80%

Table II. Course of cutaneous elements at enrollment and over time

	Enrollment, n (%)	12 months, n (%)	Last data point, n (%)	Months to achieve clearance, mean (SD)
Vascular element	n = 164	n = 153	n = 173	n = 145
Any vascular element	n = 140 (87.8)	n = 61 (39.9)	n = 57 (32.9)	
Eyelid margin capillary dilatation	89 (54.3)	45 (29.4)	35 (20.2)	7.8 (14.5)
Periungual capillary telangiectasia	85 (51.8)	20 (13.1)	9 (5.2)	3.5 (4.1)
Periungual erythema	72 (43.9)	21 (13.7)	19 (11.0)	5.3 (5.7)
Eyelid erythema	63 (38.4)	28 (18.3)	18 (10.4)	5.9 (9.5)
Palate vessel dilatation	50 (30.5)	19 (12.4)	15 (8.7)	3.3 (3.2)
Gottron sign/papules	n = 164	n = 156	n = 173	
Present (any severity)	135 (82.3)	57 (36.5)	50 (28.9)	8.0 (10.0)
Mild	87 (64.4)	51 (89.5)	32 (64.0)	
Moderate	40 (29.6)	4 (7.0)	9 (18.0)	
Severe	8 (5.9)	0	0	
Atrophic	0	2 (3.5)	9 (18.0)	
Calcifications	n = 184	n = 160	n = 173	
Present	9 (4.9)	9 (5.6)	11 (6.4)	5.6 (7.0)

of patients (n = 147) to mitigate steroid bone toxicity. Children given intravenous methylprednisolone reached clinical skin inactivity sooner than those who were not receiving it (10.4 months [SD 9.2] vs 15.7 [SD 15.6]; P = .02). Additionally, these patients had a greater change in DAS-S from baseline to 12 months (3.5 [SD 2.3] vs 2.0 [SD 1.9]; P = .002). Initiation of hydroxychloroquine was associated with higher skin disease severity at enrollment (DAS-S 6.2 [SD 1.4] vs 5.5 [SD 1.4]; P = .003); however, the subsequent change in DAS-S from treatment initiation of hydroxychloroquine to the end of the observation period was not statistically significant (P = .89).

DISCUSSION

Given the collection of data for 48 years, this study provides a historical and comprehensive look at the management of juvenile dermatomyositis. The data confirm that juvenile dermatomyositis patients present with greater skin than muscle involvement, and that skin features require more time for resolution.[36] This is an important consideration because persistent skin disease not only significantly affects quality of life but also can foster calcification and ulceration that can be life threatening. We have now shown that eyelid margin capillary dilatation is the most common microvascular feature. It requires the longest time to resolve, with time to clearance comparable to that of more recognized cutaneous manifestations such as Gottron papules/plaques. This underrecognized feature can serve as both an important diagnostic tool and an indicator of continued disease activity that may require continued therapy, despite resolution of muscle disease.

Previous studies have described vascular damage associated with life-threatening sequelae, including intestinal ischemia and perforation, interstitial lung disease, cardiac dysfunction, premature atherosclerosis, and calcinosis-associated sepsis.[14,37,38] The pathophysiology of vascular damage in the skin and elsewhere is not fully understood, but loss of nailfold end-row capillary loops is associated with decreased bioavailability of orally administered prednisone,[39] suggesting the concurrence of intestinal vascular damage and providing the impetus for initiation of intravenous methylprednisolone for most of the children in this study. Type I interferon genes[40] and chemokines (monocyte chemoattractant-1 and monocyte chemoattractant-2) are also correlated with clinical measures of disease activity.[41] A skin biopsy study identified increased mast cells and plasmacytoid dendritic cells in both involved and normal-appearing skin compared with muscle from juvenile dermatomyositis.[36] Improved understanding of the molecular changes in the skin of individuals with juvenile dermatomyositis promises to direct the use of more targeted therapies.[40]

Calcinosis is associated with delayed diagnosis and treatment, as well as a longer disease course,[23,42,43] which was confirmed in this study. Calcification early in the disease course tended to be more severe and resistant to aggressive treatment options,[5,25] suggesting that permanent damage is established early in the course. Calcinosis that

resolved was often mild at presentation or developed later in the disease course, confirming the importance of long-term monitoring.

According to current consensus treatment protocols,[44-46] most patients in this study initiated intravenous methylprednisolone, oral prednisone and methotrexate, or both after enrollment, well before published reports.[25,47] At 1 year, most patients were still receiving steroid treatment, but few had cutaneous inactivity. This study documents that skin disease is more resistant to therapy than muscle disease, reminding physicians to develop more effective therapeutic interventions targeting skin disease activity, not just muscle disease activity, in making treatment decisions.

STRENGTHS AND LIMITATIONS

With data captured during almost 5 decades, this study is the largest cohort study of untreated juvenile dermatomyositis patients from a single center, to our knowledge. Most patients were treated and evaluated by a single physician (L.M.P.), ensuring uniform scoring. However, the DAS has certain limitations. For example, nailfold capillary dropout is associated with more chronic disease and greater disease severity,[17,48] but it is not quantified in the DAS. Our group's ongoing investigation of this cohort's nailfold capillary dropout will be useful.[48,49] Testing for myositis-specific antibodies[50] more recently became available and thus they were not tested in most patients with juvenile dermatomyositis diagnosed before 2013.

This study highlights the limitations of current treatments in controlling the volatile nature of both skin and muscle disease. In 2000, a report of long-term outcomes of juvenile dermatomyositis patients showed that 52% of patients had chronic disease activity, with 35% continuing to need treatment after 7-year follow-up.[51] Similarly, many of our patients had DASs that fluctuated throughout the disease course, even after reaching clinically inactive DASs. Further research should identify reliable biomarkers of continuing disease activity in juvenile dermatomyositis that appears clinically quiescent.[52,53]

CONCLUSIONS

This cohort study confirms that both skin and muscle involvement should guide diagnosis and treatment of juvenile dermatomyositis. Clinicians should be aware of eyelid margin capillary dilatation, which tends to persist, in addition to other characteristic skin features that are better recognized. Early and aggressive treatment with therapies such as intravenous methylprednisolone can help limit the severity of skin disease.

We would like to thank Dr Chiang-Ching Huang, PhD for his guidance in conducting the statistical analysis and Marisa Klein-Gitelman, MD, MPH, Megan L. Curran, MD, and Kaveh Ardalan, MD, MS, for contributing to the care of this cohort of children.

Conflicts of interest

None disclosed.

REFERENCES

1. Mendez EP, Lipton R, Ramsey-Goldman R, et al. US incidence of juvenile dermatomyositis, 1995—1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. *Arthritis Care Res*. 2003;49(3):300-305.
2. Cho SK, Kim H, Myung J, et al. Incidence and prevalence of idiopathic inflammatory myopathies in Korea: a nationwide population-based study. *J Korean Med Sci*. 2019;34(8):e55.
3. Symmons DP, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. *Br J Rheumatol*. 1995;34(8):732-736.
4. Pachman LM, Khojah AM. Advances in juvenile dermatomyositis: myositis specific antibodies aid in understanding disease heterogeneity. *J Pediatr*. 2018;195:16-27.
5. Bowyer SL, Blane CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis: factors predicting functional outcome and development of dystrophic calcification. *J Pediatr*. 1983;103(6):882-888.
6. Hoeltzel MF, Oberle EJ, Robinson AB, et al. The presentation, assessment, pathogenesis, and treatment of calcinosis in juvenile dermatomyositis. *Curr Rheumatol Rep*. 2014;16(12):467.
7. Wu Q, Wedderburn LR, McCann LJ. Juvenile dermatomyositis: latest advances. *Best Pract Res Clin Rheumatol*. 2017;31(4):535-557.
8. Bode RK, Klein-Gitelman MS, Miller ML, et al. Disease Activity Score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Care Res*. 2003;49(1):7-15.
9. Ruperto N, Ravelli A, Murray KJ, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology (Oxford)*. 2003;42(12):1452-1459.
10. Campanilho-Marques R, Deakin CT, Simou S, et al. Retrospective analysis of infliximab and adalimumab treatment in a large cohort of juvenile dermatomyositis patients. *Arthritis Res Ther*. 2020;22(1):79.
11. Rider LG, Werth VP, Huber AM, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), Physician Global Damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). *Arthritis Care Res (Hoboken)*. 2011;63 suppl 11(0 11):S118-S157.

12. Tollisen A, Sanner H, Flato B, Wahl AK. Quality of life in adults with juvenile-onset dermatomyositis: a case-control study. *Arthritis Care Res (Hoboken)*. 2012;64(7):1020-1027.
13. Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet*. 2016;387(10019):671-678.
14. Schwartz T, Sanner H, Gjesdal O, et al. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. *Ann Rheum Dis*. 2014;73(10):1805-1810.
15. Campanilho-Marques R, Almeida B, Deakin C, et al. Comparison of the utility and validity of three scoring tools to measure skin involvement in patients with juvenile dermatomyositis. *Arthritis Care Res (Hoboken)*. 2016;68(10):1514-1521.
16. Martin N, Li CK, Wedderburn LR. Juvenile dermatomyositis: new insights and new treatment strategies. *Ther Adv Musculoskelet Dis*. 2012;4(1):41-50.
17. Christen-Zaech S, Seshadri R, Sundberg J, et al. Persistent association of nailfold capillaroscopy changes and skin involvement over thirty-six months with duration of untreated disease in patients with juvenile dermatomyositis. *Arthritis Rheum*. 2008;58(2):571-576.
18. Stringer E, Singh-Grewal D, Feldman BM. Predicting the course of juvenile dermatomyositis: significance of early clinical and laboratory features. *Arthritis Rheum*. 2008;58(11):3585-3592.
19. Ramanan AV, Feldman BM. Clinical outcomes in juvenile dermatomyositis. *Curr Opin Rheumatol*. 2002;14(6):658-662.
20. McCann LJ, Juggins AD, Maillard SM, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology*. 2006;45(10):1255-1260.
21. Robinson AB, Hoeltzel MF, Wahezi DM, et al. Clinical characteristics of children with juvenile dermatomyositis: the Childhood Arthritis and Rheumatology Research Alliance Registry. *Arthritis Care Res*. 2014;66(3):404-410.
22. Blane CE, White SJ, Braunstein EM, et al. Patterns of calcification in childhood dermatomyositis. *AJR Am J Roentgenol*. 1984;142(2):397-400.
23. Mathiesen PR, Zak M, Herlin T, Nielsen SM. Clinical features and outcome in a Danish cohort of juvenile dermatomyositis patients. *Clin Exp Rheumatol*. 2010;28(5):782-789.
24. Ravelli A, Trail L, Ferrari C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. *Arthritis Care Res*. 2010;62(1):63-72.
25. Fisler RE, Liang MG, Fuhlbrigge RC, et al. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. *J Am Acad Dermatol*. 2002;47(4):505-511.
26. Pachman LM, Fedczyna TO, Lutz JL, Lechman T. Juvenile dermatomyositis: the association of the TNFa-308A allele and disease chronicity. *Curr Opin Rheumatol*. 2001;5:379-386.
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
28. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med*. 1975;292(7):344-347.
29. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Arthritis Rheumatol*. 2017;69(12):2271-2282.
30. McCann LJ, Pilkington CA, Huber AM, et al. Development of a consensus core dataset in juvenile dermatomyositis for clinical use to inform research. *Ann Rheum Dis*. 2018;77(2):241-250.
31. Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am*. 1997;23(3):619-655.
32. Pachman LM, Liotta-Davis MR, Hong DK, et al. TNFα-308A allele in juvenile dermatomyositis: association with increased production of tumor necrosis factor α, disease duration, and pathologic calcifications. *Arthritis Rheum*. 2000;43(10):2368-2377.
33. Rider LG, Aggarwal R, Pistorio A, et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in juvenile dermatomyositis: an international myositis assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation collaborative initiative. *Arthritis Rheumatol*. 2017;69(5):911-923.
34. Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids: adverse reactions are more variable than expected in children. *J Rheumatol*. 1998;25(10):1995-2002.
35. Callen AM, Pachman LM, Hayford J, Chung A, Ramsey-Goldman R. Intermittent high-dose intravenous methylprednisolone (IV pulse) therapy prevents calcinosis and shortens disease course in juvenile dermatomyositis (JDMS). *Arthritis Rheum*. 1994;37(6):R10-R.(ABST).
36. Shrestha S, Wershil B, Sarwark JF, Niewold TB, Philipp T, Pachman LM. Lesional and nonlesional skin from patients with untreated juvenile dermatomyositis displays increased numbers of mast cells and mature plasmacytoid dendritic cells. *Arthritis Rheum*. 2010;62(9):2813-2822.
37. Berard R, Chédeville G, Saint-Martin C, Scuccimarri R. Benign pneumatosis intestinalis in a patient with juvenile dermatomyositis. *J Rheumatol*. 2010;37(11):2442-2444.
38. Eimer MJ, Brickman WJ, Seshadri R, et al. Clinical status and cardiovascular risk profile of adults with a history of juvenile dermatomyositis. *J Pediatr*. 2011;159(5):795-801.
39. Rouster-Stevens KA, Gursahaney A, Ngai KL, Daru JA, Pachman LM. Pharmacokinetic study of oral prednisolone compared with intravenousmethylprednisolone in patients with vasculitis of rheumatic disease. *Arthritis Rheum*. 2008;59(2):222-226.
40. Turnier J, Berthier C, Tsoi L, et al. Cutaneous gene expression signatures in juvenile myositis reveal a prominent IFN signature in lesional skin [abstract]. *Arthritis Rheum*. 2019;71(suppl 10):1326-1327. Abst.# 775.
41. Reed AM, Peterson E, Bilgic H, et al. Changes in novel biomarkers of disease activity in juvenile and adult dermatomyositis are sensitive biomarkers of disease course. *Arthritis Rheum*. 2012;64(12):4078-4086.
42. Pachman LM, Hayford JR, Chung A, et al. Juvenile dermatomyositis at diagnosis: clinical characteristics of 79 children. *J Rheumatol*. 1998;25(6):1198-1204.
43. Pachman LM, Abbott K, Sinacore JM, et al. Duration of illness is an important variable for untreated children with juvenile dermatomyositis. *J Pediatr*. 2006;148(2):247-253.
44. Huber AM, Giannini EH, Bowyer SL, et al. Protocols for the initial treatment of moderately severe juvenile dermatomyositis: results of a Children's Arthritis and Rheumatology Research Alliance Consensus Conference. *Arthritis Care Res*. 2010;62(2):219-225.
45. Liu K, Tomlinson G, Reed AM, et al. Pilot study of the juvenile dermatomyositis consensus treatment plans: a CARRA Registry study. *J Rheumatol*. 2020;48(1):114-122.
46. Huber AM, Kim S, Reed AM, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment

plans for juvenile dermatomyositis with persistent skin rash. *J Rheumatol*. 2016;44(1):110-116.
47. Kim S, El-Hallak M, Dedeoglu F, et al. Complete and sustained remission of juvenile dermatomyositis resulting from aggressive treatment. *Arthritis Rheum*. 2009;60(6):1825-1830.
48. Ostrowski RA, Sullivan CL, Seshadri R, Morgan GA, Pachman LM. Association of normal nailfold end row loop numbers with a shorter duration of untreated disease in children with juvenile dermatomyositis. *Arthritis Rheum*. 2010;62(5):1533-1538.
49. Smith RL, Sundberg J, Shamiyah E, et al. Skin involvement in juvenile dermatomyositis is associated with loss of end row nailfold capillary loops. *J Rheumatol*. 2004;31(8):1644-1649.
50. Tansley SL, Betteridge ZE, McHugh NJ. The diagnostic utility of autoantibodies in adult and juvenile myositis. *Curr Opin Rheumatol*. 2013;25(6):772-777.
51. Huber AM, Lang B, LeBlanc CMA, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. *Arthritis Rheum*. 2000;43(3):541-549.
52. Tawalbeh SM, Marin W, Morgan GA, Dang UJ, Hathout Y, Pachman LM. Novel serum protein biomarkers for juvenile dermatomyositis: a pilot study. *BMC Rheumatol*; 2020. https://doi.org/10.1186/s41927-020-00150-7.
53. Wienke J, Pachman LM, Morgan GA, et al. Endothelial and inflammation biomarker profiles at diagnosis reflecting clinical heterogeneity and serving as a prognostic tool for treatment response in two independent cohorts of patients with juvenile dermatomyositis. *Arthritis Rheum*. 2020;72(7):1214-1226.
54. Akikusa JD, Tennankore DK, Levin A, Feldman BM. Eye findings in patients with juvenile dermatomyositis. *J Rheumatol*. 2005;32:1986-1991.