Prevalence and early detection of myocarditis in idiopathic inflammatory myopathies: a prospective single-centre study

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Abstract

Objective

To determine the prevalence of myocarditis with newly diagnosed idiopathic inflammatory myopathy (IIM) and assess the utility of serum cardiac biomarkers as initial screening for myocarditis.

Methods

We prospectively enrolled patients with IIM at the Johns Hopkins Myositis Center between 7/1/2022-3/30/2023. 26 patients underwent cardiac serum biomarkers, electrocardiography, and cardiac imaging (transthoracic echocardiogram and cardiac magnetic resonance imaging (CMR). Myocarditis was diagnosed with CMR using 2009 Lake Louise Criteria. Clinical cardiac outcomes, including heart failure events, cardiac hospitalisation, and arrhythmia events were also assessed at follow-up.

Results

27% (7/26) met the Lake Louise Criteria for myocarditis by CMR. Of patients found to have myocarditis, 71% (5/7) were symptomatic with dyspnoea on exertion, pleuritic chest pain, or with palpitations. The most common diagnosis among those with myocarditis was IIM/SSc overlap disease (5/7, 71%), and the most common antibody was Anti-Ku (3/7, 43%). When compared to patients without myocarditis, those with myocarditis more frequently had elevations in both troponin and NT-proBNP (100% vs. 42%, p=0.003) or an abnormal EKG (100% vs. 37%, p=0.004) with reduced ejection fraction on echocardiogram yielding a poor sensitivity with only 2/7 (29%) of patients with myocarditis demonstrating an EF of <50%.

Conclusion

Myocarditis occurred in 27% of this cohort, with IIM/SSc overlap being the most common subgroup. Anti-Ku was the most prevalent autoantibody, indicating a potentially higher risk for these patients. All had elevated cardiac biomarkers and abnormal EKGs, suggesting these could be useful for screening and further tests like cardiac MRI.

Key words

myocarditis, myositis, overlap myositis, cardiac biomarkers, cardiac MRI

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a rare, heterogeneous group of autoimmune conditions characterised by skeletal muscle inflammation. The main subgroups of IIMs are dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASyS), and overlap myositis (1). Myositis-specific and myositis-associated autoantibodies are related to extra-muscular organ involvement within the various subgroups. Cardiac involvement is poorly characterised in these autoantibody-associated phenotypes.

Myocarditis is a rare complication of IIMs that can range from patients being asymptomatic to having arrhythmias or fulminant heart failure. The gold standard for diagnosis of myocarditis is an endomyocardial biopsy. However, this is often deferred due to its invasive nature and low sensitivity (2). Cardiac magnetic resonance imaging (CMR) is, alternatively, the primary modality for diagnosis using the Lake Louise Criteria (3), requiring at least 2 of 3 criteria of hyperaemia, oedema, and myocardial necrosis/fibrosis (Fig. 1). Previous IIM studies have described the detection of myocarditis via echocardiography and electrocardiogram with systolic dysfunction, diastolic dysfunction, impaired longitudinal strain, or speckle-tracking echocardiography and ST/T wave abnormalities, atrioventricular block or arrhythmias, respectively (4, 5). However, a recent systematic review found nonspecific electrocardiogram (ECG) changes and preserved ejection fraction common in IIM patients with and without myocarditis (6).

The prevalence of myocarditis within IIMs has been challenging to estimate. CMR diagnosed overt myocarditis in <1% of IIM patients in the Johns Hopkins Myositis Registry but this was a retrospective analysis where a standardised screening protocol was not implemented (7). In a prospective Dutch Cohort (8) , 18% of newly diagnosed, asymptomatic, IIM patients were found to have subclinical myocarditis compared to 25-38% in IIM patients with evidence of congestive heart failure diagnosed via biopsy or autopsy (9-11). While overt myocarditis is rare, subclinical disease is relatively common in IIMs, with evidence of myocardial pathology seen on CMR in 19-47% of patients without clinical features of cardiac disease (12-14). This diagnosis carries considerable mortality, with survival being only 53% five years after overt myocarditis diagnosis (7).

It remains unclear which IIM patients are at the highest risk for myocarditis. Previously described subtypes related to myocarditis include ASyS and scleroderma/myositis overlap (7), whereas inclusion body myositis has a low likelihood of having cardiac involvement (15, 16). Additional antibodies reported with myocarditis include SRP (17), anti-mitochondrial antibodies (18), and Anti-Jo/PL12 (7). Regarding cardiac markers, some retrospective IIM cohorts (7, 14), but not all of CMR-confirmed myocarditis have had elevated troponins (13, 14). Elevated NT-proBNP (7, 13, 14, 19) have also been observed in IIM cohorts of CMR-confirmed myocarditis.

Currently, there is a paucity of guidance on optimal screening for myocarditis among IIM patients, and there is a critical need to enhance early detection of this potentially fatal disease to facilitate early diagnosis and improvement of clinical outcomes. Previously proposed screening algorithms for myocarditis include sequential testing with cardiac troponins and CMR in patients newly diagnosed with IIM (9). The purpose of this study was to identify the prevalence and risk factors of myocarditis in IIMs, and assess the utility of baseline serum biomarkers, ECG, and echocardiography as initial screening for myocarditis in this population.

Methods

Study design and setting. This was a single-centre prospective cohort study that enrolled consecutive patients with a new clinician-verified IIM diagnosis. A new diagnosis was defined as within one year of IIM symptom onset. All patients were recruited as part of routine clinical care at the Johns Hopkins

Myositis Center in Baltimore, Maryland, between July 2022 and March 2023. IIM subgroups, including dermatomyositis and immune-mediated necrotising myositis, were defined by ACR/EULAR criteria for IIM (1, 20). Anti-synthetase syndrome (ASyS) was identified by specific antibodies, while overlap myositis with systemic sclerosis (IIM/SSc overlap) required meeting ACR/EULAR criteria for both diagnoses (21). All patients participating in this study consented to enrolment into the Johns Hopkins Myositis Center Research Registry (Institutional Review Board [IRB] 00285294).

Data collection. Eligible patients underwent cardiac serum biomarkers (troponin-I and NT-proBNP), electrocardiography, and imaging, including transthoracic echocardiogram (TTE) and cardiac MRI (CMR) at 1.5 Tesla. Lake Louise Criteria (3) was used to diagnose myocarditis by CMR, requiring 2 of 3 positive criteria for evidence of hyperaemia, oedema, and myocardial necrosis/fibrosis. A positive troponin I test was defined as any positive test above the reference range. During the study period, the institution switched from standard troponin I which was measured for the first twenty patients (reference range <0.04 ng/ml) to a high sensitivity troponin I which was measured in the subsequent six patients (reference range <20 ng/L). Clinical cardiac outcomes were defined by arrythmia (including sustained ventricular tachycardia, ventricular fibrillation, and atrial fibrillation with rapid ventricular response), reduced systolic ejection fraction on transthoracic echocardiography (<50%), or death from cardiovascular causes were obtained via Electronic Medical Record (EMR) throughout follow-up to 6/7/2023. Patient risk factors were evaluated via EMR including prior history of tobacco use and diagnosis of coronary artery disease based on identification on coronary CTA or presence of coronary artery calcification on non-contrast CT imaging of the chest. Available myositis-specific autoantibody results were assayed on banked sera using the line immunoblot platform (EUROLINE Autoimmune Inflammatory Myopathies Profile, Euroimmun). Only those with moderate or high positive titer were considered positive. Additional serologies were sent as clinically indicated, including antimitochondrial, anti-Scl-70, anti-RNA polymerase III, and anti-dsDNA antibodies using commercial assays.

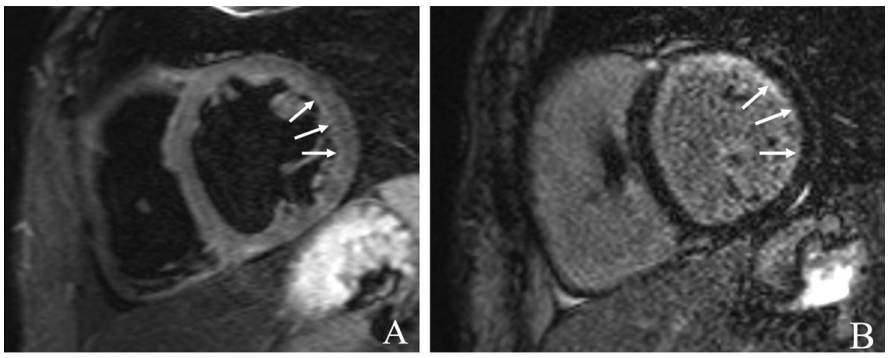

Fig. 1. Cardiac MRI depicting myocarditis. (**A**) Short-axis dark blood T2-weight image shows thin subendocardial increased signal (arrows) suggestive of oedema. (**B**) Short-axis post-contrast late gadolinium enhancement (LGE) image shows thin subendocardial enhancement (arrows) suggestive of fibrosis or myonecrosis.

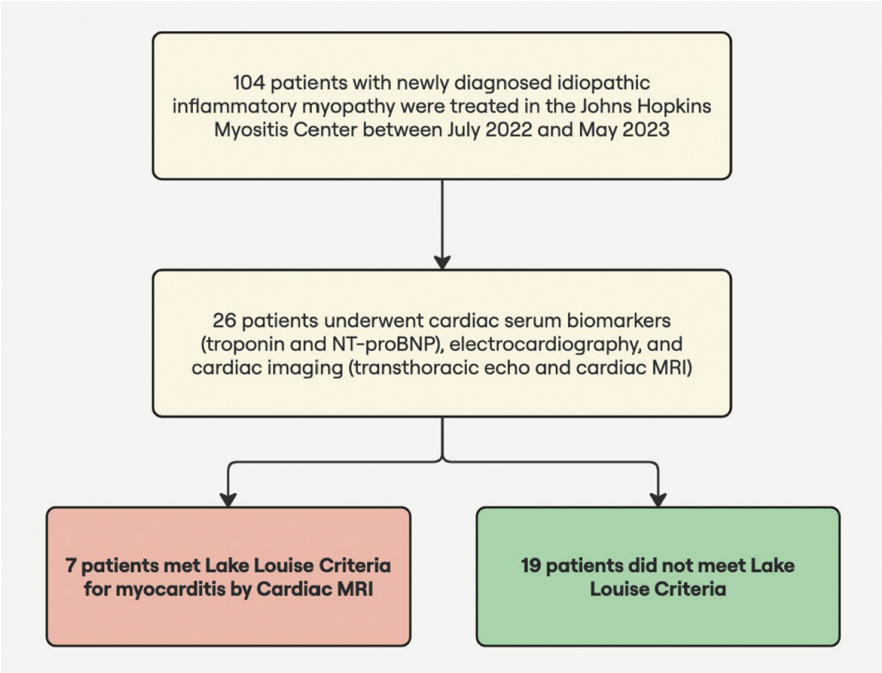

Fig. 2. Flowchart depicting the evaluation of cardiac involvement in patients with newly diagnosed idiopathic inflammatory myopathy. Patients who were approached but not enrolled voluntarily chose not to participate in the study.

Statistical analysis

Differences in clinical characteristics were compared between patients with and without myocarditis using student's *t*-tests and Fischer's exact test as appropriate. All statistical analyses were performed using Stata, version 17 (College Station, TX, USA). All statistical tests were 2-sided, and a p value ≤0.05 was considered statistically significant. Positive likelihood ratios were calculated to assess performance of troponin and NT-proBNP as screening tests.

Results

Characteristics of the study cohort. All patients with newly diagnosed IIM treated in the Johns Hopkins Myositis Center between July 2022 and March 2023, were approached for enrolment. Of the 104 patients approached, 26 agreed to enrol in the study and un-

derwent prospective screening with troponin, NT-proBNP, EKG, echocardiogram, and CMR (Fig. 2). Table I illustrates the demographics of the patient population. The cohort was predominantly female (19/26, 73%) and Caucasian (18/26, 69%). The most common IIM subtypes were IIM/SSc overlap (12/26, 46%), IMNM (6/26, 23%), ASyS (4/26, 15%) and DM (4/26, 15%). The most common antibodies were against HMGCR (n=5), Ro60 (n=5), TIF1$^{\gamma}$ (n=3), Ku (n=3), U1RNP (n=3), Ro52 (n=3), and Jo (n=2). Other comorbidities included coronary artery disease (5/26, 19%) and being a former smoker (13/26, 50%). No patients carried a diagnosis of heart failure prior to enrolment into the study. Of patients found to have myocarditis based on CMR, 71% (5/7) were symptomatic with dyspnoea on exertion, pleuritic chest pain, or with palpitations whereas the other 29% (2/7) were asymptomatic. At the time of enrolment, 62% (n=16) were on IIM targeted treatment and 38% (n=8) were subsequently started on treatment over the study period.

Myocarditis diagnostic testing. On initial laboratory evaluation, 54% patients (n=14) had elevated troponin, 58% (n=15) had elevated NT-proBNP, and 42% (n=11) had elevations in both cardiac markers. Subsequent EKGs showed 14 abnormal results (54%) including premature ventricular complexes or varying degrees of heart block. All 11 patients with elevations in both troponin and NT-pro-BNP had abnormal EKGs. Transthoracic echocardiograms showed two patients (8%) with a reduced ejection fraction <50% and one patient with a pericardial effusion (4%). Cardiac MRI (CMR) diagnosed myocarditis in 7 patients (26%).

IIM subgroups most commonly diagnosed with myocarditis. Of those diagnosed with myocarditis by CMR, the most common subgroup was IIM/SSc overlap (5/7, 71%) followed by ASyS (2/7, 29%). The most common antibodies were anti-Ku (3/7, 43%) which were only present in patients with IIM/SSc overlap and Anti-Ro52 (2/7, 29%) which was present in both patients with ASyS and one patient with SSc overlap who was negative for anti-Ku. There was no statistically significant difference between sex, peak CK value, pulmonary manifestations of their IIM, history of coronary artery disease, or smoking status (Table I).

Table I. Clinical characteristics of IIM patients with and without myocarditis. IIM patients with myocarditis had elevated cardiac biomarkers, lower EF, cardiac events when compared to those without myocarditis.

Clinical characteristics of IIM patients with and without myocarditis			
Clinical variables	**Myocarditis (n=7)**	**No myocarditis (n=19)**	***p*-value**
Age in years (mean ± SD)	44.0 ±14	51.8 ± 16	0.24
Gender			
Female	6 (85%)	13 (19%)	0.71
Male	1 (17%)	3 (19%)	
Race			
White	4 (57%)	14 (74%)	0.31
Black	1 (14%)	4 (21%)	
Other	2 (29%)	1 (5%)	
Myositis subtype			
Dermatomyositis	0 (0%)	4 (25%)	0.11
Immune mediated necrotising myopathy	0 (0%)	6 (38%)	
Overlap IIM w/SSc	5 (71%)	7 (37%)	
Anti-synthetase syndrome	2 (29%)	2 (11%)	
Maximum CK ever (U/L)	2737 ± 2858	3494 ± 43730.67	
Myositis specific and associated autoantibodies			
Anti-Jo-1	0 (0%)	2 (11%)	0.51
Anti-PL-7	2 (29%)	0 (0%)	0.07
Anti-PL-12	0 (0%)	0 (0%)	NR
Anti-TIF-1 gamma	0 (0%)	3 (17%)	0.36
Anti-Mi-2	0 (0%)	0 (0%)	NR
Anti-HMGCR	0 (0%)	5 (29%)	0.30
Anti-SRP	0 (0%)	1 (6%)	0.72
Anti-PM-Scl	0 (0%)	1 (6%)	0.72
Anti-U1 RNP	1 (14%)	1 (6%)	0.49
Anti-Ku	**3 (43%)**	**0 (0%)**	**0.003**
Anti-Ro52*	2 (29%)	1 (6%)	0.21
Anti-Ro60*	2 (29%)	2 (13%)	0.34
Troponin positive	**7 (100%)**	**5 (26%)**	**0.001**
Pro-BNP (pg/ml)	**3183 ± 3060**	**152 ± 188**	**0.0004**
Abnormal EKG	**7 (100%)**	**7 (36%)**	**0.004**
Left ventricular ejection fraction on 2D Echo	**51.1 ± 14.6**	**61.8 ± 6.38**	**0.03**
Cardiac events (arrhythmia, newly reduced ejection fraction <50%, heart failure hospitalization, or cardiovascular death)	**3 (43%)**	**1 (5%)**	**0.02**

**Anti-Ro52/60 were not mutually exclusive; these were co-reactive with other autoantibodies.

Evaluating the utility of cardiac biomarker screening tests. Upon initial evaluation, all patients with myocarditis had elevated troponins, NT-proBNP, and abnormal EKGs. In this setting, patients with myocarditis were more likely to have had an elevated troponin (100% *vs*. 37%, p=0.004) or NT-proBNP (100% *vs*. 42%, p=0.008). Elevations in both cardiac biomarkers were more specific than elevations in either biomarker and were associated with a positive likelihood ratio of 4.75 for myocarditis (100% *vs*. 42%, p=0.0003). An abnormal EKG demonstrated a positive likelihood ratio of 2.7 (100% *vs*. 37%, p=0.004). Transthoracic echocardiogram had a low sensitivity for detecting myocarditis in this cohort (29%, p=0.80).

Follow-up of patients with IIM and myocarditis. In the patients found to have myocarditis, two patients had subsequent hospitalisations for acute decompensated heart failure exacerbations associated with reduced ejection

fractions. Of those patients, one of them also received cardiac resynchronisation therapy in the setting of their reduced ejection fraction, left bundle branch block, and prolonged QRS. An additional patient with myocarditis, who had a preserved ejection fraction and no signs of symptoms of heart failure was admitted for recurrent supraventricular tachyarrhythmias for which he underwent cardioversion and loop recorder implantation. In those without myocarditis on CMR, one patient who had elevated BNP on initial evaluation but troponin and EKG within normal limits experienced heart failure hospitalization in the setting of newly diagnosed heart failure with preserved ejection fraction. There were no deaths in this cohort over the 11-month period.

Discussion

This study is one of the first to prospectively screen a cohort of newly diagnosed IIM patients for myocarditis consecutively, and the first to do so in a United States population. Our study contributes to the growing evidence that myocardial involvement exists in IIM (22). The prevalence of myocarditis in our pilot study was 27%, and we found that overlap myositis with systemic sclerosis and Anti-Ku antibody were identified as potential risk factors for myocarditis. It is important to note however that this high prevalence may be driven by the over-representation of overlap myositis with SSc cases. Based on these findings and the lack of a standardised approach for myocarditis screening in IIM, we propose a screening algorithm for myocarditis in newly diagnosed IIM patients based on the performance of non-invasive tests of cardiac biomarkers and EKG in detecting myocarditis.

The 27% prevalence of myocardial involvement in our cohort is higher than the other prospective screening Dutch cohort (8) that found a prevalence of 18% in newly diagnosed IIM patients and rather aligns with prior biopsy and autopsy studies identifying subclinical myocarditis in 25-38% in IIM patients (9-11). Identifying cardiac involvement in IIM patients is critical as the progression to overt, clinical myocarditis carries significant mortality at 53% five years after diagnosis (7). Despite the potential for severe cardiac complications, it is not always routine for rheumatologists to consider screening for cardiac involvement. Furthermore, there are not clear guidelines on a standardised approach for myocarditis screening in IIM.

Of the major subgroups represented in our study, the IIM/SSc overlap cohort made up the majority (71%) of our cases of myocarditis. This subgroup has been previously described to have myocardial involvement in up to 21% of IIM/SSc overlap patients (23) and myopathy has been identified as an independent risk factor for cardiac involvement in SSc patients (24). Our study demonstrated a higher prevalence than previously described with 42% (5/12) of our IIM/SSc overlap patients found to have myocarditis on CMR. The second most common type of myositis patients that were represented in our study was immune-mediated necrotizing myopathy, for which 0/6 patients developed myocarditis. Five were positive for HMGCR and one for anti-SRP. Our study supports the paradigm that HMGCR-associated IMNM rarely has extra muscular manifestations (25) and reinforces that this population may be at a lower risk of cardiac involvement. Interestingly, SRP has been associated with cardiac involvement but more recently has been controversial (26). Given that we only had one patient with anti-SRP, we cannot make a definitive conclusion about the prevalence of myocardial disease in this subgroup of IMNM. Of the various IIM subgroups, our study suggests the IIM/SSc overlap is high-risk for myocardial involvement.

There were unique autoantibody associations with myocarditis that were notable in our study. The most common autoantibody was Anti-Ku, a myositis-associated antibody described within several autoimmune diseases and overlap myositis patients with a specific phenotype associated with distal weakness, ILD, infrequent rash, and absence of calcinosis (27). A previous meta-analysis found no evidence of myocarditis in anti-Ku positive myositis but increased prevalence of myocarditis with patients with systemic sclerosis who were anti-Ku positive (28). Two other cohorts reported Ku positivity being associated with myocardial inflammation (29) as well as myocarditis and arrythmias (30) in IIM/SSc overlap patients. Our study adds to defining this poorly understood phenotype of anti-Ku+ IIM/SSc overlap and suggests that this specific antibody may be a risk factor for cardiac involvement.

Anti-Ro52 was another antibody present in 3/7 of patients with myocarditis, two of which were diagnosed with ASyS and one with SSc overlap. Anti-Ro52 is a nonspecific antibody that can be seen in a variety of overlap syndromes, including myositis and historically has been associated with an increased risk of interstitial lung disease, especially in patients with ASyS (31). Despite Ro52 antibodies being associated with neonatal lupus and congenital heart block when passed trans-placentally, it historically has not been associated with cardiac toxicity within adults apart from few reports of QT prolongation in patients without manifestations of autoimmune disease (32) and pericarditis when coexisting with anti-U1-RNP antibodies in patients with IIM (33). In our population, there was no overlap between those who were anti-Ku positive and anti-Ro52 positive. It remains to be known whether the co-reactivity of anti-Ro 52 has clinical significance but the known effects at the cardiac ion channels in heart block is interesting and needs further study in IIM patients with myocarditis.

Regarding the utility of screening methods for myocarditis in our IIM population, we performed a similar protocol to that of the aforementioned Dutch cohort (8), who found troponin but not BNP to be significantly elevated in those found to have myocarditis and proposed using cut-offs of 2.3-2.9 times the upper limit of normal for ruling in and out myocarditis. We also found a significant association between myocarditis and an elevated troponin yielding a sensitivity of 100% and specificity of 63%. Of note, the change in laboratory assay during the study period may overestimate the specificity

as 42% of patients without myocarditis had negative troponin I prior to transition to high sensitivity troponin I. All patients with myocarditis were positive on the lower-sensitivity assay, suggesting that this change did not impact overall sensitivity. Further, our study found that an elevated NT-proBNP was 100% sensitive for myocarditis, consistent with retrospective studies' finding that elevated NT-proBNP may predict myocardial involvement in IIM patients (13, 14, 19). The combination of an elevated troponin and an elevated BNP in this cohort yielded a specificity of 79% for myocarditis, suggesting that screening with troponin and NT-proBNP may be superior to only testing a troponin and may be a simpler alternative than using varying cutoffs of the degree above the upper limit of normal. We did not find a statistical difference between CK values in patients with or without myocarditis, as previously described (7, 19). One potentially confounding factor is the increased association of IMNM patients who often have drastically elevated CK values, and none of our IMNM patients experienced myocarditis. Our study also found abnormal EKG defined as premature ventricular contractions, premature atrial contractions, left ventricular hypertrophy, or conduction defects findings to be 100% sensitive and 63% specific for myocarditis. A reduced ejection fraction on transthoracic echo was found to be only 29% sensitive for myocarditis. Our study suggests that EKG may be another reasonable method for screening IIM patients for myocarditis alongside laboratory markers. Regarding echocardiography, our findings support prior evidence that a reduced ejection fraction has a poor sensitivity for myocarditis (6). Based on our findings, we propose a screening algorithm to evaluate patients with IIM for potential myocarditis whereby individuals with either elevated troponin and BNP or an abnormal EKG defined by premature ventricular/atrial contractions, tachyarrhythmia, or conduction defect should receive CMR (Fig. 3).

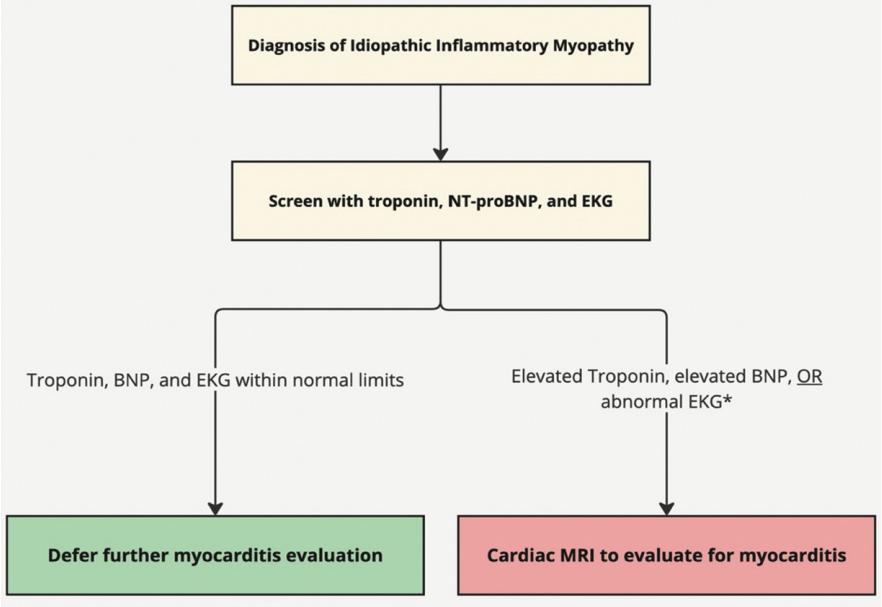

Fig. 3. Proposed diagnostic approach for myocarditis evaluation in patients with idiopathic inflammatory myopathy.
*Specific abnormalities including conduction defects, premature atrial/ventricular contractions, or tachyarrhythmia.

Our study has several limitations. First, given the single centre tertiary referral nature of our cohort, there is an inherent selection bias towards potentially more complicated cases of IIM. Second, only 25% of screened patients consented for the study, often due to a significant proportion who travel distances and could not return for study specific visits (CMR, echocardiogram). From an IIM subgroup standpoint, our study may overrepresent the SSc overlap phenotype which may overestimate the risk of myocarditis. This subgroup composed 46% of our study group whereas epidemiologic data estimates the prevalence of overlap myositis to only be 22-49% of IIMs (34) with IIM/SSc overlap making about 42% of the overall subgroup (35). External validity may be limited with this single centre changing from Troponin I to hs-troponin over the course of the study. It is worth noting that all patients diagnosed with myocarditis had positive troponin-I despite its lower population sensitivity than the high sensitivity counterpart. Nonetheless, this study adds to the body of evidence that elevated troponins in IIM may be a helpful screening test for cardiac involvement, and clinicians should not necessarily attribute this to cross-reactivity with skeletal muscle breakdown as previously described (36).

In conclusion, our study adds to the paucity of evidence regarding potential risk factors and screening modalities for myocardial involvement of idiopathic inflammatory myopathies. The relatively high prevalence of myocarditis within the IIM/SSc overlap subgroup and the associated anti-Ku antibody suggests these may be populations at higher risk for myocarditis. Additionally, our study suggests that screening patients with newly diagnosed IIM for myocarditis with troponin, NT-proBNP, and EKG may be a reasonable starting point, reserving CMR for patients with elevated biomarkers and/or an abnormal EKG. Future larger-scale studies are needed to delineate the long-term trajectory of patients with myocarditis in IIM that is paired with mechanistic studies to gain insights into how best to approach management of these high-risk patients.

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