Immunohistological Analysis of CD59 and Membrane Attack Complex of Complement in Muscle in Juvenile Dermatomyositis

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ABSTRACT. ***Objective.*** To assess the presence of CD59 and the deposition of membrane attack complex (MAC) of complement system in skeletal muscle from patients with juvenile dermatomyositis (JDM), in comparison to patients with muscular dystrophies (MD) and children with normal muscle biopsies.

Methods. Muscle specimens obtained for diagnostic purposes from 10 patients with JDM, 6 with MD, and 7 children whose biopsies showed normal histology were analyzed. Immunohistological staining was performed using Mab against CD59 (YTH 53.1) and MAC (WU 7.2).

Results. Immunohistochemical staining for CD59 was weak and irregularly distributed on muscle fibers of all patients with JDM. Two of the 9 biopsies that allowed analysis of vessels showed negative CD59 staining in all vessels; in the remaining 7 patients, there was weak staining in a proportion of the vessels. In contrast, uniform and strong or moderate immunoreactivity was detected on the sarcolemma and in intramuscular endothelium in all normal and MD samples. Immunostaining for MAC was strong in JDM muscle vessels, and weak in normal or MD muscle. An inverse relation was found between MAC deposition and presence of CD59 in vessels in 6/9 JDM biopsies and in all normal and MD samples.

Conclusion. Decreased CD59 expression in JDM muscle fibers and vessels may be associated with muscle lesions mediated by deposition of MAC of complement in JDM. (J Rheumatol 2002; 29:1301–7)

Key Indexing Terms:

JUVENILE DERMATOMYOSITIS   COMPLEMENT   CD59

MEMBRANE ATTACK COMPLEX   MUSCULAR DYSTROPHY

Juvenile dermatomyositis (JDM) is a multisystem disease characterized by acute and chronic nonsuppurative inflammation of striated muscle and skin[1]. Observations on dermatomyositis dating from the mid-1960s suggest that this disease may represent a systemic angiopathy[2]. Studies have established a primary role of complement induced vessel injury in DM, by providing consistent evidence of activation of the complement cascade with capillary damage mediated by the membrane attack complex (MAC)[3-5]. The factors responsible for initiating vascular damage, antibody deposition, and complement activation have not yet been elucidated and the target antigen in endothelial cells remains unknown.

Control of complement deposition in autologous cells is mediated by a group of complement regulatory membrane proteins acting at different levels of the complement cascade. CD59 is an 18 kDa glycosyl phosphatidylinositol anchored protein that regulates the MAC of complement by binding to C8 and C9 incorporated into MAC, blocking further C9 recruitment and polymerization and preventing full assembly of MAC[6-9].

CD59 is expressed in cells and tissues including red[9] and white blood cells[6], platelets[10], endothelium[11,12] and epithelial cells from a number of sources[13], skin[14], placenta[15], spermatozoa[16], lung, pancreas[17], thyroid cells[18], eye tissues[19], skeletal muscle tissue[20], and myocardial cells[21]. Dense granular immunostaining has been shown on the sarcolemma of human skeletal muscle fibers by immunohistochemistry, using a monoclonal antibody (Mab) against CD59[20]. Expression of CD59 on sarcolemma may prevent muscle damage subsequent to MAC deposition. This protective effect may be of importance in inflammatory muscle disorders involving activation of the complement system. On the other hand, a primary defect in CD59 expression may be associated with MAC induced lesions.

We examined muscle biopsy specimens from patients with JDM for the presence of CD59 and MAC, and compared them

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to specimens from patients with muscular dystrophies (MD) and normal muscle biopsies.

MATERIALS AND METHODS

Subjects and muscle biopsies. Biopsy specimens from deltoid muscle obtained for diagnostic purposes were analyzed. Ten samples were from children with JDM, defined according to the Bohan and Peter criteria[22] — 7 girls and 3 boys, ages 3 to 11 years. All JDM biopsy specimens showed at least 2 of the following morphological criteria: perifascicular fiber atrophy, perivascular lymphocytic infiltrate, particularly perimysial, and degenerative fiber changes such as vacuolation and/or necrosis. Six biopsies were taken from patients with MD, and 7 were from children with muscular symptoms who underwent muscle biopsy to rule out a muscle disease, and showed normal histology (2 girls and 5 boys, 3 to 14 years old). The diagnosis of the different types of MD was based on clinical examination, electromyography, and histological and immunohistological analysis.

No patient was receiving corticosteroids or any other medication prior to performing muscle biopsies.

All biopsy specimens were snap frozen in liquid nitrogen and stored for one to 18 months at –70°C until used.

Intensity of muscle symptoms in patients with JDM at the time of biopsy was classified as: (–), no muscle weakness; (+), mild muscle weakness (only upper or lower extremities involved); (++), moderate muscle weakness (upper and lower extremities involved); (+++), severe muscle weakness (upper and lower extremity weakness plus neck, swallowing, respiratory, or speech involvement).

Monoclonal antibodies. The Mab clone YTH 53.1 (anti-CD59), 18 µg/ml, was a gift of Prof. P.J. Lachmann (Molecular Immunopathology Unit, Medical Research Council, Cambridge, England); the Mab clone WU 7.2 (anti-MAC) was kindly provided by Dr. R. Wuzner, Leopold Franzens University, Innsbruck, Austria.

Immunohistochemistry. Frozen sections (5 µm thick) were cut in a cryostat, dried in air at room temperature until stabilization, and used for immunostaining. Sections were fixed on acetone for 10 min, washed with phosphate buffered saline (PBS), and treated with 0.3% hydrogen peroxide for 20 min to inactivate endogenous peroxidase. After a brief rinse with PBS, sections were immersed in skim milk (1:20 dilution) to block nonspecific immunoglobulin binding sites. After blotting of excess fluid, sections were incubated with anti-CD59 antibody (Mab YTH 53.1) or anti-MAC (Mab WU 7.2) diluted 1:100 for 2 h at room temperature. Control sections were incubated with nonimmune mouse IgG-1 and IgG-2a (Becton Dickinson Immunocytometry Systems, Carpinteria, CA, USA) and without the primary antibodies. Sections were rinsed with PBS and subsequently incubated with biotinylated rabbit anti-mouse IgG antibody diluted 1:200 (Dako Corp., San Diego, CA, USA) for 30 min, and with the avidin-biotin-peroxidase complex (ABC standard kit; Dako) for 30 min. After washing with PBS, the peroxidase reaction was carried out by incubation with 0.02% 3,3′-diaminobenzidine tetrahydrochloride solution containing 0.003% hydrogen peroxidase and 10 mM sodium azide. Methyl blue was used as a counterstain.

Positive CD59 control experiments were performed in placenta specimens (4 samples) as described[15].

Microscopic evaluation. Sections were examined with a Zena microscope (model Zenamed 2, Carl Zeiss) using a ×10 eyepiece and ×10, ×40, or ×100 objectives. Staining was assessed semiquantitatively as: (–), no staining; (+), < 25% of the structures stained; (++), 50% of the structures stained; (+++), 75% of structures stained; or (++++), 100% staining. Staining intensity was eye scored as absent, weak, moderate, and strong.

RESULTS

Clinical and laboratory data from patients with JDM and MD and children with normal muscle histology are shown in Tables 1 and 2. All patients with JDM had moderate to severe

Table 1. Clinical and laboratory characteristics of patients with JDM.

Patient	Sex	Race	Age, yrs	ΔT, mo	Muscle Groups	CK, U/l	Aldolase, U/l	LDH, U/l
JDM 1	F	W	9	1	++	655.8	67.4	4645
JDM 2	F	W	9	14	++	67.8	14.5	617.7
JDM 3	F	W	11	7	++	105	11.1	725
JDM 4	F	W	3	2	+++	21.8	18	1200
JDM 5	M	W	7	1	++	2168	—	1667
JDM 6	F	B	4	12	+++	371	—	986
JDM 7	F	B	9	2	+++	—	—	692
JDM 8	F	W	8	1	++	711	—	530
JDM 9	M	W	3	12	++	84	10.2	719.1
JDM 10	M	W	5	2	+++	5079.2	140	1070.9

W: white, B: black; ΔT: time between onset of symptoms and biopsy date. –: no muscle weakness, +: mild muscle weakness (weakness in upper or lower extremities only), ++: moderate muscle weakness (weakness in upper and lower extremities), +++: severe muscle weakness (weakness in upper and lower extremities, plus neck, swallowing, respiratory or speech involvement). Normal values (U/l): CK: up to 204; LDH: up to 423; aldolase: up to 7.6.

Table 2. Clinical and laboratory characteristics of patients with muscular dystrophies and children with normal muscle histology.

Patient	Sex	Race	Age, yrs	ΔT, mo	CK, U/l	Aldolase, U/l	LDH, U/l
N1	M	W	10	84	37	5.6	—
N2	M	W	7	78	194.2	3.9	425
N3	F	W	9	96	52	3.3	396
N4	M	W	3	36	53.8	6.3	—
N5	M	W	8	14	28.3	4.2	—
N6	F	W	14	12	60.2	—	152
N7	M	W	5	36	26	6.7	—
LGMD	F	B	19	84	5495	26	932
BD	M	W	39	120	2077	22	—
CMD	M	W	4	34	857.5	16.2	504
CMD	M	W	8	90	737.1	—	626
DD	M	W	7	24	6884.3	85	—
DD	M	W	6	12	27,673	—	2997

N1–N7: children with normal histology; LGMD: limb-girdle muscular dystrophy; BD: Becker dystrophy; CMD: congenital muscular dystrophy; DD: Duchenne dystrophy; W: white, B: black; ΔT: time between onset of symptoms and biopsy date. Normal values (U/l): CK: up to 204; LDH: up to 423; aldolase: up to 7.6.

muscle symptoms, and most of them showed elevated serum levels of lactic dehydrogenase and aldolase or creatine kinase (Table 1).

Presence of CD59 and MAC was detected by a brownish staining in vessels or muscle fibers. Semiquantitative analysis of the presence of CD59 and MAC in muscle biopsy specimens from JDM and MD patients and normal specimens is shown in Tables 3 and 4.

In all patients with JDM, we observed weak and irregular CD59 staining on the sarcolemma (Figures 1A, 1B). Two of the 9 biopsies that allowed analysis of vessels showed nega-

Patient	CD59 Expression				MAC Expression on Vessels	
	Muscle Fibers		Vessels			
JDM 1	+++	W	+	W	+++	S
JDM 2	+++	W	+	W	+	W
JDM 3	+++	W	*	*	*	*
JDM 4	+++	W	–	–	+++	S
JDM 5	+++	W	–	–	+++	S
JDM 6	+++	W	++	W	+++	W
JDM 7	+++	W	+++	W	–	–
JDM 8	+++	W	+++	W	+	W
JDM 9	+++	W	+++	W	+++	W
JDM 10	+	W	+	W	+++	M

Quantity of stained fibers or vessels: –: no staining; +: < 25% of the structures; ++, +++ and ++++: 50%, 75% and 100% of structures analyzed, respectively. Intensity of staining: –: absent; W: weak; M: moderate; S: strong. * There were no vessels in this sample.

Patient	CD59 Expression				MAC Expression on Vessels	
	Muscle Fibers		Vessels			
N1	++++	S	++++	S	–	–
N2	++++	S	++++	S	+	W
N3	++++	S	++++	S	+	W
N4	++++	S	++++	S	+	W
N5	++++	S	++++	M	+	W
N6	++++	S	++++	M	+	W
N7	++++	S	+++	S	–	–
LGMD	++++	S	++++	S	+	W
BD	++++	S	++++	S	–	–
CMD	++++	S	++++	S	+	W
CMD	++++	S	++++	S	+	W
DD	+++	S	+++	S	+	W
DD	++++	S	++++	S	–	–

N1–N7: children with normal histology; LGMD: limb-girdle muscular dystrophy; BD: Becker dystrophy; CMD: congenital muscular dystrophy; DD: Duchenne dystrophy. Quantity of stained fibers or vessels: –: no staining; +: < 25% of the structures; ++, +++ and ++++: 50%, 75% and 100% of structures analyzed, respectively. Intensity of staining: –: absent; W: weak; M: moderate; S: strong.

tive CD59 staining in all vessels; in the remaining 7 patients, there was weak staining in 25% to 75% of the vessels (Table 3, Figures 1A, 1B, and 2A). In contrast, in sections from MD and normal muscle, we observed strong and uniform CD59 staining on the sarcolemma of 75% to 100% of the fibers, and strong (11/13 cases) or moderate (2/13) staining in the majority of intramural vessels of the samples (Table 4, Figures 1C, 1D, 1E).

MAC deposition was present in the majority of the vessels in 6 of 9 JDM patients (66.7%) from whom vessels were available for analysis: strong or moderate staining was observed in 4 and weak staining in 2 of these patients (Table 3, Figure 2B). Weak MAC deposition in < 25% of vessels was found in 2 patients and no detectable MAC in one patient. No strong staining for MAC was found in vessels from MD or normal specimens. Weak MAC expression in < 25% of vessels was found in 4 of 6 MD biopsies, and no detectable MAC could be observed in 2 patients, a pattern similar to that observed in normal muscle samples (Table 4).

An inverse relation between MAC deposition in vessels and CD59 presence was observed in all MD and normal samples, and in 6/9 JDM biopsies. Strong or moderate MAC deposition in the majority of vessels and weak or absent CD59 was observed in 4 JDM specimens (JDM 1, 4, 5, and 10); conversely, we observed negative or weak MAC deposition in only 25% of the vessels, and presence of CD59, although weak, in 75% of the vessels in 2 patients (JDM 7 and 8, Table 3). In some JDM biopsies, it was possible to identify, in adjacent samples, the same vessel with negative staining for CD59 and very strong staining for MAC, as shown in Figures 2C and 2D. In JDM and MD biopsies, MAC deposition on fibers was only observed on necrotic fibers, and no MAC deposition was found on fibers from normal specimens.

DISCUSSION

The main finding of this study was the decreased CD59 expression in muscle fibers and intramuscular vessels of patients with JDM, compared to patients with MD and children with normal muscle biopsies. To our knowledge, this is the first study of CD59 expression exclusively in JDM. A study on patients with dermatomyositis, including 3 with JDM, described the presence of CD59 on muscle fibers and endothelial cells of all patients with DM[23]. However, the authors did not study muscle from patients without DM for comparison, and the 3 children with JDM enrolled in the study had minimal or no muscle weakness at the time of biopsy. In contrast, all children with JDM in our study presented with moderate or severe muscle involvement (Table 1). We believe that the sharply decreased expression of CD59 observed in all our patients may be related to the severity of their muscle involvement.

It has been shown *in vitro* that complement is spontaneously activated in muscle cells, but these cells are protected from killing by the expression of complement regulators, including CD59, membrane cofactor protein (MCP), and decay accelerating factor (DAF)[24]. In addition, it has been shown that neutralization of CD59 alone rendered cells susceptible to complement killing[24], suggesting that complement activation might play a physiologic role in muscle repair, but that excessive activation of complement could contribute to the onset and propagation of inflammation and cell destruction. In diseases such as acute myocardial infarct[21] and psoriasis[25], where the complement system is implicated in tissue pathogenesis, CD59 expression is absent where MAC deposition is present.
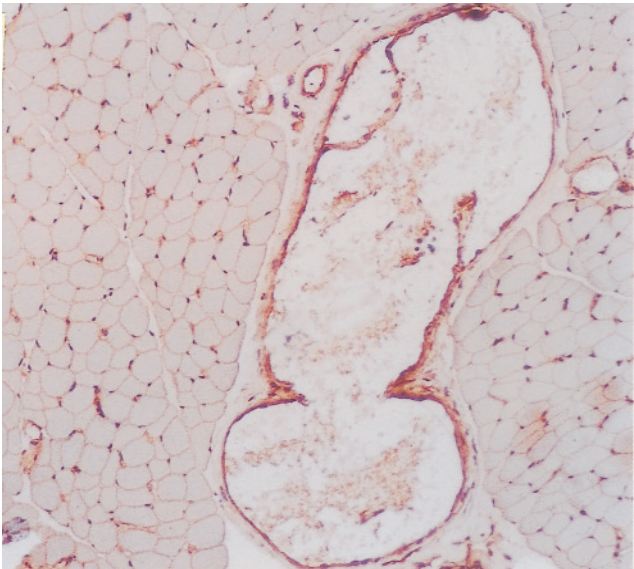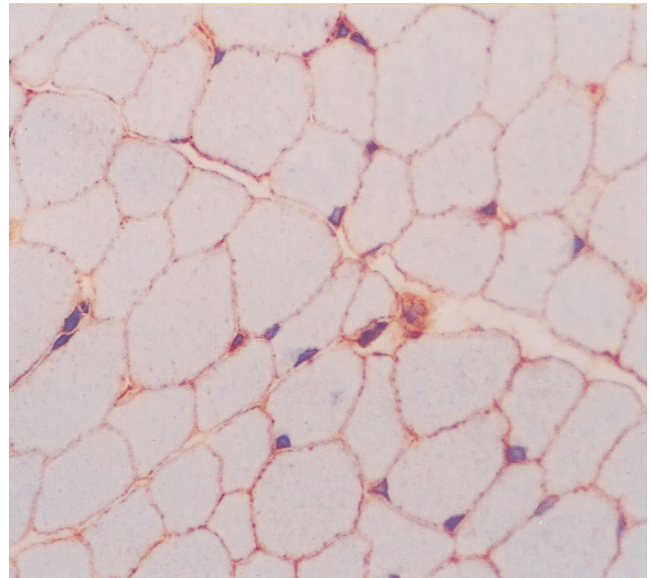
We found that MAC deposition was negative on non-
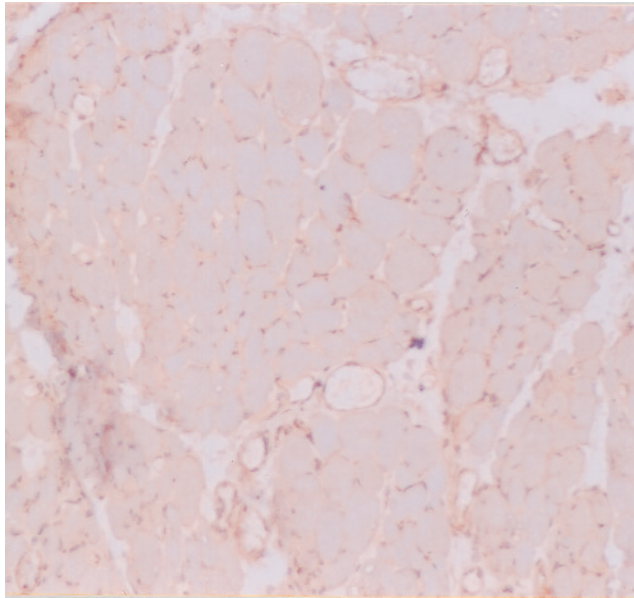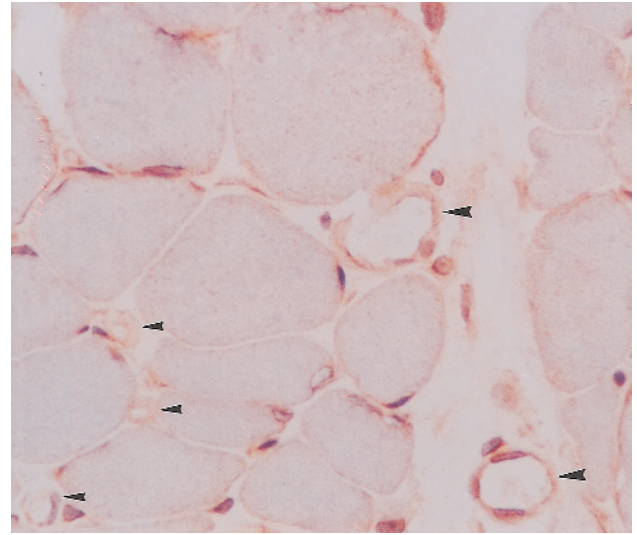
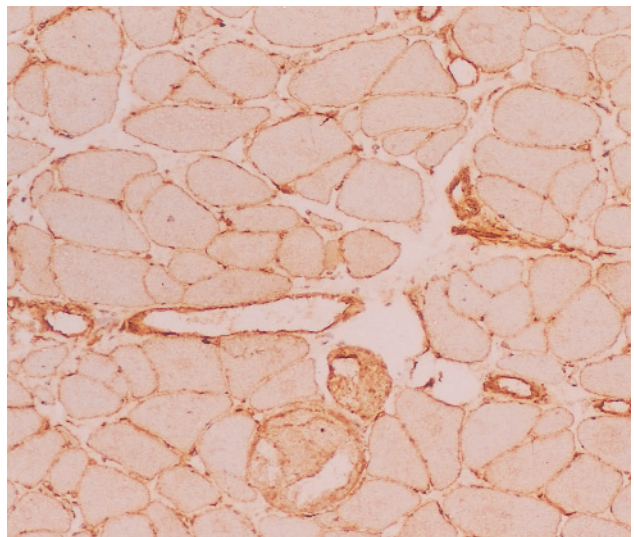*Figure 1*. CD59 in muscle biopsy specimens. A. Weak and negative CD59 staining in vessels and fibers of specimen from a 9-year-old girl with JDM (original magnification ×100). It is difficult to identify the limits of individual fibers due to the very faint and irregular staining of the sarcolemma. B. The same JDM biopsy showing in detail the negative or irregular CD59 staining on fibers; vessels with weak (large arrows) or negative (small arrows) staining for CD59 are visible (×400). C. Strong and uniformly positive CD59 staining on sarcolemma and endothelium of a normal specimen from a 7-year-old boy (×100). D. Detail of strong and uniform CD59 sarcolemma staining in the same sample of normal muscle (×400). E. Strong and uniformly positive CD59 staining on sarcolemma and endothelium of specimen from an 8-year-old boy with congenital muscular dystrophy (×200).
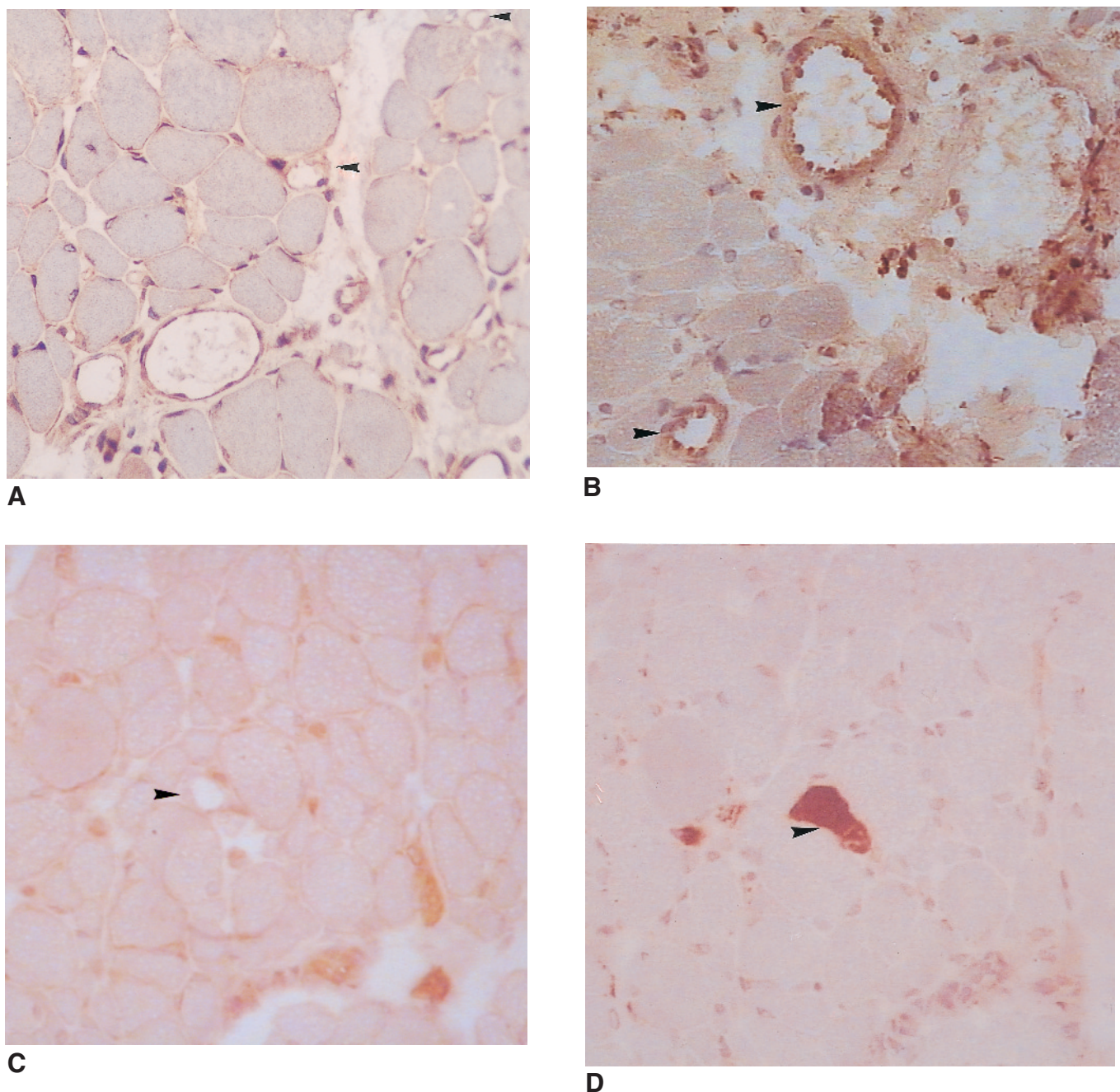
Figure 2. Presence of CD59 and MAC deposition in JDM muscle biopsies. A. Negative or weakly positive CD59 staining in muscle vessels from a 9-year-old girl with JDM (original magnification ×200). B. Positive MAC staining in 2 vessels (arrows) from the same patient (×200). C. Negative CD59 staining of a vessel (arrow) in a specimen from a 5-year-old boy with JDM (×200). D. Very strong positive MAC staining of the same vessel, in an adjacent sample (×200).

necrotic JDM fibers, as described by others[26,27]. In contrast, the majority of vessels stained positive for MAC in 6 out of 9 JDM patients, whereas staining for MAC was very faint, in only a small percentage of vessels, in all normal biopsies. Patients with muscular dystrophies, considered noninflammatory diseases, presented results similar to those with normal biopsies.

Looking at CD59 and MAC expression in vessels in individual patients with JDM, we observed that CD59 expression was negative or very weak in patients with the strongest MAC deposition (JDM patients 1, 4, 5, and 10, Table 3). Conversely, in 2 patients with negative or weak MAC staining, CD59 expression, although weak, was present in 75% of the vessels (JDM patients 7 and 8, Table 3). By contrast, similar analysis

of patients with MD and children with normal biopsies revealed that all of them presented moderate to strong expression of CD59 in vessels, with negative or very weak MAC deposition.

Our findings suggest that the diminished expression of CD59 in endothelial cells could lead to decreased protection against MAC activity. The possibility of a primary defect of CD59 is unlikely because CD59 was detected in other structures (lymphocytes and erythrocytes) in biopsies of JDM with very low or absent CD59 in fibers and vessels (data not shown). One possible explanation is that phospholipases able to cleave the CD59 glycolipid anchor could be activated in the course of the inflammatory process, rendering endothelial cells susceptible to MAC deposition. An indirect evidence of the role of inflammation could be that we found no differences between CD59 and MAC expression on muscle from patients with noninflammatory myopathies (MD), compared to normal muscle. The association between MAC microvascular deposits with early histological changes of muscle fiber ischemia in JDM has been described[27], suggesting a primary role of the complement system in the pathogenesis of this disease. We can also hypothesize that the deposition of MAC in vessels, leading to muscle ischemia, would subsequently render muscle cells incapable of maintaining synthesis of normal amounts of CD59, constituting an additional mechanism for decreased protection against MAC activity.

More studies on larger series of patients with JDM will be necessary to clarify these issues, including analysis of the presence of other membrane complement regulator proteins such as DAF and MCP. It will also be necessary to establish the time course of alterations of CD59 expression and MAC deposition in muscle.

In normal conditions, soluble CD59 can be detected in low concentrations in plasma. One interesting approach would be to measure the soluble form of CD59 in plasma in parallel with studies in muscle biopsies. A recent study reported significantly higher levels of soluble CD59 in plasma of patients who had acute myocardial infarction compared to normal individuals[28], and these levels correlated with those of soluble terminal complement complexes (SC5b-9)[28]. Levels of soluble CD59 have been detected in healthy individuals in our laboratory (unpublished data) and this will help evaluating soluble CD59 in sera of patients with JDM.

We found decreased CD59 expression on the sarcolemma and muscle vessels of patients with juvenile dermatomyositis, compared to specimens from MD and normal muscle, along with increased MAC deposition in vessels of a subset of these JDM patients, supporting the role of complement in the pathogenesis of this disease.

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