Non-ischemic Cardiomyopathy: Role of Immunologic Work-up and Cardiac MRI in Etiologic Diagnosis and Outcomes

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Abstract

Objective: Study etiology of Non ischemic cardiomyopathy (NICMP) and role of cardiac MRI in diagnosis and outcomes.

Method: prospective observational study

Inclusion Criteria: 1. Clinical feature of cardiac failure, 2. 2D ECHO Systolic dysfunction, EF <45% OR Diastolic dysfunction without regional wall motion abnormality, 3. Absent ischemic changes on ECG and/ or coronary angiography. Exclusion: Valvular & congenital heart disease, Cor pulmonale, Renal failure. Patient were subjected to CBC with absolute eosinophil count(AEC), ESR, Urine-r/m, NT-Pro-BNP, ANA, ANCA, ACE, Bone marrow, Amyloid fat pad biopsy etc., chest x ray, 2DE. HRCT Chest and coronary angiography, Cardiac MRI by 3 tesla MRI machine. Patients were treated with antic-failure drugs & as per etiology and followed at 6wk clinically (NYHA) and 2DE.

Result: forty four Patients, mean age 36 yrs F: M(22:22), many patients had feature other than cardiac failure like Raynaud’s...
Disease of the myocardium associated with atherosclerosis is termed ischemic cardiomyopathy (ICMP). Besides ischemic cardiomyopathy, a wide range of diseases of the myocardium may occur and are unrelated to atherosclerosis and are classified as nonischemic cardiomyopathy (NICMP). Whereas ischemic cardiomyopathy is usually well evaluated noninvasively using echocardiography, echocardiography is often deficient for characterization of nonischemic cardiomyopathy. Although the first line of therapy for ischemic cardiomyopathy is directed at improving myocardial blood flow in narrowed coronary arteries, such treatment has no role in patients with nonischemic cardiomyopathy. Instead, therapeutic techniques vary widely and may include a combination of medical therapy, implantable cardio defibrillators or pacemakers, or even cardiac transplantation.

Two dimensional echocardiography is most commonly used imaging modality but is limited in patient with poor acoustic window and its ability to provide specific tissue characterization is modest. Unlike echocardiography, cardiac MRI has ability to image in any desired plane and with a nearly unrestricted field of view, allowing evaluation of abnormal cardiac and extra-cardiac structures.\(^1\)

In addition there are various cardiomyopathies which are reversible in response to specific treatment if any available and identifying those conditions earlier and see the response to treatment is important.

**Table 2A: Investigation in study population**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of patients with abnormality</th>
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<tbody>
<tr>
<td>ESR (more than 15 mm/hr)</td>
<td>30</td>
</tr>
<tr>
<td>CRP (more than 6 mg/L)</td>
<td>12</td>
</tr>
<tr>
<td>Urine routine microscopy (abnormal)</td>
<td></td>
</tr>
<tr>
<td>Absolute eosinophilic count (&gt;750)</td>
<td>04</td>
</tr>
<tr>
<td>TSH (more than 5Mu/L)</td>
<td>09</td>
</tr>
<tr>
<td>ANA (antinuclear antibodies)</td>
<td>05</td>
</tr>
<tr>
<td>ANCA (antineutrophil cytoplasmic antibodies)</td>
<td>04</td>
</tr>
<tr>
<td>Serum ACE (angiotensin converting enzyme)</td>
<td>02</td>
</tr>
<tr>
<td>Abdominal fat pad biopsy (n=9)</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow aspiration and biopsy (n=7)</td>
<td>02 (had eosinophilia)</td>
</tr>
<tr>
<td>Coronary angiography (n=12)</td>
<td>0 (all had normal CAG)</td>
</tr>
<tr>
<td>CT Aortogram (consistent with Takayasu arteritis)</td>
<td>05</td>
</tr>
<tr>
<td>Mediastinal lymph node biopsy (consistent with sarcoidosis)</td>
<td>03</td>
</tr>
</tbody>
</table>

**Table 2B: Cardiac MRI assessment**

<table>
<thead>
<tr>
<th>Assessment (n=28)</th>
<th>No. of pts.</th>
<th>% of pts.</th>
</tr>
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<tbody>
<tr>
<td>Delayed enhancement</td>
<td>6</td>
<td>21%</td>
</tr>
<tr>
<td>Scarring</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Mediastinal LN pathy</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td>Abnormal septal hypertrophy</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>LV non compaction</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
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of symptom before presentation to tertiary care hospital was around 6 months (174 days) indicating delay in etiologic diagnosis. Many patients had feature other than cardiac failure as outlined in Table 1 such as Raynaud’s phenomenon, joint pain, oral ulcer, leg ulcer, digital gangrene (in patient with Microscopic polyangiitis), h/o of recent delivery, fever, h/o neurological weakness (one patient had h/o stroke with factor v Leiden mutation but coronary angiography was normal and three patients had peripheral neuropathy) that helped in diagnosis.

Table 2A depicts investigation in 30 patients compared to normal ESR in patients with idiopathic DCMP and HCM patients Thus signifies it as marker of inflammatory CMP along with other features of connective tissue disorder. ANA was positive in 5 patients with significant titer which on further evaluation diagnosed as SLE CMP. ANCA was positive in 4 patients out of which one had C-ANCA and PR3 positive and diagnosed as Wegener’s granulomatosis (GPA) and three had P-ANCA of which one was diagnosed as MPA and two as EGPA. Serum ACE was elevated in two patients out of which one was diagnosed as sarcoid CMP and the other had false positive elevation. Other two patients with sarcoid had normal se.ACE as we know that se ACE is usually elevated in 60% patient with acute disease and 20% of patient with chronic disease and has somewhat low sensitivity and specificity. CT Aortogram was done in 5 patients with BP discrepancies and was consistent with Takayasu arteritis. Coronary angiography (CAG) was done in 12 patients of which three patients had ST-T Changes but on CAG there was no evidence of coronary atherosclerotic disease and patient with factor v Leiden mutation had history of CVA at age of 38 yrs cardiac failure (EF 40%) therefore CT coronary angiogram performed but was normal.

Table 2B Depicts cardiac MRI assessment in 28 patients. Six patients had delayed enhancement pattern out of which three had mid myocardial and sub pericardial D.E. pattern with mediastinal lymphadenopathy and biopsy of LN performed been suggestive of non caseating granuloma suggestive of sarcoidosis. Abnormal septal hypertrophy was present in three patients of HCM. Scarring was present in two patients one with sarcoid CMP and other with hypothyroid CMP their EF didn’t improve with specific treatment. Left ventricular non compaction (LVNC) was present in one patient with Takayasu arteritis.

Table 3 Outlines the various etiology of NICMP in our study population. Out of 44 patients specific etiology was able to establish in 36 patients (80%). In many etiology were related to connective tissue disorder like SLE, EGPA, Takayasu arteritis, Sarcoidosis, Wegener’s granulomatosis (GPA), microscopic polyangiitis, hypereosinophilic syndrome which could have missed out if specific attention was not given to associated clinical feature and abnormalities like raised ESR despite cardiac failure active urine sediment, peripheral eosinophilia.

Table 4A depicts the improvement in NYHA grade symptom treated with anticardiac failure and those given specific treatment as per etiology with P value being 0.001. Table 4B depicts improvement in ejection fraction (EF). More than 10% EF improvement is considered as significant. Out of 30 patients who were given treatment for specific etiology 23 had significant improvement in EF (i.e. by > 10%) with p value 0.0023 significant calculated by unpaired t test and out of these 23 patient 14 had improvement in EF by >20%. Seven patients who didn’t have significant improvement in EF were hypothyroid CMP (3), Takayasu arteritis (2) with extensive disease and one patient SLE CMP with high disease activity and one SLE patient died of severe infection.

**Discussion**

NICMP is fairly less common than ICMP and many a times missed because of lack of knowledge, poor understanding of their presentation, non availability of serological and radiological investigation (cardiac MRI) and they are misdiagnosed as ischemic CMP or idiopathic CMP and treated
with anticardiac failure drugs only.

Other than few genetic and metabolic CMP many of NICMP are reversible on specific treatment as evident from our study in which etiology was established in 80% of patients and 73% of them showed significant improvement in EF within 6 week of starting specific treatment.

We studied 44 patients in a tertiary care center and excluded patient with ischemic, valvular, congenital heart disease and patient with renal failure, cor-pulmonel which are generally known and well studied causes.

Our patients’ ages were younger, male to female equal incidence (ischemic CMP usually expected more common in males than females). Associated feature like raised ESR, abnormal urinary sediment, peripheral eosinophilia indicated toward systemic disease which on further evaluation etiology was established in 80% (36) patients.

As per study by Howard et al and Paul wood, ESR is low in patient with acute decompensated cardiac failure due to raised right atrial pressure leading to decreased serum fibrinogen. Important point to remember for systemic diseases like SLE, TA, EGPA, GPA, and Sarcoidosis with cardiac involvement, ESR is usually high in comparison to idiopathic CMP, HCM, and Hypothyroid CMP with low ESR.

We illustrate the spectrum of etiology of NICMP by describing 5 representative cases:

Case 1

F/26 presented with cardiac failure 3 month post-delivery to local physician with DOE grade 3 and bluish discoloration of finger at Solapur in November 2016 and detected to be in cardiac failure with EF (20-25%) and treated with anti-cardiac failure. As per notes, patient was given Inj.Methylprednisolone probably suspecting viral myocarditis. One month later patient was admitted in private hospital in Mumbai with cardiac failure and 2DE revealed EF 35% and Moderate PAH (PASP 55mmhg) with dilated right atrium and ventricle. Coronary angiography and Cardiac MRI detected no abnormality. Patient was again treated with anticardiac failure and went back to solapur. Three months later patient developed joint pain, Raynaud’s phenomenon, oral ulcer when local physician from solapur detected ANA 1; 1000 Speckled pattern. On further investigation in our hospital patient found to have low complement C3 and C4, active urine sediment Anti-dsDNA negative anti smith positive and treated with Inj Methylprednisolone followed by Prednisolone and Mycophenolate motefil. In this patient presented in November 2016 with cardiac failure and bluish discoloration of finger, moderate PAH in January 2017 should have given indication to treating physician to ask for ANA (as a screening test for CTD in patient with Raynaud’s phenomenon or CTD associated pulmonary hypertension). If this patient’s ESR, urine routine microscopy was performed early they would have come probably positive (as detected in our hospital). Fortunately for her Inj Methylprednisolone given as treatment of probable viral myocarditis which temporarily suppressed her SLE.

SLE myocarditis is usually asymptomatic with prevalence of 8-25% in different studies and shows good response to immunosuppressants. Global hypokinesia may be a 2DE indication of myocarditis and is present in 6% of patient with SLE. In our study all five patients with SLE CMP had global hypokinesia on 2DE and out of 5 patients with SLE 3 patients had complete recovery of ejection fraction and remaining two patients did not show improvement because of high disease activity and one patient died due to severe infection.

Case 2

F/51 had DOE grade 2 for 5 yrs was admitted in our hospital with acute cardiac failure. This patient chest X-ray in private had shown fleeting opacities and was treated with anti-tuberculosis drug. On admission to our hospital she was found to have left foot drop. Many of her old CBC reports had eosinophilia with absolute eosinophil count of 3000/ mm³. ESR70, active urine sediment, 2DE EF (35%), ANCA positive thus diagnosed as EGPA with mononeuritis multiplex with CMP. Patient was treated with Inj Methylprednisolone followed by Prednisolone and pulse Cyclophosphamide. Patient improved significantly with EF 60% within 6 week.

Cardiac involvement in EGPA is usually asymptomatic and ANCA negative and associated with very bad prognosis. Among 3 patients in our study two were P-ANCA positive and one was ANCA negative. All three had significant improvement in EF. One patient with EGPA did not have eosinophilia initially on peripheral smear but his bone marrow biopsy showed eosinophilia. In study performed by S. Morimoto including 8 patients with biopsy proven Eosinophilic myocarditis, the changes of peripheral eosinophil count was monitored showing that in 3 of 4 patient with initial eosinophil count of <500/mm³, an increase to >500/mm³ occurred 7 to 12 days after onset, stressing the fact that absence of eosinophilia at admission does not exclude diagnosis of eosinophilic myocarditis.

Case 3

F/18 had DOE grade 2 since 3 month admitted with cardiac failure to our hospital. Because of BP discrepancies in both upper limb which on CT aortogram was performed. It confirmed aortoarteritis and 2DE s/o of global LV hypokinesia with EF 15-20% and her cardiac MRI showed LV non compaction cardiomyopathy a form of irreversible familial CMP with noncompacted to compacted myocardial wall ratio of 3 (more than 2.3 is significant on cardiac MRI) which was missed on 2DE. But patient showed significant response to treatment with Prednisolone, inj Tocilizumab and inj Methotrexate with improvement in EF to 60%. Follow-up cardiac MRI is awaited to look for improvement in LV non compaction.

As such myocarditis is uncommon in TA and seen in 5-10%. Out of our 5 patients of TA 3 showed significant improvement in EF where as two patients didn’t have improvement. These two patients were treated with Prednisolone and Methotrexate, where as 2 of 3 TA with CMP who improved were treated with Tocilizumab in addition to Prednisolone and Methotrexate.

Case 4

M/30 had sudden onset palpation and syncope and ECG s/o of ventricular tachycardia and 2DE s/o global LV hypokinesia with EF of 45% and cardiac MRI revealed mid myocardial delayed enhancement pattern with mediastinal LN pathy which on biopsy was s/o of non-caseating granuloma his serum ACE was normal. Patient was diagnosed as Sarcoid CMP and...
responded to prednisolone and inj
Methotrexate and shown improvement
in EF to 60%. Out of total 3 patients
with sarcoid CMP, two had improvement
in EF and in one patient with scarring
on cardiac MRI EF didn’t improve at 6
week but 2yrs later her EF improved to
50% from 30-35%.

Cardiac involvement, though
found in about 25% of patients
with sarcoidosis, is symptomatic in only
5% of cases.14 An early diagnosis is
important since early corticosteroid
therapy can help prevent malignant
arrhythmias, which can result in sudden
death. All three of our patient had
presented with ventricular tachycardia
and cardiac failure with low EF.

One 14 yr. old girl had presented with
ventricular tachycardia and cardiac failure (EF 25%) her investigation
did not revealed any cause for CMP. Pacemaker was implanted in her and
EF improved to 50%.

Case 5

F/51, had long standing Diabetes
mellitus and presented with gangrene
of left foot since 1 yr. along with DOE
grade 2 and on further evaluation found
to have Diabetic nephropathy (biopsy proven)
and peripheral neuropathy on EMG-NCV but sural nerve biopsy
was not s/o vasculitis and 2DE showed
global LV hypokinesia with EF 15-20%
with ESR of 95 and C-ANCA and
PR3 Positive, CT Para nasal sinus
suggestive of pan sinusitis and HRCT
suggestive of mild pleural effusion.
Patient was diagnosed as Wegener’s
granulomatosis (GPA) CMP and on
treatment with Prednisolone and pulse Inj.
Cyclophosphamide showed significant improvement indicated by
EF 60% and ESR decreased to 30 mm/
hr. This case is particularly indicative
towards systemic immune disease.

Cardiac involvement is known
to occur in patient with GPA and
its most common manifestation is
pericarditis, and coronary vasculitis
with myocarditis is seen in around 25%
of patients with cardiac involvement.11

We found Cardiac MRI to be
practically useful in following cases of
NICMP.

1. Three patients of hypertrophic
CMP was missed on 2DE were
detected on cardiac MRI. Increasing
use of MRI has shown that HCM is
undetected in 6-12% of patients by
2DE.12

2. If during cardiac MRI mediastinal
lymphnode are detected one can
biopsy them and prove sarcoïd
CMP as done in our patients.

3. Scarring was present in cardiac
MRI of two patients (one sarcoïd
and other hypothyroid CMP) and
they did not have improvement in
EF. Thus scarring on cardiac MRI
helps in predicting in prognosis of
NICMP patients.

4. In our study out of 28 patients in
which cardiac MRI was done none
of patient had subendocardial or
subendocardial to transmural
delayed enhancement pattern which
is classic of ischemic CMP
seen in 81-100%patients.13 None
of the patients had abnormality
in any of 17 segments vascular
territory used for differentiating
non ischemic from ischemic CMP,
thus retrospectively ruling out
ischemic CMP.15

Conclusion

1. For etiology of cardiac failure,
features like fever, joint pain,
Raynaud’s phenomenon, oral /
leg ulcer, eosinophilia, high ESR,
abnormal urine microscopy point
towards systemic immune disease.

2. In cardiomyopathy patients with
treatable cause, specific treatment
in addition to anticardiac failure
drugs lead to significant clinical
and EF improvement.

3. Cardiac MRI helps in
differentiating ischemic from non
ischemic cardiomyopathy and can
be used as alternative to coronary
angiography in patients who don’t
want to undergo intervention.

4. Cardiac MRI helps to detect Sarcoïd
CMP (Delayed enhancement and
mediastinal LN), also helps to
predict prognosis as patients with
scarring on cardiac MRI do not
usually show improvement in EF.

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