Original article

Folia Neuropathologica

Increased expression of cell adhesion molecules in inflammatory myopathies: diagnostic utility and pathogenetic insights

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Folia Neuropathol 2009; 47 (1): 33-42

Abstract

Context: *Idiopathic inflammatory myopathies (IMs) have been postulated to be of autoimmune origin on the basis of expression of markers like MHC-1 and other mediators involved in autoimmunity such as cell adhesion molecules.*

Aims: *The present study aims to analyze the expression of cell adhesion molecules ICAM-1 and VCAM-1 and their respective ligands LFA-1 and VLA-4 in IMs, and to assess whether these markers, besides MHC-class 1 antigen and membrane attack complex (MAC), could be of any help in the diagnosis of these diseases.*

Material and Methods: *Retrospective analysis of 119 muscle biopsies consisting of 55 IMs (21 dermatomyositis, 31 polymyositis and 3 inclusion body myositis) and 64 controls received in our department from January 2004 to December 2005 was carried out immunohistochemically using monoclonal antibodies.*

Statistical analysis: *Chi square test and test for validity were used for analysis of differences in expression.*

Results: *Expression of ICAM and VCAM was significantly upregulated on blood vessels and muscle fibres in IMs as compared to controls, in which expression was weak or absent. LFA and VLA-4 were expressed in inflammatory cells in all inflammatory diseases in almost equal numbers.*

Conclusions: *IMs comprise 6% of all muscle diseases and IBM is not a common IM in India as reported in the Western literature. Our findings support the hypothesis of autoimmune origin of IMs. The difference between expression of these molecules in IMs and controls also has diagnostic implications and these markers should be included along with MHC-1 antigen and membrane attack complex (MAC) in the existing diagnostic armamentarium.*

Key words: *Cell adhesion molecules, idiopathic inflammatory myopathy, inclusion body myositis, polymyositis, dermatomyositis.*

Introduction

The idiopathic inflammatory myopathies (IMs), although a heterogeneous group, share common features of symmetrical chronic progressive muscular weakness, markedly raised CPK levels, inflammation, myofibre degeneration and regeneration, and fibrosis of the connective tissue [5,6,16]. Idiopathic inflammatory myopathies are subdivided broadly into dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Major histocompatibility complex (MHC) class I expression on the sarco-

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lemma, which is absent in normal muscle fibres [1,9], has been found to be upregulated in inflammatory myopathies [15,24,30]. The antigen/s that triggers the expression of MHC-1 remains obscure. By what mechanism inflammatory cells actually enter the muscles has also not been adequately explained. It has been proposed that certain factors involved in MHC-I expression and inflammation, such as cell adhesion molecules and cytokines, play a role in the pathogenesis. An autoimmune origin of these diseases has been proposed as an explanation of their aetiopathogenesis [13,16]. Several observations – i.e. their association with other systemic autoimmune, viral, and connective tissue diseases; the presence of various autoantibodies; association with histocompatibility genes; evidence of T-cell mediated myocytotoxicity or complement mediated microangiopathy; and response to immunotherapy – all provide indirect evidence [16]. Normal muscles do not express the cell adhesion molecules very late antigen-4 (VLA), lymphocyte function antigen-1 (LFA), or vascular cell adhesion molecule-1 (VCAM), while some expression of intercellular adhesion molecule-1 (ICAM) has been observed on endothelial cells in normal muscles [3,19]. Thus recently, expression of cell adhesion molecules is being investigated to elicit the pathogenic mechanisms in IMs [8,14,17,28]; however, its diagnostic utility has not yet been evaluated in the diagnosis of these disorders.

We undertook this study to analyze the expression of various adhesion molecules: ICAM-1, LFA-1, VCAM-1 and VLA-4 in IMs and non-IMs.

The purpose of this study was to evaluate the role of these adhesion molecules in aetiopathogenesis and to assess if these markers can be used in the diagnosis of these conditions.

Materials and Methods

This was a retrospective study carried out on 119 muscle biopsies from 119 patients performed at our institute from January 2004 to December 2005. Only the cases which showed classical clinical and/or pathological features were included. Of the 119 biopsies included, 55 were of IMs and 64 were taken as controls for comparison.

Until 1975, there were no well defined criteria for the diagnosis of IMs. Bohan and Peter [5,6] first outlined the diagnostic criteria for IMs which have served clinicians and researchers very well for many years. However, the drawback was that they were introduced before IBM was recognized as a distinct entity and hence do not hold true any more. Several new diagnostic criteria have been proposed by different authors [4,7,10,11,13,18,20,23,29] in recent times but no single one has gained universal acceptance to date. Our study included cases which strictly fulfil the diagnostic criteria for each type of IM as given by Mastaglia and Phillips [23] and exclusion criteria for PM as given by Dalakas and Hohlfeld [11] and Dalakas [13]. Electron microscopic examination was carried out in all cases of suspected IBM. Staining for amyloid was performed in every case of PM as well as IBM. The IMs group comprised 31 cases of polymyositis (PM), 21 cases of dermatomyositis (DM) and 3 cases of IBM.

A. Dermatomyositis

Only cases which showed characteristic skin rashes clinically and perifascicular atrophy in the biopsy were included. The inclusion criteria were MHC class I antigen expression on the myofibres, deposition of MAC (membrane attack complex) on the endomysial capillaries and presence of predominantly B lymphocytes, plasma cells and CD4 helper cells amidst the inflammatory cell infiltrate.

B. Polymyositis

The most important inclusion criteria for PM were exclusion of DM and IBM in the muscle biopsies. The other criteria were clinically proximal muscle weakness with absence of skin rash, MHC class I antigen expression, presence of inflammatory cell infiltrate predominantly of T cells type and invasion of myofibres with cytotoxic (CD 8) cells.

C. Inclusion body myositis

Clinically characterised by absence of skin rash, predominantly distal muscle weakness and late onset of disease. Those biopsies which showed presence of atrophied fibres, mononuclear cell invasion of non-necrotic muscle fibres primarily by CD8+ cytotoxic T cells, rimmed vacuoles in the cytoplasm with or without MGT stain and numbers of COX negative fibres out of proportion to age and presence of granulofilamentous inclusions in the nucleus or cytoplasm on ultrastructural examination were included.

D. Controls

Among the controls, 64 muscle biopsies of patients diagnosed with other primary neuromuscular disorders (which also showed inflammatory infiltrates on routine H&E) or normal biopsies were taken. Clinical features, biopsy findings and immunohistochemistry using specific antibodies were used for diagnosis. Cases which showed secondary reduction in immunostaining were excluded. Of the 64 controls, 45 were muscle biopsies with inflammation comprising 14 cases of facioscapulohumeral muscular dystrophy (FSHMD),10 dysferlinopathy, 8 Duchenne muscular dystrophy (DMD), 3 Becker muscular dystrophy (BMD), 3 calpainopathy, 4 sarcoglycanopathy, and 3 limb girdle muscular dystrophy (LGMD) of unclassified type. For comparison 19 muscle biopsies without inflammation consisting of 5 spinal muscular atrophy (SMA), 3 mitochondrial myopathy, 1 centronuclear myopathy, 2 multi-mini core disease, and 8 normal muscle biopsy were also included. The eight normal muscle biopsies were from patients suspected of having muscular disease but which showed no abnormality at light microscopic and ultrastructural levels.

E. Processing and staining

Muscle biopsies were taken from the vastus lateralis of the left quadriceps. Each biopsy specimen was received in a fresh state without any fixative or additive. One small piece was fixed in 10% neutral buffered formalin, routinely processed, and paraffin embedded. Five-micron thick sections were cut and stained with haematoxylin and eosin. A second, bigger piece was immediately snap frozen in isopentane pre-cooled in liquid nitrogen at -80°C. Six-micron thick sections were cut on polylysine-coated slides for routine H&E staining, enzyme histochemistry and immunohistochemistry. Various histochemical stains were done, including modified gomori trichrome (MGT), oil red O, ATPase at pH 9.6, 4.6, and 4.3, nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinic dehydrogenase (SDH) alone as well as combined with cytochrome oxidase (Cox with SDH).

Immunohistochemical (IHC) analysis was performed by streptavidin–biotin immunoperoxidase complex method using antibody against adhesion molecules (ICAM-1 and VCAM-1) and their ligands (LFA-1 and VLA-4). Monoclonal mouse antibodies against LFA-1 (CD11a, clone CRIS-3) (Neomarkers, Fremont, USA dil 1:400), ICAM-1 (clone 15.2) (DBS, Pleasanton, CA, USA, dil 1:75), VLA-4 (clone 44H6) (Serotech, Oxford, UK, dil 1:400) and VCAM-1 (clone 1.G11B1) (Novocastra, Newcastle upon Tyne, UK, dil 1:100) were used. Immunolabelling for leucocytic common antigen (LCA), CD3 for T cell, CD20 for B cell, T cytotoxic (CD8) cells, T helper cells (CD4) and membrane attack complex (MAC) and major histocompatibility complex (MHC-I) was also done.

After rinsing in Tris buffered saline, primary antibody was applied and incubated overnight at 4°C in a moist chamber, followed by secondary antibody (biotinylated rabbit anti mouse IgG) (Dako kit, Glostrup, Denmark), followed by tertiary antibody (streptavidin-peroxidase) (Dako kit, Glostrup, Denmark). Visualization was done with freshly prepared 0.05% w/v diaminobenzidine (DAB) in Tris buffer containing 0.01% w/v hydrogen peroxidase. Frozen sections cut from normal tonsil formed the positive control for the adhesion molecules. Negative controls included omission of the primary antibody. Similar conditions were maintained and appropriate positive and negative controls were taken to achieve uniformity in immunostaining.

For ICAM-1 and VCAM-1, intensity of staining was graded subjectively as: - to +++ (-, absent; +, distinct but poorly stained/weak; ++, distinct; +++, marked) with respect to location of positivity in blood vessels (muscle microvasculature), mononuclear infiltrate and muscle fibres.

For LFA-1, VLA-4, the presence or absence of positivity on inflammatory cells and muscle fibres was noted as +: present and -: absent.

F. Analysis

Statistical analysis was conducted to compare staining of ICAM, VCAM, LFA and VLA as diagnostic markers among the subgroups of IMs and between the subgroups and the controls using the chi square test. A p-value of <0.05 was considered as significant. Utility of these markers was assessed using tests for validity. Estimates for sensitivity, specificity, positive predictive value and negative predictive value were calculated with 95% confidence interval.

Results

Prevalence

In two years (2004-2005), we received 985 muscle biopsies in our department for various reasons,

of which 62 (6%) were diagnosed as inflammatory myopathies. Seven cases of polymyositis were excluded from the present study as they were on immunosuppressive treatment. Out of the remaining 55, thirty-one cases were of PM (56%), 21 DM (38%), three IBM (~6%).

Histological features

The 21 cases of DM included in our study showed typical clinical features of skin rash and muscular weakness. All cases showed perifascicular atrophy (100%), which could be identified on H&E stained sections in 17 cases (Fig. 1A), but were appreciated in the other four cases on performing histochemistry for oxidative stains. Most of the cases were late referrals (due to the referral pattern of our institute), explaining the high percentage of perifascicular atrophy. Out of the 21 cases of DM, characteristic perimysial and perivascular inflammation was seen in 16 cases (65%), while in the remaining 5 cases (35%) no inflammatory infiltrate was identified (possibly related to sampling due to patchy distribution of disease). Though these cases did not show any inflammation, they displayed characteristic perifascicular atrophy and MHC-1 immunopositivity, on the basis of which they were diagnosed as DM. We included 31 cases of PM showing classical clinical features, markedly raised CPK levels, and characteristic symmetrical progressive muscular weakness. Inflammation was more pronounced in the endomysium. Typical endomysial inflammatory infiltrate invading non-necrotic muscle fibres (Fig. 2A) was identified in all 31 biopsies. Electron microscopy was done to rule out IBM, which might display similar features on H&E. Three IBM cases showed typical clinical features and were refractory to therapy. All showed characteristic endomysial inflammatory infiltrate, rimmed vacuoles in the cytoplasm (Fig. 3A) and intranuclear inclusions on electron microscopic examination. All three were negative for amyloid. The low number of IBM cases may reflect the referral pattern of our institute. Of the 64 controls, 45 showed a variable amount of inflammation which was mainly endomysial (Fig. 4A).

ICAM and its ligand LFA

Results for ICAM and LFA are summarized in Table I. ICAM was observed on the surface of endothelium, muscle fibres and inflammatory cells, as well

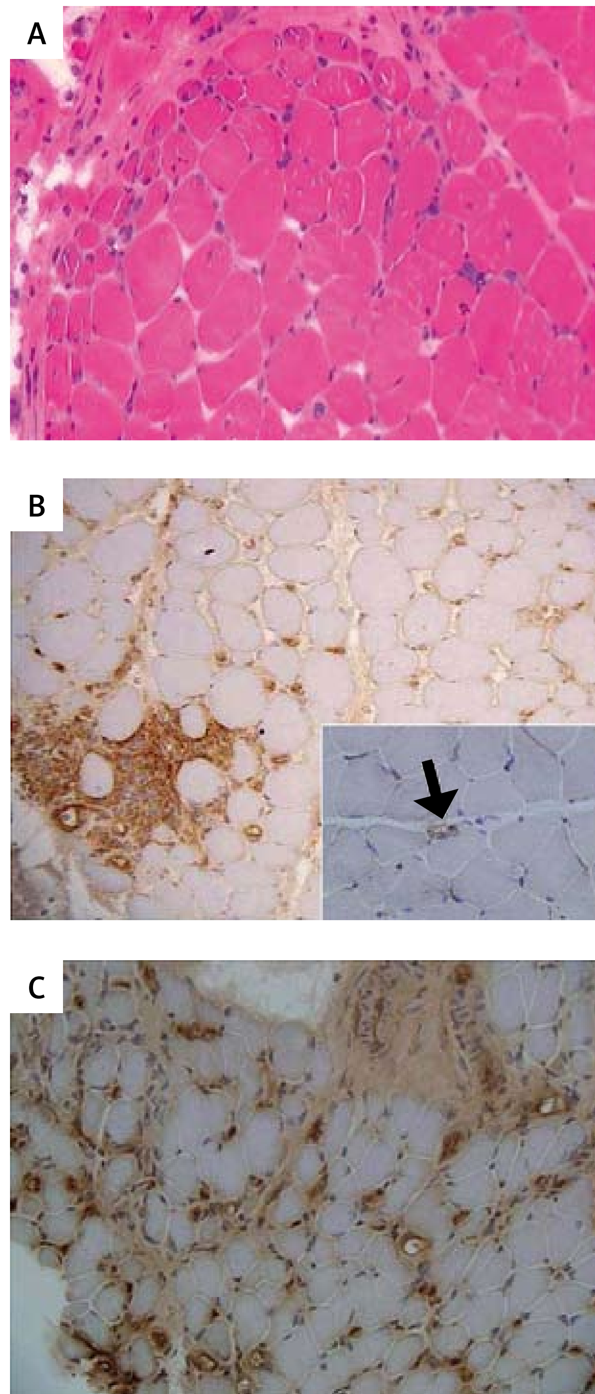

Fig. 1. Photomicrographs of dermatomyositis showing: A. Characteristic perifascicular atrophy (haematoxylin-eosin, ×200). B. Marked ICAM expression on blood vessels and inflammatory cells (ICAM-1, ×200). Inset: normal muscle as control shows weak expression on blood vessel (arrow) (ICAM-1, ×200). C. Distinct VCAM expression on blood vessels (VCAM-1, ×200)

as weak cytoplasmic staining in regenerating muscle fibres. Strong (distinct to marked) ICAM staining on blood vessels was seen in all the cases of DM (Fig. 1B) and IBM and in 97% of cases of PM (Fig. 2B) (Table II). Among the controls, ICAM expression was seen in nearly 86% (including normal muscle biopsies) but it was very weak (Fig. 1B inset, Fig. 4B) and this difference of ICAM expression was found to be significant ($p<0.05$) as compared to IMs as a whole (Table II). Muscle fibres among the cases also showed surface as well as cytoplasmic expression for ICAM, while it was absent in all the controls ($p<0.001$). A large number of inflammatory cells among the cases also demonstrated strong ICAM expression (Fig. 2B inset) and this was significantly higher than that seen on inflammatory cells among the controls ($p<0.001$). Strong LFA expression was observed on the surface of inflammatory cells in all cases showing inflammation (Fig. 3C) and there was no significant difference among IMs and controls (Fig. 4C). A few scattered muscle fibres also showed occasional positivity.

VCAM and its ligand VLA

The results for VCAM and VLA are summarized in Table I. Staining patterns for VCAM were similar to ICAM, being present on the surface of endothelium, muscle fibres and inflammatory cells, as well as weak cytoplasmic staining in regenerating muscle fibres. It was seen that VCAM was absent in all the controls, in the blood vessels, muscle fibres and inflammatory cells (Fig. 4D inset), while it was upregulated in IMs, especially in DM (Table II), where it was present in nearly half the cases. The difference among the IMs verses the non-IMs was significant ($p<0.001$). However, the intensity of expression of VCAM was mostly weak as compared to the strong positivity of ICAM (Table II; Figs. 1C, 2C and 3B). Among the subgroups, though the expression of VCAM on blood vessels in DM was nearly double that of the PM and more than IBM, this difference was not found to be significant ($p=0.064$). A lower number of muscle fibres showed VCAM expression. On inflammatory cells, significant expression was seen in cases of DM as compared to the other subgroups ($p<0.01$). VLA was expressed on inflammatory cells in cases (Fig. 3D) as well as controls (Fig. 4D) and the difference was not significant ($p>0.1$); however, the intensity of expression was weaker compared to the strong expression of LFA.

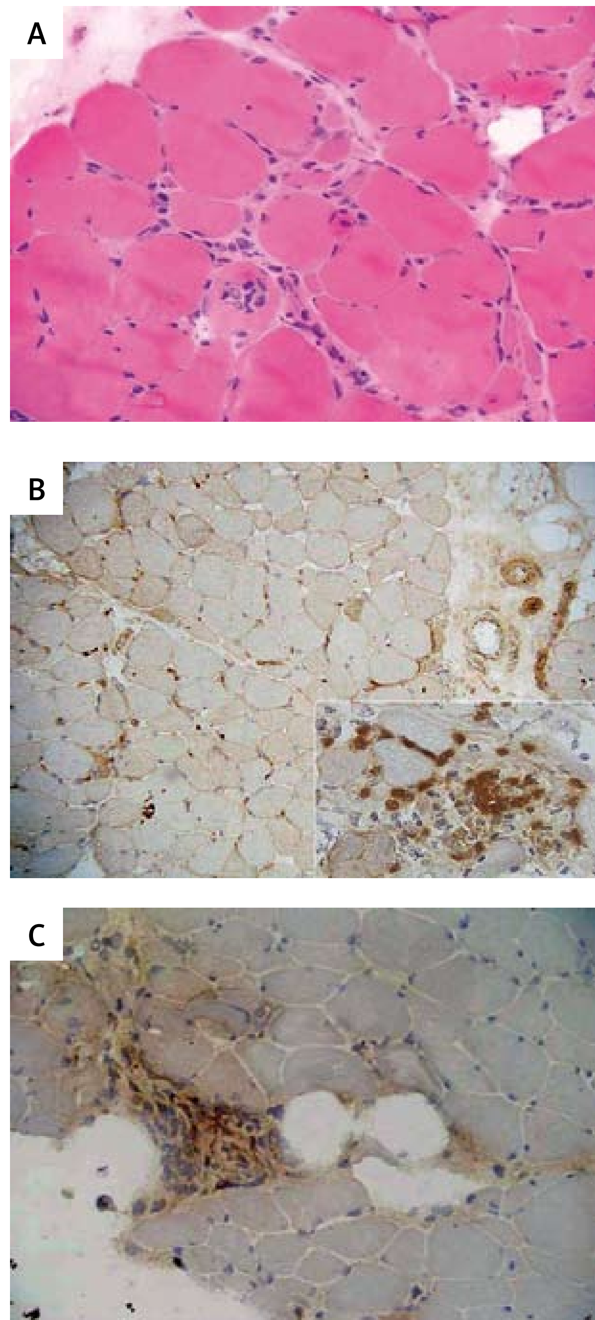

Fig. 2. Photomicrographs of polymyositis showing: A. Mild endomysial inflammatory infiltrate invading non-necrotic muscle fibres, regenerating and degenerating fibres (haematoxylin-eosin ×100). B. Intense ICAM expression on blood vessels and weak cytoplasmic and surface expression on regenerating and non-necrotic muscle fibres (ICAM-1, ×100). Inset: high power view showing strong expression on inflammatory cells (ICAM-1, ×400). C. Distinct VCAM expression on blood vessels (VCAM-1, ×200)

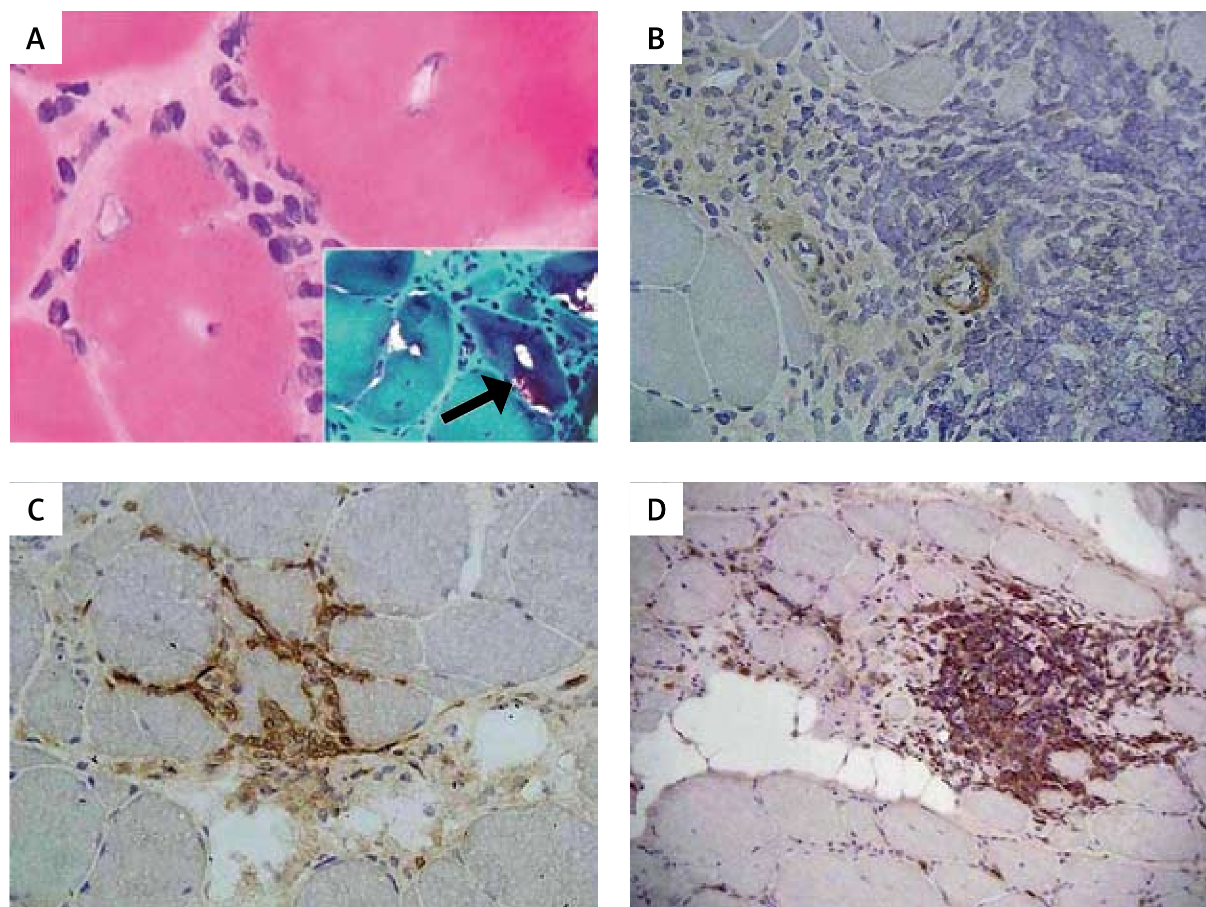

Fig. 3. Photomicrograph of inclusion body myositis showing: A. High power view of cytoplasmic rimmed vacuoles and focal endomysial inflammatory cell infiltrate (haematoxylin-eosin ×400). Inset: cytoplasmic vacuoles filled with reddish material (arrow) on histochemistry (MGT, ×400). B. Weak VCAM expression on a blood vessel surrounded by inflammatory cells which are immuno-negative (VCAM-1, ×200). C. Strong LFA expression on inflammatory cells invading non-necrotic muscle fibres (LFA-1, ×200). D. One of the cases showing strong VLA expression on inflammatory cells (VLA-4, ×100)

Diagnostic utility

Based on the differences in expression of ICAM and VCAM on the blood vessels between the IMs and controls, their diagnostic utility was calculated (Table III). Our study demonstrates that strong vascular expression of ICAM has a high sensitivity (98.2%), but low specificity (14.1%), while vascular expression of VCAM has high specificity (100%), but less sensitivity (32.7%) and both the stains have a good accuracy (52.9% and 68.9% respectively), especially for VCAM, in the diagnosis of these disorders. However, the staining for VCAM is nearly always weak, which may limit its diagnostic utility despite a high specificity.

Discussion

In general, all autoimmune disorders have a similar pathogenetic mechanism, i.e. known or unknown stimuli or antigens, bound to MHC-I molecules on antigen presenting cells are presented to CD8+ T cells, which become activated and release cytokines. The released cytokines upregulate VCAM-1 and ICAM-1, allowing transmigration of T cells through the blood vessel. The cytokines also stimulate upregulation of MHC-I, chemokine receptors and co-stimulatory molecules on the target cells, allowing the invading T cells to attach to the antigen-bound MHC-I complexes on the target cells. This is followed by release of perforin and other molecules from the auto-invasive

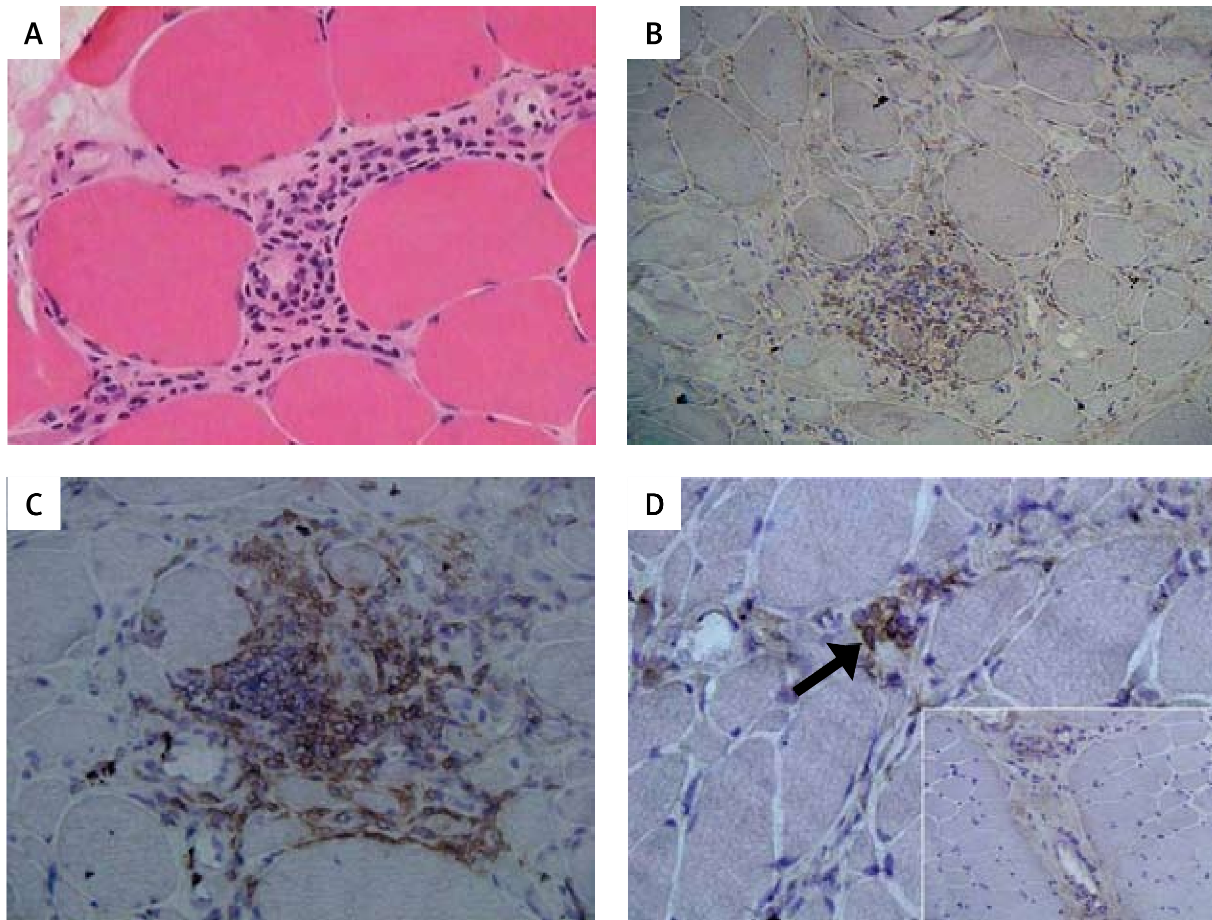

Fig. 4. Photomicrographs of controls showing (A) a case of dysferlinopathy with prominent endomysial perivascular inflammatory infiltrate (haematoxylin-eosin ×400). B. The same case with weak ICAM expression on blood vessels and inflammatory cells (ICAM-1, ×100). C. Another case of dysferlinopathy showing strong LFA expression on inflammatory cells (LFA-1, ×200). D. Distinct VLA expression on inflammatory cells in a case of FSHMD (arrow) (VLA-4, ×400). Inset: Absent VCAM staining on blood vessels and muscle fibres in a normal muscle biopsy control (VCAM-1, ×200)

Table I. Expression of adhesion molecules in IM subgroups and controls

	ICAM			VCAM			LFA*	VLA*
	Blood vessels	Muscle fibres	Inflm. cells*	Blood vessels	Muscle fibres	Inflm. cells*		
DM	21/21 (100%)	7/21 (33%)	13/16 (81.25%)	10/21 (47.6%)	2/21 (9.5%)	10/16 (62.5%)	16/16 (100%)	10/16 (62.5%)
PM	30/31 (97%)	17/31 (55%)	22/31 (71%)	7/31 (22.5%)	5/31 (16%)	5/31 (16%)	31/31 (100%)	22/31 (71%)
IBM	3/3 (100%)	3/3 (100%)	3/3 (100%)	1/3 (33%)	1/3 (33%)	0/3	3/3 (100%)	2/3 (67%)
Controls	55/64 (85.9%)	0/64	25/45 (55%)	0/64	0/64	0/45	45/45 (100%)	23/45 (51%)

*IM – Idiopathic inflammatory myopathies, DM – dermatomyositis, PM – polymyositis, IBM – inclusion body myositis, ICAM – intercellular adhesion molecule, VCAM – vascular cell adhesion molecule, LFA – lymphocyte function antigen, VLA – very late antigen, Inflm – Inflammatory. * – counted only in cases showing inflammation.*

Table II. Comparison of intensity of staining of ICAM-1 and VCAM-1 on blood vessels in IM subgroups and controls

Stain	Diagnosis	Grade				Total positive (%)
		0	1	2	3	
ICAM	DM	0	2	5	14	21/21 (100)
	PM	1	4	13	13	30/31 (97)
	IBM	0	0	2	1	3/3 (100)
	Controls	9	55	0	0	55/64 (85.6)
VCAM	DM	11	5	3	2	10/21 (47.6)
	PM	24	5	1	1	7/31 (22.5)
	IBM	2	1	0	0	1/3 (33)
	Controls	64	0	0	0	0/64 (0)

IM – Idiopathic inflammatory myopathies, DM – dermatomyositis, PM – polymyositis, IBM – inclusion body myositis, ICAM – intercellular adhesion molecule, VCAM – vascular cell adhesion molecule.

Table III. Results of tests for validity of diagnostic use of ICAM and VCAM on blood vessels in IM verses controls

Stain	Sensitivity % (CI)	Specificity % (CI)	Positive Pred Value % (CI)	Negative Pred Value % (CI)	Accuracy %
ICAM-1	98.2 (89.3-99.9)	14.1 (7-25.5)	49.5 (39.9-59.2)	90 (54-99.4)	52.9
VCAM-1	32.7 (21-46.8)	100 (92.9-100)	100 (78-100)	63.3 (53-72.5)	68.9

IM – Idiopathic inflammatory myopathies, DM – dermatomyositis, PM – polymyositis, IBM – inclusion body myositis, ICAM – intercellular adhesion molecule, VCAM – vascular cell adhesion molecule, CI – confidence interval, Pred – predictive.

T cells which damage the target cell [8,13,26]. The IMs have been proposed to be autoimmune diseases and hence recently investigated to identify the role of cell adhesion molecules and cytokines to provide evidence of autoimmunity. Increased expression of MHC-I has been documented in previous studies [3,13,15,30], including a study from our department [21].

The present study shows that the adhesion molecules ICAM and VCAM are significantly upregulated in the IMs as compared to non-IMs. The present study included a large number of cases as well as controls to substantiate these results.

In our study, distinct to marked ICAM expression is seen on blood vessels in almost all IMs, while it is expressed weakly in a significantly lower number of controls, explaining the mechanism of entry of the inflammatory cells into the muscle compartment. These findings are in contrast with the observations of Bartoccioni et al. [3], who observed weak endothelial expression of ICAM-1 in cases as well as controls, but similar to the findings of Tews and Goebel [28], who found strong endomysial capillary ICAM expression in IMs, as well as Cid et al. [8], who found ICAM was constitutively expressed in vessels of all sizes, but much more intensely in DM. However, in all these studies, the sample size was small and mostly only normal muscle biopsies served as controls (29 cases and eight normal controls in the study by Cid et al. [8]; 18 cases and eight normal controls and one pathological control in the study by Bartoccioni et al. [3]; 25 patients and 10 normal controls in the study by Tews et al. [28]).

In PM and IBM, the presence of CD8+ cytotoxic T cells, expression of MHC-I and strong co-expression of ICAM-1 and LFA-1 (as shown in our study) lends credence to the hypothesis that the main pathogenetic mechanism is injury to muscle fibres by autoreactive T cells. However, recently it has been proposed that based on the features such as vacuolization and filamentous inclusions, IBM (unlike PM and DM) may be a degenerative disorder and an autoimmune reaction may be occurring as a concurrent process [12,13]. We agree with the findings of Stein and Dalakas [27], who concluded that ICAM is upregulated on capillary endothelial cells in DM, probably due to local release of cytokines from complement-mediated microangiopathy or ischaemia within the fascicle, and may play a role in adhesion of lymphocytes to endothelial cells and each other.

Although the findings of ICAM expression on endothelial cells in our study are different from previous studies, those on muscle fibres and inflammatory cells are similar. Cid et al. [8], Tews et al. [28] as well as Bartoccioni et al. [3] also found ICAM immunore-

activity in a notable percentage on muscle fibres and inflammatory cells and suggested that the sarcolemmal ICAM may act as a receptor for its ligand on LFA on the cytotoxic cells, thus inducing muscle fibre invasion by lymphocytes and cell-to-cell interactions among the inflammatory cells.

In the present study, VCAM is significantly upregulated in IMs, specially in DM, on blood vessels, muscle fibres, and inflammatory cells. Previous studies investigating the expression of VCAM have shown variable results. Similar to our study, Tews and Goebel [28] demonstrated that compared to ICAM, the expression of VCAM was weaker and not as constant. They did not find any VCAM expression on muscle fibres. In contrast to our findings, Cid et al. [8] found that VCAM-1 expression on microvessels was significantly higher in DM than PM and IBM. Figarella-Branger et al. [17] in their review stated that VCAM is expressed in all the various subgroups on the blood vessels, though the expression on muscle fibres has been found more commonly in DM. The same was seen in our study. The higher percentage of VCAM expression seen in DM in our study as well as those observed previously could be due to specific endothelial alterations that occur in DM, i.e. deposition of complement, ischaemic changes, etc.

In our study, LFA was expressed strongly while VLA was expressed weakly on inflammatory cells, regardless of the diagnosis, in cases as well as controls. In addition, scattered necrotic and degenerating muscle fibres and those invaded by inflammatory cells also showed positivity. In previous studies also [8,14,28], similar patterns of expression have been demonstrated and serve as good markers for the degree of inflammatory cell influx. The lymphocytes and macrophages expressing CD18 and CD49d (LFA-1 and VLA-4) integrins characterize the phenotype of migrating cells [8].

To the best of our knowledge, no previous study has investigated the diagnostic utility of the adhesion molecules in IMs. Blood vessel expression of ICAM was found to be highly sensitive but less specific, while the opposite was true for VCAM. Hence including both the stains in the existing panel of diagnostic markers used in the evaluation of the IMs will reduce chances of misdiagnosis. However, even though the subgroups of IMs have different pathogenic mechanisms, the difference in cytokine expression among them is not significant enough to be of any diagnostic help.

In other autoimmune disorders monoclonal antibodies blocking functional epitopes of adhesion molecules have been used in animal models to prevent the development of inflammatory lesions and clinically apparent disease [2,25,31] and some have entered clinical trials [22]. The interaction of LFA/ICAM and VLA/VCAM suggests that IMs may also be considered among the autoimmune diseases that could potentially benefit from anti-adhesion therapy.

Conclusions

IMs comprise about 6% of all muscle diseases and IBM is not a common subtype in the Indian subcontinent as reported in the Western literature. The strong ICAM-1 expression suggests that it not only plays a role in leukocyte-endothelium interactions, but also cytotoxicity against muscle fibres by stimulating interaction between LFA-1 expressing inflammatory cells and ICAM expressing muscle fibres. Similarly, VCAM-1 and VLA-4 expression, although to a lesser extent, indicates that they also play a role in mediating the leukocyte-endothelial interactions, resulting in an influx of inflammatory cells in IMs. The expression of adhesion molecules ICAM and VCAM and the integrins LFA and VLA in our study, as well as upregulation of MHC-I demonstrated in previous studies and ours, thus supports the hypothesis of autoimmunity in the pathogenesis of IMs. In addition, the difference in expression of ICAM and VCAM in IMs makes them useful diagnostic markers to distinguish these diseases from non-IMs.

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