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Anti–Valosin-Containing Protein (VCP/p97) Autoantibodies in Inclusion Body Myositis and Other Inflammatory Myopathies

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Objective. The rationale for this study was based on reports that valosin-containing protein (VCP) mutations are found in hereditary inclusion body myositis (IBM) and VCP was detected in rimmed vacuoles of sporadic IBM (sIBM) muscle biopsies. Autoantibodies to VCP have not been reported in sIBM or other inflammatory myopathies (IIMs). The aim of this study was to determine the frequency and clinical significance of anti-VCP antibodies in sIBM and other IIMs.

Methods. Sera were collected from 73 patients with sIBM and 383 comparators or controls, including patients with IIM (n = 69), those with juvenile dermatomyositis (JDM) (n = 67), those with juvenile idiopathic arthritis (JIA) (n = 47), those with primary biliary cholangitis (PBC) (n = 105), controls that were age matched to patients with sIBM (similarly aged controls [SACs]) (n = 63), and healthy controls (HCs) (n = 32). Immunoglobulin G antibodies to VCP were detected by addressable laser bead immunoassay using a full-length recombinant human protein.

Results. Among patients with sIBM, 26.0% (19/73) were positive for anti-VCP. The frequency in disease controls was 15.0% (48/320). Among SACs, the frequency was 1.6% (1/63), and in HCs 0% (0/32). Frequencies were 17.5% (11/63) for IIM, 25.7% (27/105) for PBC, 3.0% (2/67) for JDM, and 17.0% (8/47) for JIA. The sensitivity, specificity, positive predictive value, and negative predictive value of anti-VCP for sIBM were 26.0%, 87.2%, 28.4%, and 85.9%, respectively. Of patients with sIBM, 15.1% (11/73) were positive for both anti-VCP and anti–cytosolic 5′-nucleotidase 1A (NT5c1A). Eleven percent of patients (8/73) were positive for anti-VCP, but negative for anti-NT5c1A.

Conclusion. Anti-VCP has low sensitivity and moderate specificity for sIBM but may help fill the seronegative gap in sIBM. Further studies are needed to determine whether anti-VCP is a biomarker for a clinical phenotype that may have clinical value.

INTRODUCTION

Valosin-containing protein (VCP) is an intracellular hexameric ATPase with several cellular functions (1–3). In the context of autoimmunity, of particular interest is its crucial role in facilitating degradation of damaged or misfolded proteins (1,2). Mutations of VCP have been linked to a syndrome named inclusion body myopathy (IBM) associated with Paget's disease of the bone, frontotemporal dementia, and amyotrophic lateral sclerosis, which was subsequently renamed VCP-related multisystem proteinopathy (MSP) (3). Biopsies of skeletal muscle from patients with MSP consistently show inclusions of VCP, ubiquitin, and transactive response DNA-binding protein 43, supporting the notion that VCP mutations lead to the accumulation of protein aggregates in skeletal muscle which are similar to those seen in sporadic IBM (sIBM) (2). Of note, Güttsches et al reported that the rimmed vacuoles in sIBM biopsies had increased immunoreactive VCP (4). The aforementioned observations on VCP served as the impetus for this study of autoantibodies to VCP in sIBM and other immune inflammatory myopathies (IIMs).

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Although VCP gene mutations are associated with hereditary IBM (hIBM), autoantibodies directed to VCP have not been reported in sIBM, whereas autoantibodies to cytosolic 5′-nucleotidase 1A (NT5c1A/cN1A/Mup44), although detected in other autoimmune diseases, are regarded as a biomarker for sIBM (5–8). Anti-VCP autoantibodies were previously reported in primary biliary cholangitis (PBC) and autoimmune hepatitis sera (9,10). The goal of this study was to identify the frequency and performance of anti-VCP in sIBM, other IIMs, and control individuals. In addition, due to the particular relevance of VCP to sIBM, our analysis focused on sIBM and aimed to determine whether anti-VCP was associated with clinical features of sIBM or a specific human epithelial (HEp-2) cell indirect immunofluorescence assay (IFA) staining pattern.

PATIENTS AND METHODS

Patients and controls. Patients with sIBM, IIM, or other systemic autoimmune rheumatic diseases (SARDs), controls that were age matched to the sIBM group (similarly aged controls [SACs]), and adult healthy controls (HCs) followed at McMaster University (Hamilton, Ontario, Canada), the University of Calgary (Calgary, Alberta, Canada), Duke University (Durham, North Carolina, US), and McGill University (Montreal, Quebec, Canada) were included. SAC sera were from samples submitted for routine autoantibody testing and were selected based on the age range of the sIBM cohort. In total, sera from 73 patients with sIBM, 288 comparators with SARD, 63 patients with IIMs, 105 with PBC, 67 with juvenile dermatomyositis (JDM), 47 with juvenile idiopathic arthritis (JIA), 63 SACs, and 32 HCs were included. The demographics of the IIM group were as follows: age range 20 to 89 years (median 56, mean 55); sex: 25.8% male (16/62 [1/63 undisclosed sex]); 46.0% (29/63) had dermatomyositis; 44.4% (28/63) had overlap myositis; and 9.5% (6/63) had polymyositis, immune-mediated necrotizing myopathy (IMNM), and other myopathies.

The diagnoses of sIBM and disease comparators were made in accordance with published classification criteria (11) as well as expert opinion of attending specialists. All sera were stored at –80°C until required for analysis. PBC sera were from a biobank used in a previously published study (9). All data were anonymized with an alphanumeric code. This research was approved by the Health Research Ethics Board (HREB) at each institution and was conducted in accordance with the Helsinki Declaration. Where required by the HREB, written informed consent was obtained.

Autoantibody testing. Anti-VCP in human sera was detected using a full-length human recombinant protein (Novus Biologicals) by addressable laser bead immunoassay (ALBIA) and assay development as previously validated and published (8,9,12). The adopted cut-off of 200 median fluorescence units was more than three standard deviations above the mean of anti-VCP levels in HCs. All sera were also tested for IIM-related autoantibodies by a line immunoassay (Ro-52/TRIM21 (tri-partite motif 21), OJ (isoleucyl tRNA synthetase), EJ (glycyl tRNA synthetase), PL-12 (alanyl tRNA synthetase), PL-7 (threonyl tRNA synthetase), SRP (signal recognition particle), Jo-1 (histidyl t-RNA synthetase), PM-75, PM-100 (polymyostis/scleroderma 75- and 100-kDa antigens), Ku, SAE1 (sumo activating enzyme subunit-1), NXP2 (nuclear matrix protein 2), MDA5 (melanoma differentiating-associated factor 5), TIF1γ (transcription intermediary factor 1), Mi-2α, Mi-2β: Euroimmun AG) and anti-NT5c1A/cN1A/Mup44 (cytosolic 5′-nucleotidase 1A) by ALBIA (8).

Anticellular antibodies. A HEp-2 IFA (NOVA Lite HEp-2, Inova Diagnostics) was used to detect anticellular antibodies at a serum dilution of 1:80, which were read on an automated instrument (NovaView, Inova Diagnostics) that interpolated fluorescence intensity to an end-point titer. A commercially available monoclonal anti-VCP antibody (Abcam, Cat. # ab11433; immunogen: synthetic peptide corresponding to human aa 792-806) was used as a reference for IFA staining.

Statistical analysis. The sensitivity, specificity, positive predictive value, and negative predictive value for anti-VCP were calculated for sIBM. The frequency of anti-VCP in sIBM as compared to IIM, JDM, JIA, PBC, and HCs was analyzed by the chi-square test. Logistic regression was used to determine the age-adjusted odds ratio of anti-VCP in patients with sIBM versus SACs. Univariable logistic regression was used to assess the relationship between anti-VCP and demographic characteristics (sex, age), clinical characteristics (disease severity graded on a continuous subjective scale by subspecialists [Mild: 1; Moderate: 2; or Severe: 3]), presence of quadricep weakness, deep finger flexion weakness, knee extension weakness, dysphagia, biochemical creatine kinase (CK) level (normal range 0-170 U/L), and the presence of anti-NT5c1A antibodies. Variables for the multivariable logistic regression were chosen a priori and included sex, age, presence of muscle weakness in the three muscle groups described earlier, dysphagia, and CK level. The canonical features of sIBM are quadriceps and deep finger flexion weakness, for which quantitative measurements were recorded. As previously published, a BIODEX isokinetic dynamometer was used to quantify knee extensor strength (13), and hand strength was measured using a hand-grip dynamometer and a pinch-grip dynamometer. Dysphagia was assessed using swallowing studies performed on all symptomatic patients. All analyses were conducted using the Stata/IC 15.1 (StataCorp). A P value of less than 0.05 was considered statistically significant.

Table 1. Summary of demographic, serological, and clinical data for patients with sIBM

Characteristic	N = 73
Median age [IQR], y	70.0 [62.0-75.0]
Female (N, %)	27, 37.0
Total % VCP positive	26.0
VCP+ NT5c1A− (N, %)	8, 11.0
VCP+ NT5c1A+ (N, %)	11, 15.1
Median CK [IQR], U/L	496.2 [257.5-638.0]
Dysphagia+ (N, %)	42, 57.5
Quadriceps involvement (N, %)	68, 93.2
Deep finger flexor involvement (N, %)	69, 94.5
Median disease severity [IQR][a]	2.0 [1.5-2.0]
Median knee extension [IQR],[b] Nm	18.8 [8.1-38.0]

Abbreviations: CK, creatine kinase; IBM, inclusion body myositis; IQR, interquartile range; Nm, Newton meter; NT5c1A, cytosolic 5′-nucleotidase 1A; VCP, valosin-containing protein; sIBM, sporadic inclusion body myositis.
[a]Severity measured subjectively on a 3-point scale in which 1 = mild, 2 = moderate, and 3 = severe.
[b]Average knee extension for a middle-aged male = 160-180 Nm, middle-aged female = 120-140 Nm.

RESULTS

Demographic and clinical characteristics of the patients with sIBM are in Table 1 and Supplementary Table 1. The median age of the patients with sIBM was 70.0 years (interquartile range [IQR] of 62.0-75.0). Female patients accounted for 37.0% (27/73) of patients with sIBM, and the median CK value was 496.2 U/L (IQR 257.5-638.0 U/L) at diagnosis. Disease severity ranged from 21 of 73 (28.8%) patients graded as less than moderate severity and 16 of 73 (21.9%) graded as worse than moderate severity.

The frequency of anti-VCP in patients with sIBM was 26.0% (19/73), which was numerically higher than in patients with IIM (11/63 [17.5%], $P = 0.23$) and significantly higher than in patients with JDM (2/67 [3.0%], $P = 0.004$), patients with JIA (8/47 [17.0%], $P = 0.02$), and HCs (0/32 [0%], $P = 0.0014$) (Table 2; Figure 1). When comparing mean anti-VCP titers across patient groups, the sIBM group had significantly higher mean anti-VCP titers compared to the HC ($P = 0.003$), SAC ($P < 0.0001$), or JDM ($P < 0.0001$) groups. The differences did not reach statistical significance for IIM or PBC

Table 2. Frequency of anti-VCP in patients and controls with sIBM

Disease	N	Anti-VCP positive, n (%)
sIBM	73	19 (26.0)
Anti-NT5c1A positive	46	11 (23.9)
Anti-NT5c1A negative	27	8 (29.6)
IIM	63	11 (17.5)
JDM	67	2 (3.0)
JIA	47	8 (17.0)
PBC	105	27 (25.7)
SAC	63	1(1.6)
HC	32	0 (0.0)

Abbreviations: HC, healthy control; IIM, immune inflammatory myopathy; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; NT5c1A, cytosolic 5′-nucleotidase 1A; PBC, primary biliary cholangitis; SAC, similarly aged control; sIBM, sporadic inclusion body myositis; VCP, valosin-containing protein.

disease cohorts (Supplementary Table 2). The age-adjusted odds ratio of having sIBM between those with and without anti-VCP was 22.82 (95% confidence interval [CI]: 2.88-180.53, $P = 0.003$). The frequency of patients with sIBM who were positive for both anti-VCP and anti-NT5c1A was 15.1% (11/73), and the frequency of patients with sIBM who were positive for anti-VCP but negative for anti-NT5c1A was 11.0% (8/73).

The sensitivity, specificity, and positive and negative predictive values for anti-VCP in patients with sIBM were 26.0%, 87.2%, 28.4%, and 85.9%, respectively. Excluding pediatric patients, the sensitivity, specificity, positive predictive value, and negative predictive value did not differ significantly: 26.0%, 85.6%, 33.3%, and 80.6%, respectively. Univariable and multivariable analysis (Table 3) revealed no association between demographic and clinical characteristics of patients with sIBM and anti-VCP antibodies.

In patients who were positive for anti-VCP, no specific IFA staining pattern on HEp-2 cells was associated with anti-VCP (Supplementary Table 3), and none of the patients showed the nuclear or cytoplasmic HEp-2 IFA staining pattern resembling that shown by the monoclonal anti-VCP antibody (Supplementary Figure 1).

DISCUSSION

We report that anti-VCP autoantibodies were found in 26.0% of patients with sIBM with moderate to high specificity (87.2%) but low sensitivity (26.0%). To date, anti-NT5c1A has been a key autoantibody biomarker identified in individuals with sIBM (5–8). We suggest that anti-VCP may help fill part of the seronegative gap for the 11.0% of patients with sIBM who did not have anti-NT5c1A autoantibodies. Although in our study anti-VCP frequencies and mean titers were not significantly different between sIBM and IIM groups, this analysis should be replicated in larger sIBM and IIM cohorts. Anti-VCP is not alone as an autoantibody that is detected in both sIBM and other autoimmune diseases. Notably, Sjögren syndrome (14) and anti-SS-A/Ro60 antibodies (15) have also been linked to sIBM. Like anti-NT5c1A (8) and some other myositis autoantibodies (16), there was no consistent HEp-2 IFA staining pattern associated with anti-VCP antibodies on HEp-2 cells. Therefore, the HEp-2 IFA staining pattern is likely not a useful screening test for the detection of anti-VCP. To elucidate the true clinical utility of anti-VCP, further studies are needed to validate anti-VCP as a biomarker for IIM, including sIBM, and to determine whether there is a clinical phenotype that may have clinical value.

Our interest in autoantibodies directed against VCP in IBM was sparked by reports that VCP mutations were detected in hIBM (2), and prompted further by a recent report of increased immunoreactive VCP in sIBM rimmed vacuoles (4). It is interesting that autoantibodies in sIBM and IIM recognize VCP, a key component of this macromolecular complex. VCP is a ubiquitously distributed cellular protein that shuttles between the nucleus and

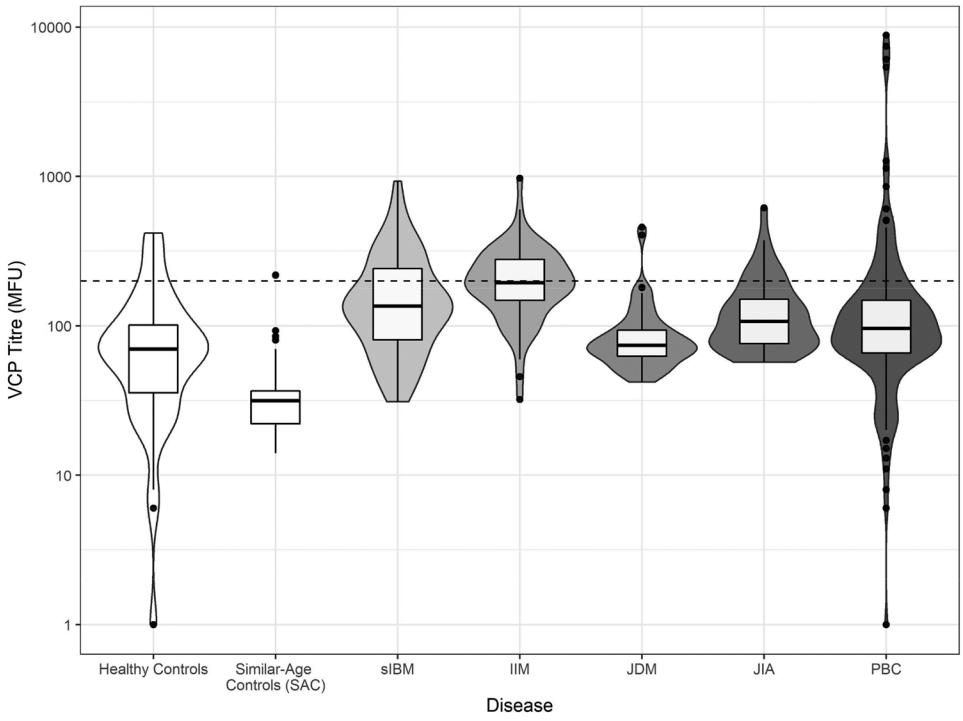

Figure 1. Violin plot of the density of anti–valosin-containing protein (anti-VCP) antibodies in sporadic inclusion body myositis (sIBM), other myopathies, and controls. The lower and upper lines of each box are the first and third quartiles of median fluorescence units (MFU), respectively; the line in the middle of the box is the median MFU for that group; lower/upper whiskers extend ±1.58 * interquartile range/square root(n): in cases in which this value extends beyond the minimum/maximum MFU value, the minimum/maximum MFU is used as the bottom/top of the whisker. The dots above/below the whiskers are outliers (beyond the pseudo-95% confidence interval), and each dot represents its own data point. The density of MFUs for the different values is shown in the shaded violin portion of the plot. Dashed line: cut-off for anti-VCP immunoassay = 200 MFU. IIM, immune inflammatory myopathy; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; PBC, primary biliary cholangitis.

cytoplasm, with the N-domain playing a crucial role in nuclear entry (17). Mutations of the N-domain of VCP result in localization in cytoplasm, whereas mutations in the C-domain result in retention in the nucleus or nucleoli (17).

In the context of IIMs, it may be relevant that VCP is a multiprotein complex that, along with cofactors, regulates expression of myosin-directed chaperone uncoordinated 45 to promote proper formation of sarcomeres and assembly of myosin in skeletal muscle (18). In patients with VCP-related MSP, mutated VCP has been found to result in impaired nucleocytoplasmic shuttling and retention of VCP in the nucleus or cytoplasm (17). Defective myosin assembly may portend myofiber fragility, reduced mechanical assembly, and formation of inclusion bodies from accumulated, unassembled myosin in the sarcoplasm (19). Other recent studies have reported that impairment of VCP function, caused by structural mutations or altered expression,

Table 3. Univariable and multivariable analysis of demographic and clinical features with anti-VCP antibodies in patients with sIBM (n = 73)

Characteristic	Univariable analysis		Multivariable analysis[a]	
	Odds ratio [95% CI]	*P*	Odds ratio [95% CI]	*P*
Age	1.03 [0.97-1.09]	0.35	1.04 [0.97-1.12]	0.28
Female	0.36 [0.11-1.23]	0.10	0.23 [0.05-1.05]	0.06
CK level	1.00 [0.99-1.00]	0.80	1.00 [0.99-1.00]	0.92
Dysphagia	0.76 [0.27-2.19]	0.62	1.35 [0.32-5.72]	0.68
Deep finger flexor weakness	1.06 [0.10-10.84]	0.96	2.46 [0.11-53.78]	0.57
Disease severity	1.05 [0.47-2.38]	0.90	1.36 [0.29-6.26]	0.70
Knee extension	1.01 [0.99-1.02]	0.38	1.02 [0.99-1.06]	0.17
Quadricep weakness	1.44 [0.15-13.75]	0.751	13.61 [0.19-983.51]	0.23

Abbreviations: CI, confidence interval; CK, creatine kinase; VCP, valosin-containing protein; sIBM, sporadic inclusion body myositis.
[a]Multivariable analysis adjusted for sex, age, presence of muscle weakness, dysphagia, and CK level.

contributes to the development of various diseases (e.g., cancer, heart, and neurodegenerative diseases) by interfering with protein degradation, subcellular translocation, and calcium homeostasis through an effect on endoplasmic reticulum, mitochondria, and the ubiquitin-proteasome system (reviewed in Sun and Qiu, 2020) (20). These observations may have relevance to the role of the proteasome (21,22), oxidative damage, autoimmunity, and mitochondrial pathology in IIMs (23,24).

The strengths of this study include the multicenter collaboration representing a range of clinical and demographic cohorts. This is also the first study to compare the prevalence of anti-VCP autoantibodies among multiple rheumatic and nonrheumatic diseases. Our sIBM cohort was composed of 73 individuals, which is a larger cohort than many other studies reporting on sIBM serology. Nevertheless, our study should be replicated in larger sIBM and IIM cohorts.

In summary, we report that anti-VCP autoantibodies have a moderate specificity for sIBM and therefore may be useful in the diagnosis of sIBM in an appropriate clinical context and may help fill part of the seronegative gap in sIBM. Additional studies evaluating clinical and serological correlations of this autoantibody are necessary to provide clinicians with further diagnostic and prognostic context.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Amlani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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