Case reports

Healing of acute myocarditis with left ventricular assist device: morphological recovery and evolution to the aspecific features of dilated cardiomyopathy

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Key words:
Acute myocarditis; Dilated cardiomyopathy; Left ventricular assist device.

Dilated cardiomyopathy may result from an acute myocarditis. Little is reported *in vivo* documenting the progression from the acute inflammatory disease to the healing phase. We describe the consecutive light and electron microscopy studies performed on five myocardial sample series in a 47-year-old female patient who was referred to our hospital with acute myocarditis. She was sustained with left ventricular assist device (LVAD) for 63 days, and then she died of cerebral hemorrhage.

The first three consecutive endomyocardial biopsies (days 2, 4, 36 from onset) documented the acute and early healing phase of the inflammatory disease. In the last two biopsies (days 50 and 64 from onset) active inflammation and myocyte necrosis were absent. The histopathological features were those commonly observed in most patients diagnosed with dilated cardiomyopathy, namely myocyte hypertrophy, nuclear size and shape irregularities, and interstitial fibrosis. Overall, the myocyte morphology significantly improved and LVAD support likely contributed to the structural recovery.

The major conclusions to be drawn from this case are: 1) the aspecific pathologic findings of dilated cardiomyopathy patients may result from an acute myocardial inflammation; 2) immediate endomyocardial biopsy in patients with clinically diagnosed myocarditis minimizes the risk of missing the diagnosis of inflammatory disease; to this aim a precise definition of "early onset" is especially needed; 3) LVAD support may contribute to the morphological recovery of severely damaged myocytes.

(Ital Heart J 2001; 2 (1): 55-59)

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Supported by grants: Ricerca Corrente e Ricerca Finalizzata, IRCCS Policlinico San Matteo, Pavia, Italy.

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Introduction

The inflammatory infectious etiology of dilated cardiomyopathy (DCM) has dominated the scenario of the pathogenesis of this disease since its original description and classification[1,2]. More recently, the increasing knowledge of molecular genetics and the approach to the family studies by non-invasive screening of index-patient relatives, has led the cardiologist's attention to the subgroup of "familial diseases" which constitute 25% of all DCMs[3,4]. Therefore, in an evidence-based clinical setting, most DCMs (75%) are non-familial or "sporadic"[3,5]. For this latter group, the etiopathogenetic hypothesis is still based on inflammatory/infectious and/or autoimmune/immune-related (mediated) mechanisms, which are supported by:

- experimental studies showing that enteroviral infection in mice causes myocarditis which evolves throughout cardiomyopathy[6];
- sierological evidence of higher titers of anti-Coxsackie antibodies in DCM patients than in normal controls[7];
- rare demonstration of enteroviral isolates from myocarditis hearts[8,9];
- molecular analysis, documenting the presence/persistence of enteroviral genome in the affected myocardium[10-12].

A major limit in diagnosing post-myocarditis DCM is the rare *in vivo* demonstration that biopsy proven myocarditis evolves throughout cardiomyopathy[13]. This demonstration is particularly needed in order to prove that DCM may represent the evolutive/healing phase of an acute myocarditis and to show how, in endomyocardial biopsy (EMB), myocarditis heals, thus providing morphologic markers useful for

the interpretation of pathological findings. Furthermore, the few available studies provide the acute early diagnostic observation and the very late control findings. The intervals between acute healing and healed disease remain to a great extent undefined.

We have recently reported two cases of acute myocarditis, one dying within a few hours of admission and one surviving on left ventricular assist device (LVAD) support for 63 days. Both myocardites were enteroviral in origin. Our prior study focused on enteroviral infection of the skeletal muscle, where typical viral aggregates accumulate[14]. The patient who survived longer, underwent 5 myocardial tissue sampling procedures. The findings observed in these consecutive pathological studies provide a clear documentation that the "non-specific" features observed in the healing phase of an acute myocarditis coincide with those observed in most DCMs and that tissue healing of acute myocarditis occurs in less than 2 months. The role of LVAD support in myocyte recovery is discussed.

Data report and description

A 47-year-old female patient was admitted to a peripheral hospital for sudden onset of acute congestive heart failure, the suspected cause of which was myocarditis (echocardiographic ejection fraction 40%). Diuretics, vasoactive amines, and steroids were started.

Two days later she was referred to our cardiology center and admitted to the Coronary Care Unit for severe worsening of the ventricular function with cardiogenic shock (ejection fraction 20%). Steroids were suspended, diuretics were given at high doses, and dopamine and dobutamine were continued. Immediately an intra-aortic balloon pump was inserted (with standard heparin) and, 2 days later, an LVAD was implanted for 63 days. During her hospitalization, 5 myocardial tissue samplings were performed (4 EMB with 4 to 6 samples for each procedure, and 1 ventricular apex resection at LVAD implantation). The enteroviral etiology of myocarditis was proven both with electron microscopy and molecular analysis. A parallel enteroviral myositis was documented at ultrastructural and molecular levels[14]. The first EMB that provided the diagnosis of acute myocarditis was performed at admission, and urgently processed as frozen biopsy. The histopathologic diagnosis was done in 20 min from sampling (Fig. 1A and B).

The pathological study of multiple large samples of the left ventricular apex removed at LVAD implantation confirmed severe, acute, necrotizing myocarditis (Fig. 1C and D).

In LAVD support, the patient progressively improved, and a control EMB performed 32 days after implantation showed persistent inflammation, early features of healing, with loose fibrosis, vascular neogenesis, and hemosiderin deposits (Fig. 2A). A further

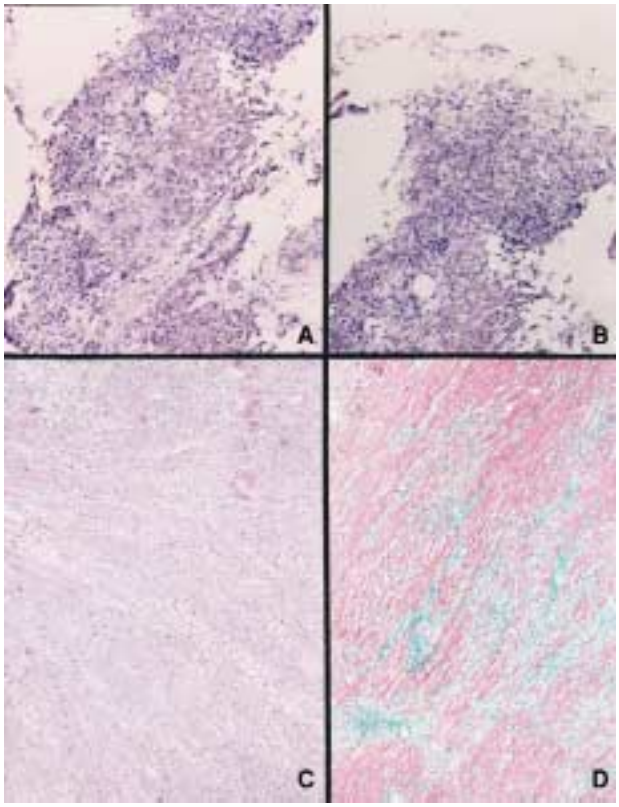

Figure 1. A *and* B: *frozen, Giemsa-stained sections of the first endomyocardial biopsy showing the acute inflammation and myocyte necrosis;* C *and* D: *hematoxylin-eosin and Movat pentachrome stains of paraffin sections obtained from samples of the ventricular apex excised at left ventricular assist device implantation.*

control biopsy performed 14 days later showed healing myocarditis with fibrosis and nearly absent tissue inflammation (Fig. 2B). Finally, the clinical improvement of her overall conditions led to plan the weaning from LAVD support and a further EMB was performed 64 days after the onset of the disease. This biopsy showed no feature consistent with the inflammatory origin of the disease. The myocardial samples showed mild interstitial fibrosis, focal variations of the irregular shape and size of the myocytes, as commonly seen in EMB of DCM patients (Fig. 2C).

Ultrastructural study showed acute myocyte damage with myofibrillar loss with extensive involvement of the nuclear and sarcoplasmic structures, interstitial edema and inflammation in biopsies 1, 2 and 3, and repairing features with interstitial fibrosis in biopsies 4 and 5. Myocytes showed restructuring patterns, with normalization of sarcomeric structures, and secondary disarray likely due to the overall remodeling of the tissue related to the repair processes (Fig. 3). Table I summarizes the hemodynamic data obtained at admission, 1 and 2 months later.

Unfortunately, the patient died of cerebral hemorrhage 67 days after admission, when LAVD weaning was proximal.

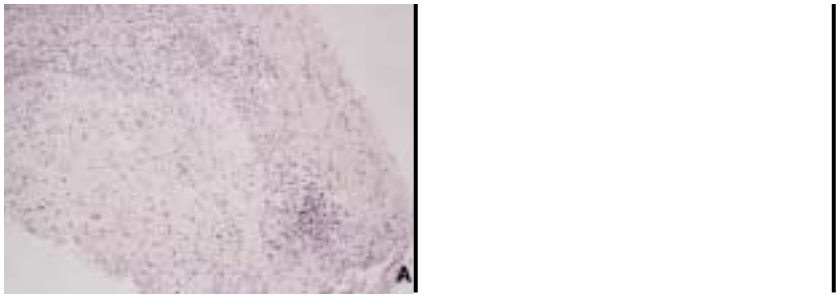

Figure 2. A: *third endomyocardial biopsy showing persistent inflammation, and early repair features;* B: *fourth endomyocardial biopsy showing resolving myocarditis with minimal residual inflammatory cells, and interstitial fibrosis;* C: *fifth endomyocardial biopsy showing absence of inflammation, some interstitial fibrosis, variable myocyte sizes and nuclear shapes. These latter features are those usually seen in endomyocardial biopsies of patients with dilated cardiomyopathy.*

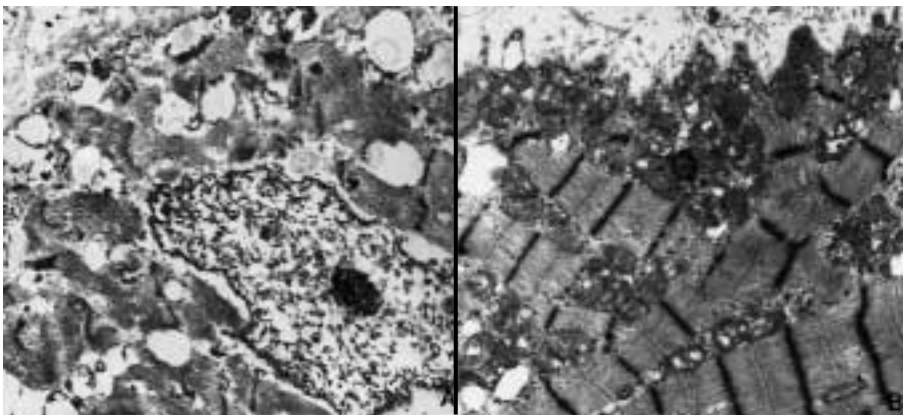

Figure 3. *Electron micrographs of the first and last endomyocardial biopsy. In* A *note the acute myocyte damage, and in* B *the repair features with secondary disarray and interstitial fibrosis (uranyl acetate-lead citrate stain).*

Table I. Hemodynamic data recorded at admission, 1 and 2 months later.

	CO (l/min)	CI (l/min)	PAPs	PAPd	PAPm	PCWP
Admission	1.19	0.71	36	27		27
1 month later	3.93	2.57	16	4	8	4
2 months later	4.04	2.66	19	6	11	9

CI = cardiac index; CO = cardiac output; PAPd = diastolic pulmonary artery pressure; PAPm = mean pulmonary artery pressure; PAPs = systolic pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

Discussion

The present case documents that the pathological features observed in the EMB of an healed myocarditis coincide with those commonly seen in EMBs of patients diagnosed with idiopathic DCM, and that tissue healing processes take less than 2 months to complete.

The diagnosis of DCM relies on clinical and morphofunctional criteria: EMB mostly contributes to exclude specific disorders. In numerous cardiology centers several patients are diagnosed with DCM and managed independently on pathological exclusion of myocarditis. The additional benefits deriving from EMB contribution are still matter of debate, and EMB remains a useful tool in centers dedicated to research and heart transplantation programs. In these centers, EMB contributes to the diagnosis in about 10% of familial DCMs (dystrophin defects, 6.5% of consecutive affected males[15], mitochondrial defects, about 3% of all DCMs[16], lamin A/C gene defects in DCM patients with atrioventricular block and/or associated myopathy[17], rare forms of dystrophin-associated glycoprotein defects[18], emerin defects[19], carnitine deficiency[20]), and in about 30% of non-familial DCM, including myocarditis[21] and inflammatory cardiomyopathies[22], with and without viral persistence.

To increase the contributory role of EMB in non-familial DCM, the biopsy timing is essential: in recent onset DCMs, early EMB tests the myocarditis hypothesis. In our patient no marker of the prior inflammatory disease was retained in the myocardial tissue 48 days after the first biopsy showing active myocarditis. Therefore, the risk of missing the diagnosis in patients referred to tertiary centers after preliminary evaluation and management of recent onset cardiac heart failure in peripheral centers is proportional to the interval elapsing from onset of symptoms to EMB. The last two biopsies in our patient would have been poorly informative without

the prior three. The features observed in the last two biopsies are identical to those commonly seen in EMB of most DCM patients. No morphological marker useful for an etiological diagnosis persisted. Adding the immunohistochemical stains for T lymphocytes (CD45RO) and macrophages (CD68) and for immunological activation markers (HLADR), the number of inflammatory cells is easily counted but does not usually provide, by itself, an evidence-based diagnosis of post-myocarditis DCM[21]. The related consideration is: how many etiological diagnoses are missed at EMB in early onset DCMs, when "early onset" does not correspond to a "quantitative" definition? In the current clinical setting, "early onset" is equally used to define few days, few weeks, and, sometimes, few months. Therefore, besides the major need for scheduling EMB immediately after admission when a myocarditis is clinically suspected, a major effort to provide a quantitative value to the generically defined "early onset" is necessary. The correct diagnostic work-up could help to precisely assign a DCM to the post-myocarditis group. In fact, this latter diagnosis often derives from clinical hypothesis rather than from biopsy-proven evidence.

The myocyte morphology in our patient improved from the first to the last biopsy. The LVAD support reduced the hemodynamic demands of the failing left ventricle, and likely favored myocyte recovery. A series of functional studies carried out on myocytes isolated from failing and then LVAD-supported hearts indicate a beneficial role for mechanical circulatory support in myocardial functional improvement[23], especially in patients with chronic heart failure due to DCM[24]. Reversal of chronic ventricular dilation[25] and myocyte hypertrophy[26] in patients with end-stage DCM and prolonged mechanical unloading have been reported. In our patient the myocyte necrosis observed in the ventricular apex cut during implantation was severe and extensive (Fig. 1D). Although the LVAD contribution to the morphological recovery is difficult to separate from the spontaneous healing process, our hypothesis is that the mechanical unloading favors the healing mechanisms that follow acute inflammatory damage. The LVAD implantation however implies additional risks, mostly related to the hemorrhagic and thromboembolic complications that sometimes nullify the clinical benefits[27].

In conclusion, although single case reports add little to the overall knowledge of a given disorder, the present case helps refocusing diagnostic work-up of acute myocarditis and indicates the need for early EMB when myocarditis is clinically suspected, as well as for a more "precise" clinical definition of "early onset" disease. Furthermore, the possibility of LVAD support for acute congestive heart failure due to myocarditis, after the negative outcome of the immunosuppression trial[28], opens new strategies for the management of the acute phases of the disease.

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