What more can we learn from muscle histopathology in children with dermatomyositis/polymyositis?

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Abstract

Objective

To correlate disease course and complications in children with juvenile dermatomyositis (JDM) and polymyositis (JPM) with specific features of muscle pathology on biopsy.

Methods

This is a retrospective cohort analysis of 59 children diagnosed with JDM or JPM between 1965 and 1998 and followed at the Cincinnati Children's Hospital Medical Center (CCHMC) for a mean duration of 7.3 years (range 1.1-24.5 years). Disease course was characterized as limited, chronic non-ulcerative or chronic ulcerative, similar to previously defined disease course subtypes reported by Crowe et al. (1). All subjects had diagnostic muscle biopsies performed at CCHMC and had disease for at least two years' duration in order to classify their disease course as either limited or chronic. Features of muscle histopathology that were evaluated included loss of the intramuscular capillary bed, infarct, perifascicular myopathy, direct immunofluorescence (DIF) staining of the intramuscular vasculature and specifically, the locale of DIF staining, i.e., small arteries or capillaries. Disease complications that were assessed included calcinosis, contractures, muscle atrophy, lipodystrophy, gastrointestinal ulceration, cutaneous ulceration and death. Data analysis was completed using Chi-square or Fisher's exact tests and logistic regression modeling.

Results

Twenty-two children (37%) had limited disease, 24 (41%) had chronic non-ulcerative disease and 13 (22%) had chronic ulcerative disease. Neither loss of the intramuscular capillary bed nor perifascicular myopathy on muscle biopsy significantly correlated with disease course or the various complications evaluated in this study. DIF staining of intramuscular vessels overall was not significantly associated with clinical disease course, but the localization of DIF staining to intramuscular arteries (rather than to capillaries) was significantly associated with the outcome of chronic ulcerative disease. Nine of the 13 children with chronic ulcerative disease had DIF-arterial staining on muscle biopsy (69%), significantly greater than DIF-arterial staining in children with limited disease (32% had DIF-arterial staining) ($p = 0.04$), chronic non-ulcerative disease (8% had DIF-arterial staining) ($p = 0.0002$), and non-ulcerative disease overall (limited + chronic non-ulcerative disease groups combined) (20% had DIF-arterial staining), with $p = 0.001$. Additionally, lack of DIF-arterial staining on biopsy was significantly correlated with patients not having gastrointestinal ulceration ($p = 0.002$), cutaneous ulceration ($p = 0.004$) and/or death ($p = 0.02$) as disease-related complications. Infarct on muscle biopsy was significantly associated with the development of chronic ulcerative disease ($p = 0.02$), being present on biopsy in 23% of children with chronic ulcerative disease compared with none of the patients with chronic non-ulcerative disease and 4% of those with limited disease. Infarct on muscle biopsy correlated with the outcomes of death ($p = 0.01$) and gastrointestinal ulceration ($p = 0.03$), but not with the development of cutaneous ulceration ($p = 0.18$).

Conclusions

DIF-arterial staining and infarct on muscle biopsy are significantly associated with the development of chronic ulcerative disease in JDM and JPM, while perifascicular myopathy and loss of the intramuscular capillary network are not associated with disease course. The presence of DIF-arterial staining and infarct on biopsy should suggest early use of second-line therapeutic agents to more quickly bring disease activity under control.

Key words

Juvenile dermatomyositis, histopathology, vasculopathy, clinical, complications.

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Introduction

In 1982, William Crowe and colleagues correlated histopathology identified on pre-treatment muscle biopsy specimens with clinical outcome in 29 patients diagnosed with juvenile dermatomyositis (JDM) or polymyositis (JPM), followed at the Cincinnati Children's Hospital Medical Center (CCHMC) between 1958 and 1980. These investigators reported that loss of the intramuscular capillary network with subsequent development of zonal (or perifascicular) myopathy, infarction, endarteropathy and lymphocytic vasculitis on muscle biopsy were associated with chronicity of disease and were the hallmarks of the severe form of disease in which skin and gut ulceration resulted from vascular occlusion (1). Additionally, arterial occlusion was found to coincide with the presence of muscle infarction on biopsy.

To evaluate muscle histopathology in that study, both light and electron microscopy were performed. Direct immunofluorescence (DIF) staining with fluorescein-labelled antibodies to IgM, C3d and fibrin, alone or in combination, was not performed consistently on biopsied tissues in that study. In the 14 of 29 muscle biopsies that underwent DIF staining, differences in arterial, capillary or venular staining were not specifically correlated with disease course or clinical outcomes. The authors reported that children with limited disease were as likely to have immunoreactive vessels (or DIF staining) as those with chronic disease, and DIF staining of vessels had no prognostic significance (1).

Prior to the Crowe *et al.* study, Whitaker and Engel reported on the deposition of complement and immunoglobulins in the intramuscular vasculature of patients with idiopathic inflammatory myopathy in 1972, linking the intravascular deposition of these immunoproteins with the pathogenesis of myopathy seen in this group of diseases (2). In a later study, Kissel *et al.* used immunocytochemical techniques to demonstrate localization of the terminal C5b-9 membrane attack complex (MAC) to the intramuscular microvasculature, using an immunofluorescent antibody directed against antigens in this complex (3). Muscle biopsies from ten (83%) of their 12 patients with JDM demonstrated immunofluorescence staining of the MAC in the microvasculature, compared with none of the 52 control specimens used in this study. These findings suggested that complement, as shown to be deposited, bound and activated in the intramuscular microvasculature to form the terminal MAC, has a primary role in mediating vessel injury in JDM. Five years later, Kissel *et al*. further characterized the relationship between vascular complement deposits and the histologic changes seen in biopsied muscle tissue obtained from patients with dermatomyositis, demonstrating a significant correlation between the percentage of muscle fascicles with fibers having focal myofibrillar loss on biopsy, a histopathologic change seen early in the evolution of ischemic muscle injury, and the percentage of fascicles having capillary deposits of the MAC (4).These data supported their hypothesis that the complement-mediated vasculopathy is a pivotal immunopathogenic event in the evolution of muscle damage seen in dermatomyositis. All of these studies have demonstrated the value of obtaining muscle biopsies in this patient population, not only to confirm diagnosis, but also to provide information on the pathogenesis of disease and perhaps guide clinical management.

In the last 25 years, advances in technology have made possible the detection of muscle inflammation using modalities other than muscle biopsy. Since the late 1980's, magnetic resonance imaging (MRI) of the proximal limb musculature has been used with increasing frequency as an adjunct to the Bohan and Peter diagnostic criteria (5 - 8), particularly to target areas of active myopathy for biopsy (9, 10). The ease and clarity of MRI in assessing diseased muscle non-invasively have raised the question as to whether the Bohan and Peter criteria should be updated to include MRI of the proximal musculature as a means of demonstrating myopathy and diagnosing dermatomyositis (9). In one report, MRI

was found to be more sensitive than muscle biopsy in detecting active muscle disease (89% vs. 66%), with a positive predictive value almost equivalent to that of biopsy (97% vs. 100%) and a greater negative predictive value (64% vs. 38%, respectively) (7).

Other reports note that the radiographic finding of muscle edema, one of the hallmarks of muscle inflammation detected by MRI, with increased signal intensity on T2 weighted, fat-suppressed images (11, 12), is not specific to the inflammatory myopathies and can also be seen in the settings of muscle injury (whether transiently present during and briefly following exercise or due to significant trauma, resulting in rhabdomyolysis), infection (myositis without phlegmon or abscess formation), radiation therapy, subacute denervation, compartment syndrome, early myositis ossificans, and sickle cell crisis (11, 13). Because of the potential for MRI to yield false positive results in detecting patients with inflammatory myopathy, it has been recommended that MRI be used to examine changes in diseased muscle non-invasively once diagnosis has been established and to assess disease activity, but that it should not replace muscle biopsy for diagnostic evaluation of patients with inflammatory myopathies (14).

Given these varying opinions regarding the usefulness of MRI to non-invasively diagnose myositis in children with JDM and JPM, the purpose of this study was to re-evaluate the importance of obtaining muscle biopsies prior to beginning systemic therapy by looking at the prognostic value of certain histopathological features with respect to disease course and potential complications in children with JDM and JPM. Our working hypothesis was that children with JDM or JPM who have DIF staining of intramuscular arteries rather than capillary- or no vascular staining on muscle biopsy are at significantly increased risk of developing chronic ulcerative disease, due to greater compromise of blood flow to the muscle fascicles, skin and gastrointestinal mucosa, resulting in local ischemia and infarction.

Methods

Study design and sample population

This study is a retrospective cohort analysis in which muscle histopathology and clinical course were reviewed for 59 children diagnosed with JDM or JPM between April 1965 and November 1998, and who were followed at the Special Treatment Center (STC) for Juvenile Arthritis at CCHMC. Clinical data was drawn from the ARAMIS (Arthritis and Rheumatism Association Medical Information System) database established at CCHMC and into which each child in the cohort was enrolled after their parents gave informed consent for the child's participation. Informed consent to review, reevaluate and report on muscle tissue pathology was obtained from each child's parents at the time the child underwent open muscle biopsy. The format for collecting clinical data and reviewing muscle histopathology on previously obtained muscle biopsy specimens was approved by the CCHMC Institutional Review Board prior to undertaking this study.

Inclusion criteria

Children included in the study were diagnosed with JDM or JPM, using the Bohan and Peter criteria for definite or probable dermatomyositis or polymyositis (5). Throughout the period of study, almost all patients suspected of having an inflammatory myopathy based on their clinical presentation had muscle biopsies to confirm the diagnosis, as it was and has been the standard of care at CCHMC to perform open muscle biopsies to confirm the diagnosis of JDM or JPM, ideally before the initiation of therapy. Four children with sclerodermatomyositis were included in the cohort, as they had prominent cutaneous manifestations and muscle weakness as well as laboratory and biopsy abnormalities that satisfied the Bohan and Peter criteria for definite dermatomyositis. All members of the cohort had disease for at least two years' duration at the time of chart review in order to accurately classify their disease course as limited or chronic, as per Crowe *et al.* (1). All members of the cohort had diagnostic open muscle biopsies performed at CCHMC that underwent light and electron microscopy as well as DIF staining. Forty-eight of the 59 muscle biopsies (81%) had been obtained prior to the initiation of systemic therapy in these patients, but 11 children had been treated with medications such as oral corticosteroids (8 children), hydroxychloroquine (2), methotrexate (1), aspirin (2) and another non-steroidal anti-inflammatory drug (1), before their initial evaluation at CCHMC. The eight children (14% of the cohort) who were treated with oral steroids prior to undergoing muscle biopsy had begun therapy an average of four months (and no more than 9 months) prior to their initial evaluation at CCHMC; none had had pre-treatment muscle biopsies performed.

Exclusion criteria

Children excluded from the study were those with muscle-biopsy proven myositis who did not carry a primary diagnosis of JDM, JPM or sclerodermatomyositis (i.e., children with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) or post-infectious transient myositis, who did not meet the Bohan and Peter diagnostic criteria for dermatomyositis or polymyositis). Children who did not undergo muscle biopsy at CCHMC were also excluded. In total, eight children with myositis were excluded from the study: two carried other primary diagnoses (one SLE, one MCTD); two children with ulcerative JDM had disease less than two years' duration at the time of this project's chart review; three children had incomplete follow-up records because they had moved from the area, and one child did not have a muscle biopsy done at CCHMC. The one child with JDM who was excluded from the study for not having undergone muscle biopsy at CCHMC, a girl with severe chronic ulcerative disease from Belize, had been biopsied in her home country, although her biopsy slides remained in Belize and there were no remaining tissue blocks available from her biopsy for DIF staining for this project.

Muscle biopsy methodology

Open surgical muscle biopsy specimens were obtained from an affected proximal extremity. In the early part of the study (up to the mid-1980's), muscle biopsy location was determined by documentation of abnormalities on EMG in the contralateral muscle group. In those patients who had a non-informative EMG, muscle biopsy was performed in areas of documented muscle weakness and/or tenderness. In the latter part of the study, areas of muscle edema and inflammation documented on MRI determined the muscle biopsy site. In most patients, the upper anterolateral aspect of the quadriceps muscle was chosen. Under the supervision of one pathologist (KEB) for the duration of this study, muscle tissue was flash frozen, and cryostat sections were subjected to a battery of histochemical stains and direct immunofluorescence reactions, as previously described (1). Fluorescein-labelled antibodies, obtained from DAKO, and directed against IgA, IgG, IgM, C3c, C3d and fibrinogen, were used in all cases. In 1985, antibodies to C5 and C1q, also from DAKO, were added. Those specimens from the Crowe *et al.* study (1) that had not undergone DIF staining initially (15 of the original 29 biopsy specimens) were subjected to the same battery of histochemical and DIF stains that the other 14 specimens in the group had had as well as the more recent 30 muscle specimens.

New lots of antibodies were tested against control tissue before use. Working concentrations of antibody were selected to minimize background immunofluorescence. Positive control tissue for direct immunofluorescence (DIF) consisted of kidney tissue from patients with glomerulonephritis. During the period of study, this panel of antibodies was applied to muscle specimens with a variety of histopathological diagnoses, some of which were the seat of minor inflammatory infiltrates. None of these additional control samples displayed selective discrete reactivity in capillaries, small arteries or veins.

Data collection

Pathology specimens Glass slides, the DIF worksheets, photomicrographs and the medical record reports were reviewed by the pathologist (KEB), who was in almost all cases the pathologist of record, and his assistant, JDS. The following data were extracted and tabulated: histopathological presence of perifascicular myopathy, tissue infarct, apparent loss of the capillary network in the periphery of fascicles compared to the central region, and the presence or absence of discrete immunoreactivity with fluorescein-labelled antisera to IgA, IgG, IgM, C3c, C3d, C5, C1q and/or fibrinogen, alone or in combination, in arteries, veins and capillaries, as well as in muscle fibers. Quantitative assessment of capillary loss was not performed. Intensity of DIF staining was graded in the original worksheets and varied within a given case from vessel to vessel. Borderline or equivocal reactions were classed as negative. Because intensity of DIF reactions is a subjective measure and dependent on both equipment and photographic conditions, it was not used as a criterion for this study. In our experience, inflammatory infiltrates, while almost always present in children with dermatomyositis, tend to be light and focal (see Fig. 1). For this reason, no attempt was made to grade inflammation in the biopsy specimens.

Clinical Data Collection Patients' medical records were reviewed for demographic data, such as gender and race/ethnicity, initial clinical presentations, including degree of muscle weakness and age at diagnosis, duration of follow-up and clinical outcomes, including disease course and complications. Date of diagnosis often corresponded with date of the initial STC visit, although some children had been diagnosed with JDM or JPM prior to being followed at CCHMC. Duration of follow-up was determined by

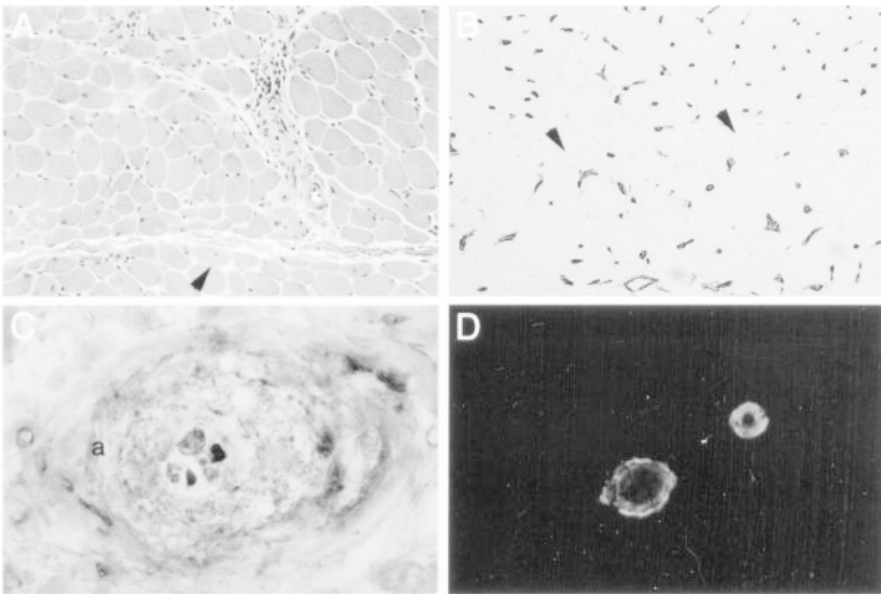

Fig. 1. A. Typical features of JDM in this thigh muscle specimen include a sparse, chiefly lymphocytic, perivascular infiltrate with slight spillover into the muscle fascicles and regional concentration of partly atrophied, myopathic muscle fibers along the margins of muscle fascicles (arrowhead). Cryostat section. Hematoxylin and eosin stain. X125.

B. Severe atrophy of muscle fibers along the margins of fascicles (arrowheads) is associated with loss of stainable capillary network as indicated by selective depletion of CD31-reactive capillary endothelium in perifascicular zones. Compare to the much higher normal capillary density among the undamaged muscle fibers within the interior of the muscle fascicles. CD31 immunostain. X125.

C. Intramuscular artery in thigh muscle of a patient with JDM exhibits luminal occlusion by cellular debris. The wall of this vessel contained deposits of IgM, C3d, C5 and fibrinogen using direct immunofluorescence microscopy. Cryostat section. Hematoxylin and eosin stain. X500.

D. Patent intramuscular arteries in thigh muscle of patient with JDM are the seat of irregular fragmentary linear deposits of C5, as shown here, as well as C3d. Other immunoreactants were absent in this specimen. There was no vasculitis. Cryostat section. Direct immunofluorescence microscopy. X250.

subtracting the date of the last clinic or hospital visit at the time the cohort was closed from the date of diagnosis; it was then expressed in years as was age at diagnosis. Initial muscle weakness was described as (1) mild, when the child was weak by examination but had normal function overall, (2) moderate, when the child was significantly disabled, having difficulty performing some activities of daily living (ADL's) independently, and (3) severe, when the child was profoundly weak, requiring assistance with most ADL's and/or being non-ambulatory. This grading of muscle weakness was similar to the system used by Crowe *et al*. (1) to categorize the severity of muscle weakness at the time of initial muscle biopsy.

Clinical outcomes evaluated were known complications of JDM and JPM and included muscle atrophy, calcinosis, joint contractures, lipodystrophy, gastrointestinal ulceration, cutaneous ulceration and death. The presence of lipodystrophy, which was defined for this study as disruption of the distribution of body fat, characterized by significant loss of subcutaneous fat, was recorded on either standardized data collection forms in the ARAMIS database or in the patients' clinic charts by the pediatric rheumatologists following these children. Additionally, joint exams were performed on these children at each of their follow-up visits at the STC as part of a complete physical examination, and the presence of contractures (whether reducible or fixed) was noted either in their clinic charts and/or on standardized ARAMIS joint exam forms completed by pediatric rheumatologists for each patient encounter.

Disease course was assigned using categories similar to those first outlined by Crowe *et al.* (1). "Limited disease" was defined as involving muscle weakness and rash that responded well to steroid therapy and resolved within two years of treatment; with limited disease, medication was successfully withdrawn by the end of the initial two-year period with no recurrence of disease activity over time. Chronic disease was defined as disease activity for greater than two years and included periods of disease inactivity, if these remissions were either medication-free but then followed by exacerbations requiring reinstitution of systemic therapy (accounting for a polycyclic course of disease activity) (15), or they required the continued use of medication to keep disease activity in check. Chronic disease was further divided into two subgroups: those with non-ulcerative disease and those with ulcerative disease. The chronic non-ulcerative (CNU) disease category included patients whose disease was active for more than two years, but who never developed ulcerative gastrointestinal or cutaneous lesions. While Crowe *et al*. defined the "chronic, non-ulcerative childhood polydermatomyositis (CDM/-PM)" group of patients as having significant residua of the disease, including weakness, limitation of motion, contractures or calcinosis without having ulcerative sequelae, we expanded the definition of CNU disease to include patients who had active disease for more than two years, without ever developing ulcerative sequelae, *with or without the development of significant disease residua*. Chronic ulcerative (CU) disease was defined as disease persisting for more than two years and involving gastrointestinal ulceration, as evidenced by severe abdominal pain with melena, pneumatosis intestinalis or visceral perforation, and/or cutaneous ulceration that resulted directly from the primary vasculopathy of JDM, not secondary to calcinosis or other causes. In defining the three disease course subtypes in this manner, all 59 patients in the cohort could accurately be categorized into one of these three groups.

Data Analysis

Demographic descriptors of the sample, such as gender and race, and initial degree of muscle weakness were created as categorical variables and were analyzed using the proc frequency procedure in the Statistical Analysis System (SAS, Version 8; SAS Institute Inc., Cary, NC). Age at diagnosis and duration of follow-up were treated as continuous variables. The proc univariate procedure demonstrated that neither of these two variables was normally distributed.

The presence of specific histopathological features on muscle biopsy, including 1) perifascicular myopathy, 2) loss of the intramuscular capillary network, 3) tissue infarct and 4) direct immunofluorescence (DIF) of the intramuscular microvasculature (arteries and/or capillaries), as well as disease course and clinical outcomes were assessed as categorical variables. In analyzing associations between muscle biopsy findings and the identified disease courses and complications, Chi-square testing was initially undertaken. For 2-x-2 and 2-x-3 contingency tables that did not include all members of the cohort (i.e., comparisons between two disease course subtypes) and/or that had fewer than five patients in one or more cells of the table, Fisher's exact test was used, and p-values were reported using two-tailed probabilities. Disease course subtypes that were compared included limited disease, CNU disease, and CU disease, as well as chronic disease (CNU + CU disease groups combined) compared with limited disease, and non-ulcerative disease (limited + CNU disease groups combined) compared with CU disease.

Lastly, building a multivariate regression model was undertaken. Those histopathological features on muscle biopsy that were found to be significantly associated with disease course and/or complications by Chi-square/Fisher exact testing were selected as predictor variables. The predictor variables were dichotomous, defined as either present or absent on muscle biopsy. The dependent variable was disease course, specifically the presence or absence of CU disease. Logistic regression was used for model building since both the predictor and dependent variables were dichotomous.

DIF-positivity, DIF-arterial staining, and infarct, as independent variables, were first run as univariate logistic regression models with the outcome event of interest being the presence of chronic ulcerative disease. Additionally, an interaction term between infarct and DIF-arterial staining (DIF-arterial

staining x infarct) was run as a combined predictor variable in a univariate logistic regression model, as Crowe *et al.* had found that these two histopathologic features were frequently simultaneously present on biopsy (1). Only variables with significant p-values for slope coefficient estimates in the univariate models were subsequently used to build a multivariate logistic regression model, with entry-level p-values ≤ 0.1. Comparisons of expanded and reduced models were made using the Akaike Information Criterion (AIC) value and the area under the receiver operating characteristic curve (16) as well as the p-value of the Hosmer and Lemeshow Goodness-of-Fit test (17) to assess the fit of the model to the data. For the final model(s), the odds ratio(s) for the development of CU disease and the 95% confidence intervals were calculated.

Level of statistical significance was set at $p \leq 0.05$; p-values were not adjusted for multiple comparisons. P-values obtained from the various comparisons made, including those greater than 0.05, are presented for completeness.

Results

Thirty-nine of the 59 children in the cohort were girls (66%), a gender ratio similar to what has been reported previously in the literature (18, 19, 20). Seventy-five percent of the cohort was Caucasian (N = 44); the other members of the cohort were African-American (12 patients), Hispanic (2 patients) and Vietnamese (1 patient). Fifty-six children in the cohort (95%) had definite or probable juvenile dermatomyositis, using the diagnostic criteria of Bohan and Peter (5). Four children (7%) with JDM also had features of scleroderma (localized) but met the diagnostic criteria of Bohan and Peter for definite JDM. Three children had polymyositis (5%). The mean age at diagnosis was 7.9 ± 4.0 years, with a range of 1.7 to 16.3 years. Mean duration of follow-up was 7.3 ± 5.1 years; length of follow-up ranged from 1.1 to 24.5 years. Thirty-one children (52%) presented initially with moderate muscle weakness, while ten patients (17%) presented with severe muscle weakness, requiring assistance with most ADL's and/or being non-ambulatory. Eighteen children (31%) had mild muscle weakness initially. Children with CU disease were significantly less likely to present with mild muscle weakness, compared to those children who had non-ulcerative disease (8% compared to 37%, respectively, p = 0.05).

Fifty-four of the 59 muscle biopsy specimens (92%) had histopathological features consistent with a diagnosis of JDM or JPM, although five patients with JDM (8% of the cohort) had normal muscle biopsy results. The frequencies of the histopathological features that were evaluated on all muscle biopsies are presented in Table I. Perifascicular myopathy was the most common of the four main histopathologic features examined in this study, being present on 35 of the 59 muscle biopsies (59%). Thirty biopsies (51%) demonstrated direct immunofluorescence staining (DIF-positivity), either of intramuscular arteries or capillaries. No DIF staining of intramuscular venules was noted. Of the 30 DIF-positive specimens, 18 had arterial staining (31% of all biopsies), and 12 had capillary staining (20% of all biopsies). Infarct was present on four muscle biopsies (7%), and loss of the intramuscular capillary network around the periphery of muscle fascicles was seen in 24% of biopsies.

Twenty-two children of the cohort (37%) had a limited disease course, similar to the one-third of children with JDM, reported by Bitnum *et al.* in the pre-steroid therapy era, who recovered completely without significant debilitation or death (21). CNU disease was the most common disease course subtype of the cohort, accounting for 41% of the patients. The three children with polymyositis were indistinguishable from patients with chronic non-ulcerative JDM, except that they never developed skin lesions consistent with JDM, and thus were included in the CNU group; none of the children with JPM developed ulcerative disease manifestations. Thirteen children (22%) had CU disease, with gastrointestinal and/or cutaneous ulceration(s) developing directly due to the primary disease process.

Contractures and calcinosis were the most frequently encountered disease complications among those that were evaluated in this study, affecting 34% and 31% of the cohort, respectively (see Table I). Clinically evident muscle atrophy occurred in 10 children (17%). Contractures, calcinosis and muscle atrophy were all significantly associated a chronic disease course (CNU + CU disease groups combined), with p = 0.01 for contractures, p = 0.008 for calcinosis and p = 0.009 for muscle atrophy. More specifically, contractures, calcinosis and muscle atrophy were significantly associated with CU disease (p = 0.04, p = 0.02 and p = 0.005, respectively), but not with CNU disease alone (p = 0.78, p = 0.92 and p = 1.0, respectively).

Nine patients (15%) developed generalized or localized areas of lipodystrophy. Eight children (14%) had chronic arthritis as a feature of their disease, including all three children with polymyositis. Neither of these two complications was significantly associated with disease chronicity (p = 0.13 for lipodystrophy and p=0.24 for arthritis) or disease course subtype (see Table I). Cutaneous ulceration secondary to the primary vasculopathy of JDM occurred in 12 children (20% of the cohort), all of whom had CU disease. Only one child with CU disease did not have ulcerative skin lesions, although she developed gastrointestinal ulceration, with visceral perforation during the course of her illness. Gastrointestinal ulceration occurred in 5 children (8%), only occurring in children with CU disease. Three patients in the cohort (5%) died; all had CU disease. Two children died as direct consequences of gastrointestinal ulceration and visceral perforation. Chronic ulcerative disease was significantly associated with the development of cutaneous ulceration (as inherent in the definition of this disease course subtype, with p = 0.0000) as well as with gastrointestinal ulceration (p = 0.0002) and death (p = 0.009).

On muscle biopsy, neither perifascicular myopathy nor loss of the intramuscular capillary network was significantly associated with disease course

Table I. Histopathological features of muscle biopsies, disease course subtypes and complications (statistically significant associations by Chi-square/Fisher's exact testing are in bold).

Parameters	Overall	Disease Course Subtype			P-Values*
		Limited N = 22 (37%)	CNU+ N = 24 (41%)	CU^ N = 13 (22%)	
Muscle biopsy findings					
Abnormal	54/59 (92%)	19/22 (86%)	22/24 (92%)	13/13 (100%)	
Perifascicular myopathy	35/59 (59%)	12/22 (54%)	15/24 (62%)	8/13 (62%)	P = 0.89
Direct immunofluorescence (DIF) positivity (either arteries or capillaries)	30/59 (51%)	11/22 (50%)	10/24 (42%)	9/13 (69%)	P = 0.30
DIF arterial staining (vs. capillary or no staining)	18/59 (31%)	7/22 (32%)	2/24 (8%)	9/13 (69%)	**P = 0.0005**
DIF arterial staining, comparing arterial vs. capillary staining (all DIF +)	18/30 (60%)	7/11 (64%)	2/10 (20%)	9/9 (100%)	**P = 0.001**
DIF capillary staining (vs. arterial or no staining)	12/59 (20%)	4/22 (18%)	8/24 (33%)	0	**P = 0.05**
Infarct	4/59 (7%)	1/22 (4%)	0	3/13 (23%)	**P = 0.02**
Loss of capillary network	14/59 (24%)	4/22 (18%)	6/24 (25%)	4/13 (31%)	P = 0.63
Complications					
Contractures	20/59 (34%)	3/22 (14%)	9/24 (38%)	8/13 (62%)	**P = 0.02**
Calcinosis	18/59 (31%)	2/22 (9%)	8/24 (33%)	8/13 (62%)	**P = 0.004**
Muscle atrophy	10/59 (17%)	0	4/24 (17%)	6/13 (46%)	**P = 0.002**
Lipodystrophy	9/59 (15%)	1/22 (4%)	4/24 (17%)	4/13 (31%)	P = 0.1
Chronic arthritis	8/59 (14%)	1/22 (4%)	4/24 (17%)	3/13 (23%)	P = 0.27
Cutaneous ulceration	12/59 (20%)	0	0	12/13(92%)	**P = 0.0000**
Gastrointestinal ulceration	5/59 (8%)	0	0	5/13 (38%)	**P = 0.0002**
Death	3/59 (5%)	0	0	3/13 (23%)	**P = 0.009**

*Chi-square/Fisher's exact test results, using presence/absence of parameter and disease course subtype – from 2x3- contingency tables.
+ CNU = Chronic non-ulcerative disease.
^ CU = Chronic ulcerative disease.
^ CU = Chronic ulcerati sve disease.

(p = 0.89 and p = 0.63, respectively) or more specifically, with disease chronicity (p = 0.76 and p = 0.54, respectively). Additionally, neither of these histopathologic features was significantly associated with the development of any of the disease complications evaluated in this project (see Table II).

Infarct on muscle biopsy was significantly associated with the development of chronic ulcerative disease (p = 0.02), being present on biopsy in 23% of children with CU disease compared with none of the patients with CNU disease and 4% of those with limited disease. The positive predictive value of infarct on biopsy for the outcome of CU disease was 75%, as three of the four children with infarct on muscle biopsy developed CU disease. The negative predictive value (NPV) of infarct for CU disease was 82%, 45 of those patients who did not have infarct on muscle biopsy (N = 55) not developing CU disease. Infarct was not significantly associated with the development of chronic disease overall (p = 1.0).

Infarct was significantly associated with the complications of gastrointestinal ulceration (p = 0.03) and death (p = 0.01). Infarct was not significantly associated with the development of cutaneous ulceration (p=0.18), or the complications of muscle atrophy, lipodystrophy, calcinosis or contractures (see Table II).

DIF-positivity (either arterial or capillary staining) was not significantly associated with disease course (p = 0.30), but its absence on muscle biopsy was significantly associated with patients not developing gastrointestinal ulceration (p = 0.05), the negative predictive value of DIF-positivity being 100% for this complication. The positive predictive value of DIF-positivity for gastrointestinal ulceration was 17%, with only five of the 30 patients who had DIF-positivity on muscle biopsy developing gastrointestinal ulceration. DIF-positivity was not significantly associated with any of the other complications listed in Table II.

DIF-positivity was then further categorized into two subgroups based on the locale of DIF staining, ie. DIF-arterial staining and DIF-capillary staining. Lack of DIF-capillary staining was significantly associated with the development of CU disease (p = 0.05); none of the patients with CU disease had DIF-capillary staining on muscle biopsy, compared with 18% of patients with limited disease and 33% of those with CNU disease. DIF capillary staining was not significantly associated with disease chronicity or lack thereof (p = 1.0). No further analyses were undertaken using DIF-capillary staining as a predictor for the complications evaluated in this study.

DIF-arterial staining as an independent histopathologic feature on muscle biopsy was evaluated relative to disease course and with regard to the complications listed in Table II. DIF-arterial staining on muscle biopsy was significantly associated with the development of CU disease, being present on 69% of biopsies obtained from children with CU disease, compared with 32%

Table II. Features of muscle pathology vs. outcomes/complications.
*(statistically significant associations by Chi-square/Fisher's exact testing are in bold).

Outcomes/Complications	Histopathological features				
	Direct Immunofluorescence (DIF) Positivity (either arterial or capillary staining)	DIF Arterial Staining (compared to either capillary or no vessel staining)	Infarct	Loss of Capillary Bed	Perifascicular Myopathy
Gastrointestinal ulceration	**P = 0.05***	**P = 0.002***	**P = 0.03***	P = 0.08	P = 0.64
Cutaneous ulceration	P = 0.33	**P = 0.004***	P = 0.18	P = 0.45	P = 0.74
Death	P = 0.24	**P = 0.02***	**P = 0.01***	P = 0.56	P = 1.00
Muscle atrophy	P = 0.18	P = 1.00	P = 0.13	P = 1.00	P = 0.51
Lipodystrophy	P = 0.73	P = 1.00	P = 0.49	P = 1.00	P = 0.72
Contractures	P = 0.52	P = 0.51	P = 0.60	P = 0.87	P = 0.08
Calcinosis	P = 0.51	P = 0.75	P = 1.00	P = 1.00	P = 0.18

from patients with limited disease (p = 0.04), and 8% from those with CNU disease (p = 0.0002). This significant association held true both when comparing DIF-arterial-positive biopsies to the DIF-arterial-negative group (DIF-capillary-positive biopsies + those with no DIF staining) (p = 0.0005), and when comparing DIF-arterial-positive biopsies to the DIF-capillary-positive specimens (all specimens being positive for DIF staining), with p = 0.001 (see Table I).

DIF-arterial staining, when compared with biopsies that were negative for DIF-arterial staining, was significantly associated with the outcomes of gastrointestinal ulceration, cutaneous ulceration and death (p = 0.002, p = 0.004 and p = 0.02, respectively). All five children who developed gastrointestinal ulceration had DIF-arterial staining on muscle biopsy (100%), compared with 24% (N = 13) of the 54 patients who did not have gastrointestinal ulceration. Sixty-seven percent (N = 8) of the 12 children who developed cutaneous ulcerations had DIF-arterial staining on muscle biopsy, compared with 21% (N = 10) of the 47 patients who did not have cutaneous ulcerations. All three children who died had DIF-arterial staining on muscle biopsy (100%), compared with 27% (N = 15) of the 56 patients who did not die. DIF arterial staining was not significantly associated with the complications of muscle atrophy, lipodystrophy, contractures and calcinosis.

The histopathological features of DIF-positivity, DIF-arterial staining and infarct were then used as independent predictor variables to build univariate logistic regression models for which CU disease was the outcome event of interest. Another univariate logistic regression model was built using the interaction term of (DIF-arterial staining x infarct) as another predictor variable, since both of these histopathological features were found to be significantly associated with CU disease by Fisher's exact tests. The results of these univariate logistic regression models are presented in Table III, including the estimated odds ratio for each of the histopathological features and the interaction term, with 95% confidence intervals and associated p-values for their slope coefficient estimates. Only the univariate models using DIF-arterial staining and infarct as predictor variables had significant p-values (p = 0.002 and p = 0.03, respectively). The univariate models using DIF-positivity and the interaction term, (DIF-arterial staining x infarct), were not found to have significant p-values, and thus these variables were eliminated from further modeling.

DIF-arterial staining and infarct were then incorporated into a bivariate logistic regression model, for which the -2 Log Likelihood statistic had a p-value of 0.001 and the Score statistic had a p-value of 0.005. The AIC for the bivariate model that included DIF-arterial staining and infarct was 54.385, smaller than the AIC's for the reduced univariate models in which the two variables were evaluated separately; the AIC for the DIF-arterial staining univariate model was 55.168 and the AIC for the infarct univariate model was 60.654. The smaller AIC for the bivariate model conveyed a better fit to the data than either of the univariate models. Area under the receiver operating characteristic curve (AUC) was slightly greater for the bivariate model including the DIF-arterial staining and infarct terms (0.758) than the AUC's of the univariate models (0.748 for the DIF-arterial staining univariate model and 0.605 for the infarct univariate model), also indicating a better fit of the bivariate model to the data than either univariate model. When the bivariate model was analyzed for good-

Table III. Univariate logistic regression models using selected muscle biopsy features, with chronic ulcerative disease (CU) as the outcome event.

Variable	Estimated odds ratio	95%Confidence interval (Wald)	P-values	AIC for the model
DIF positivity	2.68	(0.72, 9.96)	p = 0.14	63.921
DIF arterial staining	9.25	(2.32, 36.94)	p = 0.002	55.168
Infarct	13.5	(1.27, 143.64)	p = 0.03	60.654
(DIF-arterial staining x infarct) - interaction term	>999.99	(<0.001, >999.99)	p = 0.97	56.553

ness-of-fit using the Hosmer-Lemeshow Goodness of Fit Test (16), the p-value was 0.74.

Despite the seemingly better fit of the bivariate model to the data, however, it was not accepted as the final logistic regression model because in the bivariate model, the infarct term did not maintain the statistical significance it had in the univariate model, the p-value for its slope coefficient estimate in the bivariate model now being 0.12. The DIF-arterial staining term remained highly significant in the bivariate model, with a p-value of 0.005. While an odds ratio was generated for infarct and the outcome of CU disease (OR = 7.86) in the bivariate model, the lower limit of the 95% confidence interval for infarct dropped below 1.00 (0.58), making it insignificant. The bivariate logistic regression model was then set aside, the two univariate models instead being used to assess the odds ratios for DIF-arterial staining and infarct in independently predicting the outcome of CU disease.

Thus, using the odds ratio estimated from the DIF-arterial staining univariate logistic regression model, a child with DIF-arterial staining on muscle biopsy is 9.25 times more likely to develop CU disease than a child without DIF-arterial staining on biopsy, the 95% confidence interval ranging from 2.3 to 36.9. Using the odds ratio estimated from the infarct univariate logistic regression model in which the outcome event is CU disease, a child with infarct on muscle biopsy is 13.5 times more likely to develop CU disease than a child without this feature, the 95% confidence interval ranging from 1.3 to 143.6.

Discussion

In summary, we reviewed the clinical course and outcomes for 59 children with JDM or JPM, using disease course subtypes similar to those first outlined by Crowe *et al.* (1). In the current study, disease course was identified as either limited or chronic, chronic disease persisting for more than two years and including periods of disease inactivity, if these were later followed by flare-ups or required continued use of medications to keep disease activity in check. Chronic disease was further stratified into ulcerative and non-ulcerative disease subtypes. Disease complications evaluated in this study included contractures, calcinosis, muscle atrophy, lipodystrophy, gastrointestinal ulceration, cutaneous ulceration and death. Muscle biopsies from all 59 children in the cohort were reviewed for the presence of DIF staining of the intramuscular microvasculature, the locale of DIF staining (arterial or capillary, if present), infarct, loss of the intramuscular capillary network and perifascicular myopathy. These histopathological findings were then analyzed in relation to the patients' clinical disease course, specifically their disease course subtype and the development of selected disease-related complications.

In contrast to what had been suggested earlier by Crowe *et al*. in their 1982 report (1), loss of the intramuscular capillary network and the presence of perifascicular myopathy on muscle biopsy in this study were not associated with chronicity or severity of childhood dermatomyositis or polymyositis. Neither histopathological feature was associated with the development of CU disease, although both had been proposed by Crowe *et al*. to be two of the "hallmarks of the severe form of disease in which skin and gut ulceration resulted from vascular occlusion" (1). Additionally, neither perifascicular myopathy nor loss of the intramuscular capillary network was significantly associated with the development of calcinosis, muscle atrophy, contractures, lipodystrophy, gastrointestinal ulceration, cutaneous ulceration or death.

Also in contrast to the theory postulated by Crowe *et al.* in their 1982 report that DIF staining of the intramuscular vasculature had no prognostic significance, the results of this study suggest that the presence of DIF-arterial staining on muscle biopsy increases the odds of a child with JDM or JPM developing CU disease to more than nine times that of a child without this finding on muscle biopsy (OR = 9.25, with 95% confidence intervals 2.32 to 36.94). Additionally, we found that 69% of those children with CU disease had DIF-arterial staining on muscle biopsy compared with only 20% of those children who did not develop CU disease (CNU + limited disease groups combined) (p = 0.001). While the sensitivity of DIF-arterial staining for CU disease was 69% and the specificity 80%, the positive predictive value (PPV) of DIF–arterial staining for CU disease was 50%, and the negative predictive value (NPV) was 90%. The PPV of DIF-arterial staining being only 50% may have been influenced by the small number of children in the cohort who developed CU disease (only 22% of the cohort in total). With the inclusion of a greater number of children with CU disease over time, the PPV of DIF-arterial staining for CU disease likely will increase. For example, two children with ulcerative JDM who were excluded from the study because they had been newly diagnosed, not having had disease for at least two years, are both known to demonstrate DIF-arterial staining on muscle biopsy. Their inclusion in this study would then increase the PPV of DIF-arterial staining for CU disease to 55% (or 11 patients having CU disease out of 20 muscle biopsies positive for DIF-arterial staining).

DIF-arterial staining as a predictor for various disease-related complications was also evaluated, although the negative predictive values of DIF-arterial staining for the outcomes of gastrointestinal ulceration, cutaneous ulceration and death were greater than the positive predictive values of this histopathological feature for these outcomes. For example, the NPV of DIF-arterial staining for gastrointestinal ulceration was 100%, since none of the patients without DIF-arterial staining on muscle biopsy developed this complication; the PPV of DIF-arterial staining for gastrointestinal ulceration, however, was only 28%, as only five of the 18 patients with DIF-arterial staining developed gastrointestinal ulceration. Similarly, the NPV of DIF-arterial staining for cutaneous ulceration was 90%, as 37 of the 41 patients without DIF-arterial staining on biopsy did not develop cutaneous ulcerations. The

PPV of DIF-arterial staining for cutaneous ulceration, however, was 44%, with eight of the 18 patients who had DIF-arterial staining on biopsy developing cutaneous ulcers. None of the children without DIF-arterial staining on biopsy died, the NPV of DIF-arterial staining for death being 100%. The PPV of DIF-arterial staining for death, however, was 17%, as only three of the 18 patients with DIF-arterial staining on biopsy died.

The small number of patients with the outcomes of death and gastrointestinal ulceration may account, to some degree, for the low PPV's noted. It is important to note, however, that despite the lack of high PPV's of DIF-arterial staining for the outcomes of gastrointestinal ulceration and death, that all of the children who died (N = 3) and all who developed gastrointestinal ulceration (N = 5) had CU disease and DIF-arterial staining on biopsy. For the complication of cutaneous ulceration, increasing the number of children with CU disease (many of whom develop cutaneous ulcerations) over time likely will improve the PPV of DIF-arterial staining for this complication. Again referring to the two children with ulcerative JDM who were not included in this cohort because they had been newly diagnosed and had not had disease for two years' duration, their inclusion in the analysis would then increase the PPV of DIF-arterial staining for cutaneous ulceration to 50%, since both of them are known to have DIF-arterial staining on biopsy and have already developed cutaneous ulcers.

Another potential explanation for the relatively unremarkable PPV's of DIF-arterial staining for CU disease (by Fisher's exact test) and for the outcomes of gastrointestinal ulceration, cutaneous ulceration and death may be that the effects of DIF-arterial staining are not only related to its presence, but also to the strength, or intensity of its staining. Patients who have high-intensity DIF-arterial staining on muscle biopsy may be even more likely to develop CU disease and its complications, perhaps due a greater degree of arterial involvement and/or occlusion with resulting ischemia, than children with low-intensity or absent DIF-arterial staining. Qualification, or quantification, of the intensity of DIF-arterial staining on muscle biopsy may improve the PPV of this histopathological feature, providing greater prognostic information regarding patients' expected disease course and the likelihood of developing certain disease-related complications.

Another important finding from this study is that infarct on muscle biopsy is significantly associated with the development of CU disease. From the univariate logistic regression model in which infarct is the predictor variable for the outcome of CU disease, we learn that the presence of infarct on biopsy increases the odds of a child with JDM or JPM having CU disease to more than 13 times that of a child who does not have this histopathologic feature on biopsy (OR=13.5, with the 95% confidence interval extending from 1.27 to 143.65). Additionally, by Fisher's exact test, the association of infarct with the development of CU disease was also demonstrated; infarct had a PPV of 75% for CU disease. Only four children had infarct on muscle biopsy; all but one had CU disease. As mentioned above with regard to the PPV of DIF-arterial staining for CU disease, the PPV of infarct for CU disease may increase as more children with CU disease are evaluated and included in the cohort. Infarct also had a good NPV for CU disease (82%), such that children without infarct on muscle biopsy were significantly less likely to develop CU disease compared to those patients with infarct on biopsy.

Infarct as a predictor for various complications was also evaluated, although the NPV's of infarct for the complications of gastrointestinal ulceration and death were greater than the PPV's of infarct for these two outcomes. The PPV of infarct for each of these complications was 50%, two of the four children with infarct on biopsy developing gastrointestinal ulceration and later dying. The NPV of absence of infarct on biopsy was 94% for gastrointestinal ulceration and 98% for death. Thus, children with JDM or JPM who did not have infarct on muscle biopsy were exceedingly unlikely to develop gastrointestinal ulceration or to die as a consequence of their primary inflammatory myopathy. Given that only four muscle biopsies had infarct on them, however, the PPV's of infarct for these two complications may have been influenced by there being too few cases of infarct overall to fully analyze the strength of these associations and whether the PPV's are greater than 50%.

Other significant findings in this study are that CU disease is significantly associated with the development of contractures, calcinosis, and muscle atrophy as well as with the development of cutaneous ulceration, gastrointestinal ulceration and death. Contractures affected 62% of the CU group compared with 26% of the non-ulcerative disease group. Calcinosis developed in 62% of the CU group compared with 22% of the non-ulcerative disease group. Muscle atrophy was present in 46% of the CU group compared with only 9% of the non-ulcerative disease group. Ninety-two percent of the children in the CU group developed cutaneous ulcerations compared with none of the patients in the other two disease course groups. Thirty-eight percent of the CU group had gastrointestinal ulceration compared with none of the patients in the non-ulcerative disease group. Twenty-three percent of the children in the CU group died compared with none of the children in the other two disease course groups.

In addition to analyzing histopathological features on muscle biopsy that might predict the clinical course of children with JDM or JPM and/or the occurrence of certain disease-related complications, perhaps one of the most important aspects of this study's results lies its successful quantitation of the risks that DIF-arterial staining and infarct on biopsy independently confer on children with JDM or JPM for the development of CU disease. To our knowledge, this quantitation of risk has not been previously reported in the literature. Being able to quantitate or estimate the odds of a child with JDM or JPM developing CU disease based on

his or her having DIF-arterial staining or infarct on muscle biopsy is important in the medical decision-making process for these children. This predictive information could be used to guide early treatment decisions in those patients suspected of being at risk to develop CU disease, who, while constituting the smallest disease course subtype group in our series, are at substantial risk of death and ulcerative complications. Children with JDM or JPM who have greater potential for a more severe disease course would be identified earlier as being at substantially greater risk and would likely be started on more aggressive therapy earlier in their clinical course. Children with JDM or JPM without infarct or DIF-arterial staining on biopsy, as per this study's results are substantially less likely to develop CU disease, gastrointestinal ulceration and cutaneous ulceration as well as are less likely to die as a consequence of their inflammatory myopathy and so may not need to be treated as aggressively initially, i.e., with the simultaneous use of corticosteroids and second-line agents (methotrexate, cyclosporine, IVIG and/or cyclophosphamide). The prognostic information obtained from the results of muscle biopsy would better guide the level and spectrum of therapies employed initially to suit the patients' predicted disease severity. In this way, clinical information that can be predicted from the histopathological features present in diseased muscle underlines the continued importance of using muscle biopsy as a tool that not only diagnoses disease but can also guide management of JDM and JPM.

References

1. CROWE WE, BOVE KE, LEVINSON JE, HILTON PK: Clinical and Pathogenetic Implications of Histopathology in Childhood Polydermatomyositis. *Arthritis Rheum* 1982; 25: 126-39.
2. WHITAKER JN, ENGEL WK: Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. *N Engl J Med* 1972; 286: 333-8.
3. KISSEL JT, MENDELL JR, RAMMOHAN KW: Microvascular deposition of complement membrane attack complex in dermatomyositis. *N Engl J Med* 1986; 314: 329-34.
4. KISSEL JT, HALTERMAN RK, RAMMOHAN KW, MENDELL JR: The relationship of complement-mediated microvasculopathy to the histologic features and clinical duration of disease in dermatomyositis. *Arch Neurol* 1991; 48: 26-30.
5. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-7.
6. KAUFMAN LD, GRUBER BL, GERSTMAN DP, KAELL AT: Preliminary observations on the role of magnetic resonance imaging for polymyositis and dermatomyositis. *Ann Rheum Dis* 1987; 46: 569-72.
7. FRASER DD, FRANK JA, DALAKAS MC, MILLER FW, HICKS JE, PLOTZ PH: Magnetic resonance imaging in the idiopathic inflammatory myopathies. *J Rheumatol* 1991; 18: 1693-700.
8. FUJINO H, KOBAYASHI T, GOTO I, ONITSUKA H: Magnetic resonance imaging of the muscles in patients with polymyositis and dermatomyositis. *Muscle Nerve* 1991; 14: 716-20.
9. TARGOFF IN, MILLER FW, MEDSGER TA, ODDIS CV: Classification criteria for the idiopathic inflammatory myopathies. *Curr Op in Rheum* 1997; 9: 527-35.
10. PACHMAN LM: Juvenile dermatomyositis (JDMS): new clues to diagnosis and pathogenesis. *Clin Exp Rheumatol* 1994; 12 (Suppl.10): S69-S73.
11. HERNANDEZ RJ, KEIM DR, SULLIVAN DB, CHENEVERT TL, MARTEL W: Magnetic resonance imaging appearance of the muscles in childhood dermatomyositis. *J Pediatr* 1990; 117: 546-50.
12. HERNANDEZ RJ, KEIM DR, CHENEVERT TL, SULLIVAN DB, AISEN AM: Fat-suppressed MR imaging of myositis. *Radiology* 1992; 182: 217-9.
13. MAY DA, DISLER DG, JONES EA, BALKISSOON AA, MANASTER BJ: Abnormal Signal Intensity in Skeletal Muscle at MR Imaging: Patterns, Pearls, and Pitfalls. *RadioGraphics* 2000; 20: S295-S315.
14. LUNDBERG I, CHUNG YL: Treatment and investigation of idiopathic inflammatory myopathies. *Rheumatology* 2000; 39: 7-17
15. SPENCER CH, HANSON V, SINGSEN BH, BERNSTEIN BH, KORNREICH HK, KING KK: Course of treated juvenile dermatomyositis. *J Pediatr* 1984; 105: 399-408.
16. *Logistic Regression Examples Using the SAS® System, Version 6, First Edition*, Cary, NC: SAS Institute Inc., 1995; 21.
17. LEMESHOW S, HOSMER DW, JR: A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 1982; 115: 92-106.
18. PACHMAN LM: Juvenile Dermatomyositis: A Clinical Overview. *PIR* 1990; 12: 117-24.
19. PACHMAN LM: Juvenile Dermatomyositis: Pathophysiology and Disease Expression. *Pediatr Clin North Am* 1995; 42: 1071-98.
20. MILLER LC, MICHAEL AF, KIM Y: Childhood dermatomyositis. *Clin Pediatr* 1987; 26: 561-6.
21. BITNUM S, DAESCHNER CW, TRAVIS LB, DODGE WF, HOPPS HC: Dermatomyositis. *J Pediatr* 1964; 64: 101-30.