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Demographic features and prevalence of myocarditis in patients undergoing transarterial endomyocardial biopsy for unexplained cardiomyopathy



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KEYWORDS

Unexplained cardiomyopathy;
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Abstract *Background:* The diagnosis of myocarditis is still a challenge. The true incidence of the disease is unknown due to great variation in clinical manifestations.

Objective: The aim of this study was to identify the demographic features and in-hospital prevalence of myocarditis in patients undergoing transarterial endomyocardial biopsy (EMB) for unexplained cardiomyopathy.

Patients and methods: This was a prospective observational study. We recruited all patients with unexplained cardiomyopathy presented at Assiut University Hospital from January 2014 till December 2014. The inclusion criteria were namely acute symptoms of heart failure, worsening of ejection fraction (EF) despite optimized therapy, hemodynamically significant arrhythmias, heart failure with concurrent rash, fever, or peripheral eosinophilia and new-onset cardiomyopathy in the presence of known amyloidosis. We excluded patients with uncontrolled hypertension, diabetes mellitus, ischemic, congenital, rheumatic heart disease, peripartum cardiomyopathy, cardiotoxic exposure, alcoholic and familial cardiomyopathies. All patients were subjected to full examination with ECG, echocardiography and coronary angiography, and then 3 EMB samples via femoral artery were taken from the LV. The histopathological examination of all biopsies was done.

Results: Out of the 1100 patients admitted to our department, 15 patients (1.4%), who had unexplained cardiomyopathy were included in our study. Seventy-three percent were males with mean age 37.8 ± 17 y. 87% were from rural areas, and 73.3% presented with dyspnea grade III to IV for a duration period that varied from 2 to 8 weeks. 33% had an EF > 40%. 33 EMB samples from 11 patients were examined. 7 out of 11 patients (63.6%) proved to have myocarditis on pathological examination, 5 of them had active myocarditis, 1 had chronic myocarditis and 1 had borderline myocarditis. Three patients (27.3%) had no pathological evidence of inflammation and one patient

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(9.1%) had cardiac amyloidosis. Four out of 15 patients (26.7%) did not undergo EMB because of LV thrombus or bleeding tendency. None of our patients had any complication from EMB.

Conclusion: The **in-hospital** prevalence of myocarditis is high among patients with unexplained cardiomyopathy. EMB via femoral artery is safe and essential in confirming the diagnosis.

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1. Introduction

Myocarditis is clinically and pathologically defined as “inflammation of the myocardium”. The true incidence of the disease is unknown due to a great variation in clinical manifestations from asymptomatic changes on electrocardiogram to fulminant heart failure, arrhythmias and sudden cardiac death [1]. The diagnosis of myocarditis is still a challenge, due to the non-specific pattern of clinical presentation and the lack of standardized diagnostic algorithm [2]. Cardiac magnetic resonance (CMR) is the ideal technique to detect soft tissue changes such as edema and inflammation [3,4]. However, imaging techniques such as CMR or echocardiography can only provide non-invasive tissue characterization but fail in revealing the true underlying causes that determine prognosis and treatment of the disease. Invasive removal of a sufficient number of tissue samples by endomyocardial biopsy (EMB) is always necessary when an exact diagnosis is needed [5–8]. EMB is an invasive, nonsurgical diagnostic technique, which makes it possible to obtain histological samples of myocardial tissue through the use of biopsy forceps [9]. Cardiac biopsy was initially performed in the 1950s by means of limited thoracotomy [10–14]. The role of EMB in the diagnosis and treatment of cardiovascular diseases is still controversial. However, EMB is the gold standard for heart disease when the common non-invasive methods do not make precise histopathological diagnosis possible [15–19]. EMB samples can be taken from the right or left ventricle, via the venous or arterial route [20]. EMB may be guided by fluoroscopy, 2-D echocardiography, or both [9,21,22]. However, fluoroscopy alone is the most common method used [23].

Also, because of the lack of available facilities and clinical experience, EMB appears to be infrequently used to diagnose myocarditis [20,22,23]. Reported complications range from minor site hematoma, to right ventricular perforation; and were reported in less than 1% of patients [24].

The aim of this study was to identify the demographic features and in-hospital prevalence of myocarditis in patients undergoing transarterial endomyocardial biopsy (EMB) for unexplained cardiomyopathy.

2. Methods

2.1. Study group and design

We performed a prospective observational study. From January 2014 to December 2014, 1100 patients who were admitted to the cardiology department at Assiut University Hospital complaining of dyspnea on exertion or chest pain were assessed for eligibility. Fifteen patients with unexplained

cardiomyopathy were included. The inclusion criteria were as follows: acute symptoms of heart failure refractory to standard management, substantial worsening of EF despite optimized pharmacological therapy, development of hemodynamically significant arrhythmias, particularly progressive heart block and ventricular tachycardia, heart failure with concurrent rash, fever, or peripheral eosinophilia, new-onset cardiomyopathy in the presence of known amyloidosis, sarcoidosis, or hemochromatosis. The exclusion criteria were patients with a history of ischemic heart disease, uncontrolled hypertension, diabetes, congenital or rheumatic heart disease, patients with familial cardiomyopathy, peripartum cardiomyopathy, patients with cardiotoxic exposure and alcoholic patients [25]. The trial protocol was reviewed and approved by the institutional review committee, and all patients granted their informed consent to be included in the trial. The demographic and clinical data were collected using a standardized “procedural datasheet”.

2.2. Patients diagnosis protocol

All patients were subjected to full history taking to identify the most common symptoms of myocarditis such as chest pain, breathlessness, fatigue, palpitations and fainting attacks. The history of flu-like symptoms (a cough, fever, malaise) and medications was used. Then this was followed by full physical examination and 12 lead electrocardiogram (ECG). All patients had detailed echocardiography (ECHO) study by an independent operator to analyze the suspected etiology of heart failure symptoms. It was only after ECHO assessment that patients were included into the study as unexplained cardiomyopathy.

2.3. Cardiac catheterization

Coronary angiography (CA) was carried out on all included patients to exclude coronary artery disease before doing the EMB. CA was performed using the femoral approach in all our patients with 6 F catheters through the common femoral artery according to standard guidelines [26].

2.4. Endomyocardial biopsy (EMB)

EMB was taken from the left ventricle (LV). 6 French femoral artery sheaths were inserted into the left or the right femoral artery. Judkins right (JR) 3.5 guiding catheter was introduced via the femoral sheath into the LV. A Cook® Flexible Biopsy forceps (with a standard cup for tissue sampling of 5.2 Fr volume 2.25 mm³) were used to take EMB. At least 3 samples of biopsy from the interventricular septum, apex and lateral wall of the LV were taken under fluoroscopic guidance in right

anterior oblique and left anterior oblique views [10–14]. 2500 IU of heparin was given in the sheath at the beginning of CA in all patients. At the end of EMB, mandatory 2D echo assessment was done for all patients for the exclusion of any complications. The main reported complications were pericardial effusion or new onset mitral incompetence due to chordal involvement.

2.5. Histopathological analysis

From each patient, 3 endomyocardial biopsies were taken into 3 separate bottles containing 10 mL of 10% formalin and were referred to a specialist in cardiac pathology for fixation and further assessment [9,27,28]. Tissue specimens were processed and 5 μ m sections were cut and stained with hematoxylin and eosin or other specific stains according to each case. Sections were examined by light microscopy and the following features were evaluated: these were the presence of inflammatory cells, number, and distribution of inflammatory cells, the presence of necrosis or fibrosis. The confirmed diagnosis of myocarditis was according to the Dallas criteria [29].

2.6. Study end points

Our study aimed to identify the in-hospital prevalence of unexplained cardiomyopathy among all patients presented with dyspnea or chest pain, and it also had the purpose of elucidating the rate of confirmed myocarditis among these patients and its subtypes by the histopathological analysis of EMB. The analysis of the safety of EMB from the LV using the femoral artery sheath was another end point of the study.

2.7. Statistical analysis

Categorical data were presented as counts and proportions (percentages). The normal distribution of continuous data was tested using a Kolmogorov–Smirnov test. Continuous and normally distributed data are presented as mean \pm 1 standard deviation. These comparisons were performed using the SPSS version 16.0 software package (SPSS Inc., Chicago, IL), and a *p*-value of ≤ 0.05 was considered to be significant.

3. Results

3.1. Patients' characteristics

The baseline demographic and clinical characteristics of the study group are summarized in Table 1. Fifteen patients with unexplained CM were significantly younger compared to other screened patients and 73.3% of them were males. One patient was known to have hepatitis C, and 86.6% were from rural areas. Clinical examination of admission and history of previous drugs were not significantly different between those with suspected unexplained CM and other screened patients except for age (Table 1). The younger patients were presented in the unexplained CM group with less use of diuretic treatment compared with other screened patients. None of our patients had significant eosinophilia in their blood picture analysis.

3.2. Symptoms, ECG and ECHO findings

The baseline clinical presentation of the included patients with ECG and ECHO findings is summarized in Table 2. Most of the patients presented with dyspnea grade III to IV, varied

Table 1 Patients' demographic criteria.

Variable	Unexplained CM <i>N</i> = 15	Patients screened <i>N</i> = 1085	<i>p</i>
Age (years)	37.8 \pm 17.7	60.9 \pm 10.7	0.002
Male gender <i>n</i> (%)	11 (73.3%)	801 (73%)	NS
Geographical distribution			NS
Rural	13 (86.6%)	868 (80%)	
Urban	2 (13.3%)	217 (20%)	
Hypertension <i>n</i> (%)	0	499 (46%)	–
Diabetes mellitus <i>n</i> (%)	0	401 (37%)	–
Hepatitis C infection <i>n</i> (%)	1 (6.6%)	217 (20%)	0.02
Smoking <i>n</i> (%)	5 (33%)	509 (47%)	NS
Known ischemic heart, <i>n</i> (%)	0	358 (33%)	–
Dyslipidemia, <i>n</i> (%)	4 (26%)	325 (30%)	NS
Systolic BP (mmHg)	122 \pm 62	134 \pm 30	NS
Diastolic BP (mmHg)	76 \pm 26	80 \pm 14	NS
Pulse (bpm)	99 \pm 26	88 \pm 14	NS
Weight (kg)	80 \pm 17	77 \pm 12	NS
Height (m)	166 \pm 7	164 \pm 7	NS
Hemoglobin (mg/dl)	11 \pm 3	12 \pm 2	NS
Platelets (u/L)	273 \pm 77	261 \pm 66	NS
INR impaired <i>n</i> (%)	2 (13%)	217 (20%)	NS
Chronic Diuretics therapy	4 (26%)	499 (46%)	0.01
Chronic ACEI or ARB therapy	4 (26%)	358 (33%)	NS
Chronic BB therapy	2 (13%)	217 (20%)	NS

Data are presented as mean \pm standard deviation, number (%) of patients, ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, Beta blockers; CM, cardiomyopathy.

Table 2 Complaint and electrocardiographic and echocardiographic findings in the study patients.

Variables	Unexplained CM, N (%)
<i>Clinical presentation</i>	
Attacks of palpitations	1 (6.7)
Chest pain	2 (13.3)
Dyspnea	11 (73.3)
Orthostatic hypotension	1 (6.7)
<i>ECG changes</i>	
Sinus rhythm	14 (93.3)
Atrial fibrillation	1 (6.7)
Normal axis	9 (60)
Left axis deviation	6 (40)
Diffusely Inverted T wave	4 (26.7)
Normal QRS duration	11 (73)
LBBB	4 (27)
<i>ECHO analysis</i>	
EF \leq 40%	10 (67)
EF $>$ 40%	5 (33)
Normal chamber dimensions	2 (13)
Dilated all chambers	9 (60)
Dilated atria only	1 (7)
Concentric LVH	2 (13)
Dilated LV	1 (7)

EF, Ejection fraction; CM, Cardiomyopathy; LBBB, Left bundle branch block; LV, left ventricle.

for a duration from 2 to 8 weeks (73%) and sinus tachycardia (93%). A normal ECG axis between -30 and $+90$ was present in 60% of patients. Through the means of detailed ECHO assessment, we found 10 patients (66.7%) had a picture of dilated cardiomyopathy (DCM) with an ejection fraction (EF) \leq 40% and global hypokinesia. On the other hand, 5 patients (33.3%) had EF $>$ 40% with normal wall motion, 2 of them had normal dimensions, another 2 had concentric LVH and one patient had dilated the atria (Table 2).

3.3. Distribution of patient according to biopsy results

The results of pathological examination of the 33 EMB samples are summarized in Fig. 1. Seven patients proved to be myocarditis according to the Dallas criteria [29]. Five of them had active myocarditis showing infiltration with inflammatory cells (polymorphs and lymphocytes) and focal necrosis of cardiomyocytes. The remaining 2 patients had borderline myocarditis where no necrosis was present in cardiomyocytes but there was infiltration with inflammatory cells as presented in Fig. 2. Three patients had no pathology detected and were considered negative for myocarditis, and one patient had cardiac amyloidosis with amyloid deposition identified by Congo red stain (Fig. 2). 10 patients included in the study had DCM, by EMB, 4 of them (40%) were found to have myocarditis.

Four patients did not undergo biopsy because of contraindications to the maneuver, 2 had LV thrombus and 2 had a bleeding tendency with INR $>$ 3.

4. Discussion

The main finding in our study was as follows:

1. The in-hospital prevalence of unexplained CM was 1.4% and myocarditis was 0.63%.
2. Myocarditis proved by pathological examination of EMB represents 64% of these patients.
3. EMB from the LV using Cook biopotes via transfemoral artery sheath is safe and essential in confirming the diagnosis.

With all modesty, to the best of our knowledge, this is the first report on the use of transarterial EMB for the diagnosis of myocarditis in Upper Egypt. EMB is mandatory in suspected myocarditis of unknown etiology [9]. According to the Dallas criteria [29], acute myocarditis is defined by lymphocytic infiltrates in association with cardiomyocyte necrosis. Borderline myocarditis is characterized by inflammatory infiltrates

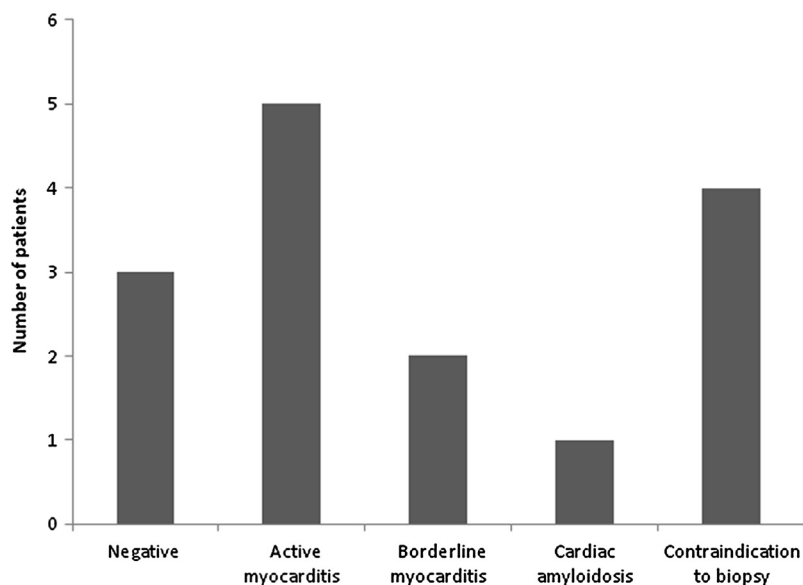


Figure 1 Distribution of patient according to biopsy result.

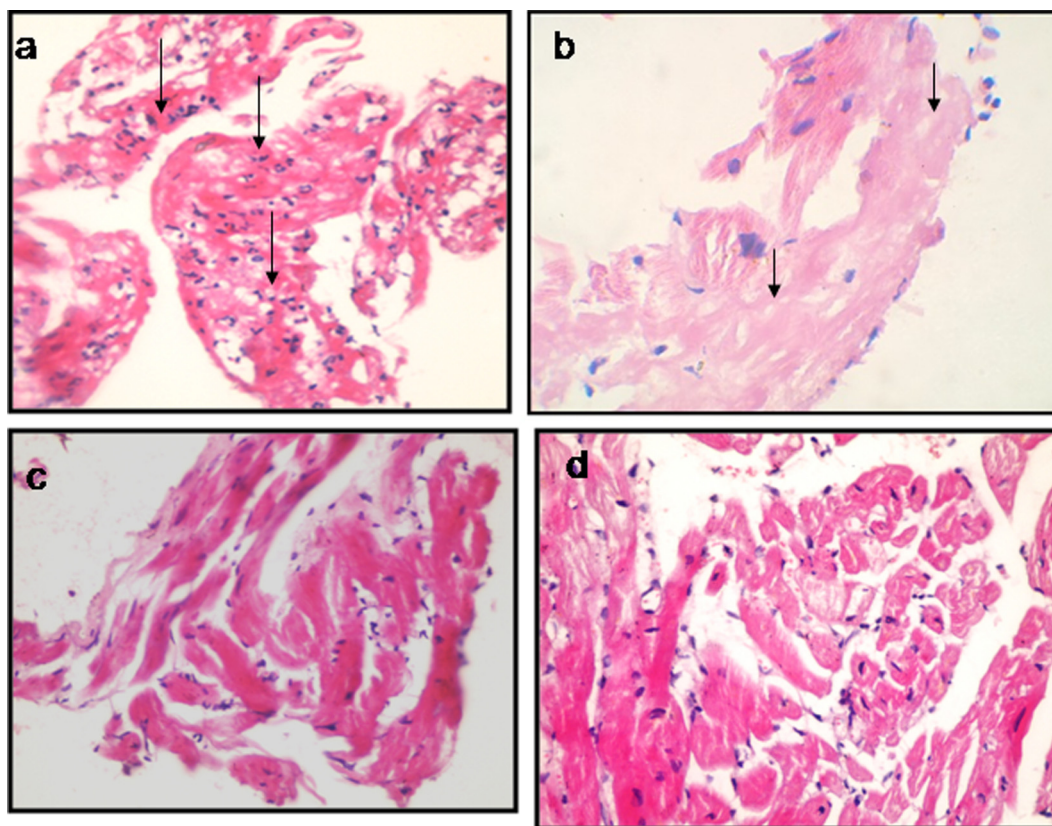


Figure 2 (a) Acute myocarditis showing diffuse infiltrate by mixture of polymorphs and lymphocytes (arrows) with cardiomyocyte necrosis. (b) Cardiac amyloidosis showing homogenous structureless pink material (amyloid) in between cardiac muscles. (c) Borderline myocarditis: demonstrating few inflammatory cells without cardiomyocytes necrosis. (d) EMB showing the absence of inflammation or necrosis and diagnosed as negative for myocarditis (H&Ex400).

without evidence of cardiomyocyte necrosis. Limitations of Dallas criteria are high inter-observer variability in interpreting biopsy (especially borderline myocarditis) [29]. EMB is considered to be positive for inflammation by immunohistochemical detection of focal or diffuse mononuclear infiltrates with > 14 cells/mm², in addition to enhanced expression of HLA class II molecules [7].

None of our patients had any reported complication after doing EMB in accordance with Karjalainen and Heikkilä [30].

The actual prevalence of myocarditis is unknown in our locality, in accordance with previous reports because the infrequency of the disease requires a large study population and the patient will have to be examined during the early course of the disease leading to wide variation in the results found [31]. During our study that took one year from the beginning to the end of 2014, 15 patients were diagnosed as unexplained cardiomyopathy and suspected to have myocarditis due to their clinical presentation out of 1100 patients admitted to cardiology department complaining of dyspnea or chest pain. Only 7 of these patients were diagnosed to have myocarditis by EMB within hospital prevalence of myocarditis 0.63%. This number is a bit higher compared to a study done by Karjalainen and Heikkilä [30] which included 672 Finnish soldiers in Central Military Hospital in Helsinki over a 20 year period. All cases with suspected heart disease (chest symptoms, changes in ECGs, detection of markers of myocardial injury in serum, DCM of recent onset) in the hospital were subjected to

EMB, in order to reach a final diagnosis, and 99 patients were diagnosed myocarditis by EMB within hospital prevalence 0.014%. Another study was done in China in nine hospitals by Lv et al. [32] on 1709 patients in a 3 year period, and the prevalence rate was found to be 0.041%. The difference in the prevalence rates can be explained by the small number of our studies.

In our study only 7 out of 15 patients (46.6%) were positively diagnosed as having myocarditis by pathological examination, and this is in agreement with Yilmaz et al. [20] who had a 2-center study on 755 patients with clinically suspected myocarditis. Myocarditis was the most frequent diagnosis in the study group and was found in 329 (43.6%) of patients. It is also in agreement with Kasner et al. [33] who had a study on 43 patients with clinically suspected myocarditis, and 14 (41.2%) of the patients were found to have active myocarditis. On the other hand, Gilotra et al. [34] studied 236 patients who presented with acute unexplained HF during the period from 2000 to 2009 and had undergone EMB, and 48 (20.3%) of suspected patients were found to have myocarditis in the biopsy. Also Mavrogeni et al. [3] studied 20 patients with clinically suspected myocarditis. He found only 25% of patients had proven myocarditis by EMB. It is also published in a review article by Veinot [35] that in cases of clinically suspected myocarditis, only 17–29% are biopsy confirmed.

Results of EMB are usually affected by two opponents, and the 1st opponent is the fading of infiltration of inflammatory

cells after treatment or in the late stage of the disease. The 2nd opponent is sampling errors [36]. These aforementioned factors made us to adopt the methodology in this study by taking the biopsies during the early stage of the disease and taking biopsies from different areas of LV which may help to get higher results.

In the present study, 10 of the 15 patients (66.6%) had the picture of dilated cardiomyopathy with EF > 40%, and myocarditis was found in 4 patients (40%) of them. This is in agreement with Towbin et al. [37], who had a study on 1426 patients diagnosed as having DCM, 89 centers shared in this study in North America during the period from 1990 to 2003, primary DCM was determined by strict criteria, and patients with disease due to immunologic, endocrine, drug toxicity or any other cause were excluded. The most common cause, they found for DCM by EMB was myocarditis in 46% of patients. However, Tian et al. [36] found in a study on 53 patients that suffered from unexplained cardiomyopathy during the period from 2006 to 2009, 19 of the said patients were diagnosed as DCM by echocardiography, all the patients underwent EMB and 5 (26.3%) of the 19 were found to have myocarditis by biopsy. Also, the consensus statement on EMB from the association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology, stated that myocarditis is found in about 10% of cases of clinical DCM [1].

This study had several limitations, among which were the small number of biopsy samples, the absence of ECG and ECHO data for all screened patients, and the lack of follow-up. One other shortcoming of this study was the lack of immune histochemical analysis of biopsy samples and molecular analysis with DNA-RNA extraction and RT-PCR amplification of the viral genome to rule in/out viral etiology was not performed. However, this is our first report and our main concern was to develop the system to implement EMB sampling technique and set in motion the process of the preservation of samples and the onward collaboration with a specialist in the pathology department to handle and study all cardiac specimens in this early report of our continuing project on unexplained CM patients.

5. Conclusion

The in-hospital prevalence of myocarditis is high among patients with unexplained cardiomyopathy. EMB via femoral artery is safe and essential in confirming the diagnosis.

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Conflicts of interest

The authors have declared that no competing interests exist.

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