

# Myocarditis mimicking acute myocardial infarction: role of endomyocardial biopsy in the differential diagnosis

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## Abstract

**Objective**—To test the hypothesis, using endomyocardial biopsies, that unexplained cases of apparent acute myocardial infarction were caused by myocarditis.

**Material**—Between 1992 and 1998, 12 patients were admitted to the coronary care unit with severe chest pain, ST segment elevation, increased serum creatine kinase and MB isoenzyme, and with wall motion abnormalities on echocardiogram highly suggestive of acute myocardial infarction. These patients were further investigated by endomyocardial biopsy, as their coronary angiograms were normal. A diagnosis of myocarditis was made according to the Dallas criteria. A panel of antibodies was used for immunohistochemical characterisation of inflammatory cell infiltrate. Polymerase chain reaction (PCR) was used to detect viral genomes in seven cases.

**Results**—Haematoxylin and eosin staining of the endomyocardial biopsy showed active myocarditis in six patients and borderline myocarditis in one. Immunohistochemistry was positive for inflammatory cell infiltrates in 11 patients, including all the seven who were positive on haematoxylin and eosin staining according to the Dallas criteria. Only one patient had no evidence of inflammation. PCR was positive in two patients, both for Epstein–Barr virus. Follow up showed complete resolution of echocardiographic abnormalities in all patients except one.

**Conclusions**—Myocarditis can mimic acute myocardial infarction in patients with angiographically normal coronary arteries, leading to errors of treatment. In patients with apparent myocardial infarction and a normal coronary angiogram, endomyocardial biopsy may help in the diagnosis of myocarditis. The sensitivity of endomyocardial biopsy was enhanced by using immunohistochemical and molecular biological techniques.

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Keywords: acute myocardial infarction; endomyocardial biopsy; myocarditis

It is not rare to find that patients admitted to an intensive care unit with chest pain, localised ischaemic ECG abnormalities or pathological Q waves, segmental left ventricular dysfunction on echocardiographic or cineangiographic evaluation, and mild elevation of creatine kinase have normal coronary arteries. The diagnosis in these patients is difficult as they may not have an acute coronary syndrome. Myocarditis needs to be kept in mind when considering the differential diagnosis.

Unfortunately, the clinical diagnosis of myocarditis remains a challenge owing to the non-specific pattern of the clinical presentation and the lack of universally accepted and standardised diagnostic criteria. As the spectrum of clinical presentation is broad—including asymptomatic ECG abnormalities reported during enterovirus epidemics, vague symptoms of flu-like syndrome, congestive heart failure of recent onset, cardiogenic shock, and sudden death—many false positive and false negative clinical diagnoses may be expected.<sup>1,2</sup> Endomyocardial biopsy,<sup>3</sup> despite its low sensitivity because of frequent sampling errors and the lack of quantitative diagnostic criteria,<sup>4–7</sup> remains the best way to diagnose myocarditis. Recent papers showed that myocarditis can masquerade as acute myocardial infarction.<sup>8–13</sup>

Our aim in this study was to define the role and diagnostic accuracy of endomyocardial biopsy in detecting myocardial inflammation

compatible with myocarditis in patients with chest pain and a normal coronary angiogram; we investigated whether immunohistochemical characterisation of inflammatory cells and molecular biological techniques could increase the sensitivity of the procedure.

## Methods

From January 1992 to 1998, we studied 12 patients admitted to the coronary care unit of Padua University with severe chest pain, ECG abnormalities, and an increase in serum creatine kinase and MB fraction suggestive of acute myocardial infarction, but who had normal coronary arteries on angiography. These patients then underwent endomyocardial biopsy to confirm the clinical diagnosis of myocarditis.

## CLINICAL AND HAEMODYNAMIC STUDY

The medical records of the 12 patients were carefully reviewed and the following clinical and haemodynamic data collected: age, sex, presence of cardiovascular risk factors, prodromal symptoms, ECG findings, echocardiograms on admission and on discharge, serum creatine kinase and MB fraction isoenzyme concentrations, serology, treatment, and follow up.

Diagnostic right and left heart catheterisation was carried out by the standard technique. Pressure in all the chambers was measured and

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Table 1 Clinical and ECG findings

Patient	Age(years)/ sex	IHD risk factors	Flu-like syndrome	ECG alterations on admission	CK-MB (peak)	Serology Ab titres	Days in hospital
1	27/male	None	Enteric	Anterior	234/12	Neg	22
2	21/female	None	Flu	Inferolateral	979/122	Infl A,B	16
3	22/male	Smoking	Enteric	Inferior	1186/83	Neg	9
4	26/male	None	Flu	Inferior	680/46	Neg	7
5	35/male	None	None	Anterolateral	660/66	EBV	10
6	24/female	Hormones	Fever	Inferolateral	661/77	Neg	13
7	35/male	Smoking	Fever	Lateral	847/59	Infl A,B	15
8	19/male	None	Flu	Inferior	572/95	Mycopl	10
9	18/male	None	Enteric	Lateral	2415/351	Neg	13
10	30/male	None	Flu	Anterolateral	774/20	Infl A,B	11
11	37/female	None	None	Lateral	246/30	Neg	17
12	56/female	Smoking	None	Anterior	221/50	NP	13

CK- MB, creatine kinase MB isoenzyme; EBV, Epstein-Barr virus; IHD, ischaemic heart disease; Infl A,B: influenza A, B virus; Mycopl, *Mycoplasma pneumoniae*; Neg, negative; NP, not performed.

the cardiac output determined by the Fick principle. Left ventricular end diastolic volume and ejection fraction were also calculated. Selective coronary angiography and right ventricular endomyocardial biopsy were performed.

#### ENDOMYOCARDIAL BIOPSY

Five biopsy specimens from the right side of the interventricular septum were obtained in each patient with a disposable Cordis biptome, using the long sheath technique and the femoral vein approach. In four patients a sample of frozen tissue was also available. Fixation was performed with microwave assistance.

Paraffin embedded serial sections 4  $\mu$ m thick were cut and routinely stained with haematoxy-

lin and eosin, trichrome Heidenhein, and periodic acid Schiff (PAS) stains. The Dallas criteria were used to diagnose the presence of myocarditis.<sup>4</sup>

In all the samples immunohistochemistry for the characterisation of inflammatory infiltrate was carried out using the following antibodies<sup>14</sup>: CD45 (Dako 1:20), CD43 (Dako 1:40), CD45RO (Dako 1:100), CD20 (Dako 1:100), CD68 (Dako 1:50), factor VIII (Dako 1:200), and anticytomegalovirus (Dako 1:50). The positivity of the antigen-antibody reaction was demonstrated using the avidin-biotin-peroxidase complex method. Sections of formalin fixed lymph nodes served as a positive control. Immunohistochemically stained lymphocytes were independently evaluated by two pathologists. Patients with on average at least 2.5 lymphocytes/high power field (400 $\times$  magnification) in the 10 fields counted were considered to have an inflammatory infiltration.<sup>15 16</sup>

Molecular analysis by polymerase chain reaction (PCR) was carried out in seven of the 12 patients to detect enterovirus, adenovirus, Epstein-Barr virus (EBV), cytomegalovirus, and influenza virus A and B. Total RNA and genomic/viral DNA were isolated simultaneously from fresh frozen or formalin fixed myocardial specimens using Tris saturated phenol (pH 6.6) RNAzol solution, as previously described.<sup>17</sup> The quality of the nucleic acid extraction was determined using glyceraldehyde-3-phosphate dehydrogenase primers for RNA<sup>18</sup> and  $\beta$  globin primers for DNA.<sup>19</sup> To evaluate the presence of the above mentioned viruses in the endomyocardial biopsies, PCR and reverse transcriptase (RT)-

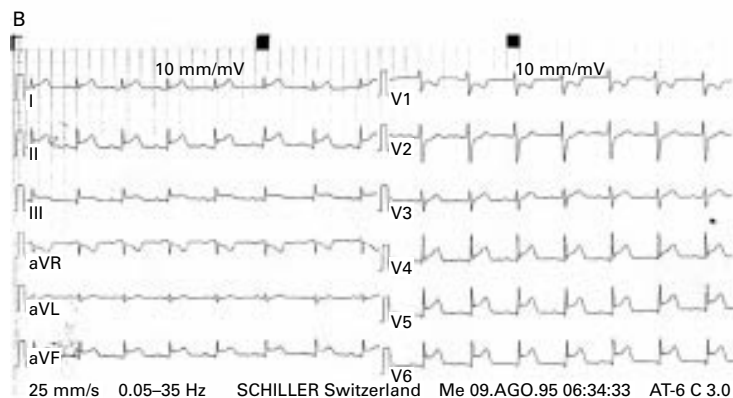
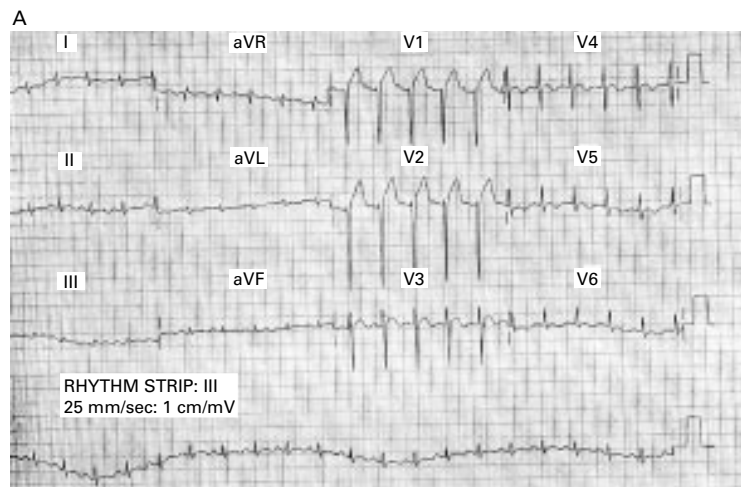


Figure 1 ECG traces on admission for patient 1 (A) and patient 6 (B). Note the ST segment elevation.

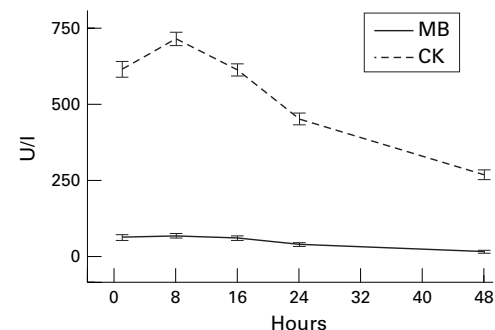


Figure 2 Time course of elevation of cardiac enzymes (creatinine kinase (CK) and MB isoenzyme fraction). Values are expressed as means, error bars = SEM.

Table 2 Echocardiographic findings

Patient	On admission				On discharge			
	LVEDV	LVEF	Pericardium	LV alterations	LVEDV	LVEF	Pericardium	LV alterations
1	90	40	Mild effusion	Diffuse	50	72	Normal	None
2	60	73	Echogenicity	None	55	70	Echogenicity	None
3	Not available				95	65	Echogenicity	None
4	Not available				48	66	Normal	None
5	63	56	Echogenicity	None	73	67	Echogenicity	None
6	59	57	Normal	Apex	53	63	Normal	None
7	89	44	Normal	Diffuse	56	48	Normal	Septum
8	Not available				64	71	Normal	None
9	105	45	Echogenicity	Diffuse	73	69	Echogenicity	None
10	63	68	Normal	None	70	65	Normal	None
11	68	34	Mild effusion	Apex	50	68	Echogenicity	None
12	49	56	Normal	Apex	Not available			

LVEDV, left ventricular end diastolic volume (ml/m<sup>2</sup>); LVEF, left ventricular ejection fraction (%); LV, left ventricle.

PCR were performed using primers and conditions previously reported.<sup>17 20 21</sup>

### Results

The clinical data and ECG findings are summarised in table 1. The mean (SD) age of the patients was 29 (10) years (range 18–56 years). Four patients had a risk factor for ischaemic heart disease: smoking in three and oral contraceptive use in one. Nine patients reported an acute viral infection shortly before admission.

All the patients were admitted to hospital because of persistent typical anginal chest pain suggestive of an acute myocardial infarct. None showed signs of congestive heart failure. No pericardial friction rub was detected in any of the patients. The ECG findings on admission (fig 1) showed anterior ST segment elevation in two patients, anterolateral in two, lateral in three, inferolateral in two, and inferior in three. Peak creatine kinase and MB isoenzyme fraction ranged from a minimum of 234/12 U/l to a maximum of 2415/350 U/l. The time course of the elevation of the cardiac enzymes showed that the peak occurred in all patients within 16 hours of hospital admission; complete normalisation of these variables was observed within 48 hours in all except the two cases (patients 2 and 9) who had the highest values on admission (fig 2). Serum titres of IgM antibodies for detecting infectious agents were significantly raised for influenza virus A and B in three patients, for *Mycoplasma pneumoniae* in one, and for EBV in one.

Echocardiographic findings on admission are given in table 2. Data were available for nine patients. Global hypokinesia of the left

ventricle was present in three patients, and hypokinesia confined to the inferior apical region in a further three. In three patients no abnormalities could be detected. A decrease in left ventricular contractility (ejection fraction < 50%) was seen in four patients, and was associated with left ventricular dilatation in only one of these. A pericardial effusion or increase in pericardial echogenicity were present in five of the nine patients investigated. By the time of discharge, left ventricular function had normalised in all but one patient, who retained a mild reduction of the ejection fraction.

Haemodynamic data are summarised in table 3. Catheterisation was performed within 11 days after admission. Left ventriculography revealed normal ventricular contraction in four patients, global hypokinesia in four, and segmental hypokinesia in four. The mean (SD) ejection fraction was 54 (8)% (range 40–68%), and it was less than 45% in only two patients. Left ventricular end diastolic volume ranged from 45 to 105 ml/m<sup>2</sup> (mean 75 (20) ml/m<sup>2</sup>), and there was evidence of mild left ventricular dilatation in three patients (> 90 ml/m<sup>2</sup>). Left ventricular end diastolic pressure was > 14 mm Hg in six patients (mean 14.9 (6.5) mm Hg, range 5–25 mm Hg), while mean pulmonary artery pressure was normal. Cardiac index was preserved in all the patients (mean 3.7 (0.7) l/min/m<sup>2</sup>, range 2.9–4.8 l/min/m<sup>2</sup>). Selective coronary angiography showed normal coronary arteries in all the patients. No vasospasm was inducible in any patient. When we compared the site of ECG abnormalities with the areas of depressed contractility at ven-

Table 3 Haemodynamic findings

Patient	EMB (day)	LVEDP	PAP	CI	LVEDV	EF	Hypokinesia
1	2	20	18	3.2	63	40	Global
2	11	5	10	4.8	71	68	Absent
3	1	20	20	4.1	98	44	Global
4	0	12	15	3.5	79	55	Absent
5	2	10	10	4.7	105	55	Ant-lat, apex
6	2	20	11	4.6	54	47	Apex
7	3	20	20	3.4	78	58	Global
8	0	25	20	3.1	103	58	Posterior apex
9	1	10	12	3.6	73	45	Global
10	14	7	8	4.0	90	59	Absent
11	8	20	8	2.9	45	65	Absent
12	11	10	15	2.9	49	56	Ant-lat

Ant-lat, anterolateral; CI, cardiac index (l/min/m<sup>2</sup>); EF, ejection fraction (%); EMB, endomyocardial biopsy; LVEDP, left ventricular end diastolic pressure (mm Hg); LVEDV, left ventricular end diastolic volume (ml/m<sup>2</sup>); PAP, pulmonary artery pressure (mm Hg).

Table 4 Endomyocardial biopsy findings

Patient	Timing (days)	Dallas criteria	Fibrosis	CD45	CD20	CD43	CD45RO	CD68	PCR
1	2	ALM	No	+	-	+	+	+	NP
2	11	Neg	+	+	-	-	-	-	NP
3	1	ALM	+	+	-	+	+	+	NP
4	0	Neg	+	-	-	-	-	-	NP
5	2	Neg	+	+	-	+	+	+	EBV
6	2	Neg	No	+	-	-	+	-	Neg
7	3	ALM	+	+	-	+	-	+	Neg
8	0	Neg	+	+	-	+	+	-	NP
9	1	ALM	No	+	-	+	+	+	Neg
10	4	BM	+	+	-	-	+	+	Neg
11	8	ALM	+	+	-	+	+	+	Neg
12	11	ALM	No	+	-	+	+	+	EBV

ALM, active lymphocytic myocarditis; BM, borderline myocarditis; Neg, negative; NP, not performed; PCR, polymerase chain reaction.

triculography, we found concordant results in four patients and discordant results in the remainder.

The endomyocardial biopsy findings are summarised in table 4. Active myocarditis according to the Dallas criteria was diagnosed in six patients (fig 3A) and borderline myocarditis in one. Of these patients, four had global hypokinesia on echocardiography or ventricu-

lography, and two had regional hypokinesia. The ejection fraction evaluated at cardiac catheterisation did not differ significantly between patients with a positive biopsy and those with a negative biopsy, at 52.4 (9.3)% *v* 56.6 (7.6)%. In all seven cases with a diagnosis of myocarditis according to the Dallas criteria (six active, one borderline), immunohistochemical characterisation of the inflammatory cell infiltrate revealed positivity for CD45 (common leucocyte antigen) (fig 3B), CD43 (T and B lymphocytes) (fig 3C), CD45RO (activated T lymphocytes), and CD68 (monocytes/macrophages) (fig 3D), and negative staining for CD20 (B lymphocytes). In four of the remaining five cases, which were negative according to the Dallas classification, immunohistochemistry showed the presence of an inflammatory infiltrate. Thus in only one of the 12 patients no inflammation was detectable in the myocardium.

PCR was positive for  $\beta$  globin in all seven samples tested, confirming that a sufficient amount of DNA was extracted and analysed in each sample. Positive RT-PCR for glyceraldehyde-3-phosphate dehydrogenase was obtained in three of the seven samples tested. In the remaining four patients (one of whom had positive influenza virus serology), no or only weak amplicons were obtained. In two patients PCR was positive for viral genome: in both these cases EBV genome was found (fig 4); one also had an increase in EBV serum antibody titres.

Two patients received thrombolytic treatment with alteplase, intravenous heparin infusion, and glyceryl trinitrate within six hours of the onset of chest pain, without complications. Six patients received anti-inflammatory treatment afterwards: one with active lymphocytic myocarditis received corticosteroids at immunosuppressive doses for a short period; the others received indomethacin and aspirin.

Chest pain resolved within the first day. On discharge, none of the patients had Q waves on their ECG recordings, though ECG abnormalities persisted in the three patients who had negative T waves on admission. All patients were discharged in New York Heart Association functional class I within 13 (4) days.

## Discussion

In this paper we evaluated retrospectively 12 consecutive patients admitted to our intensive

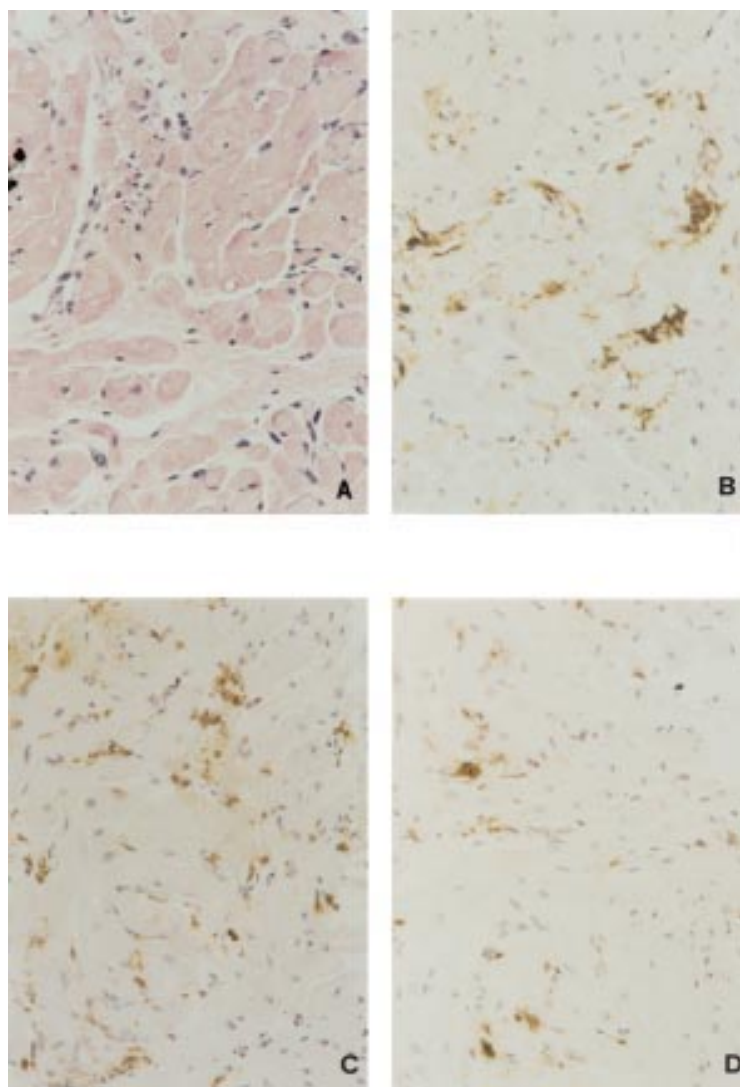
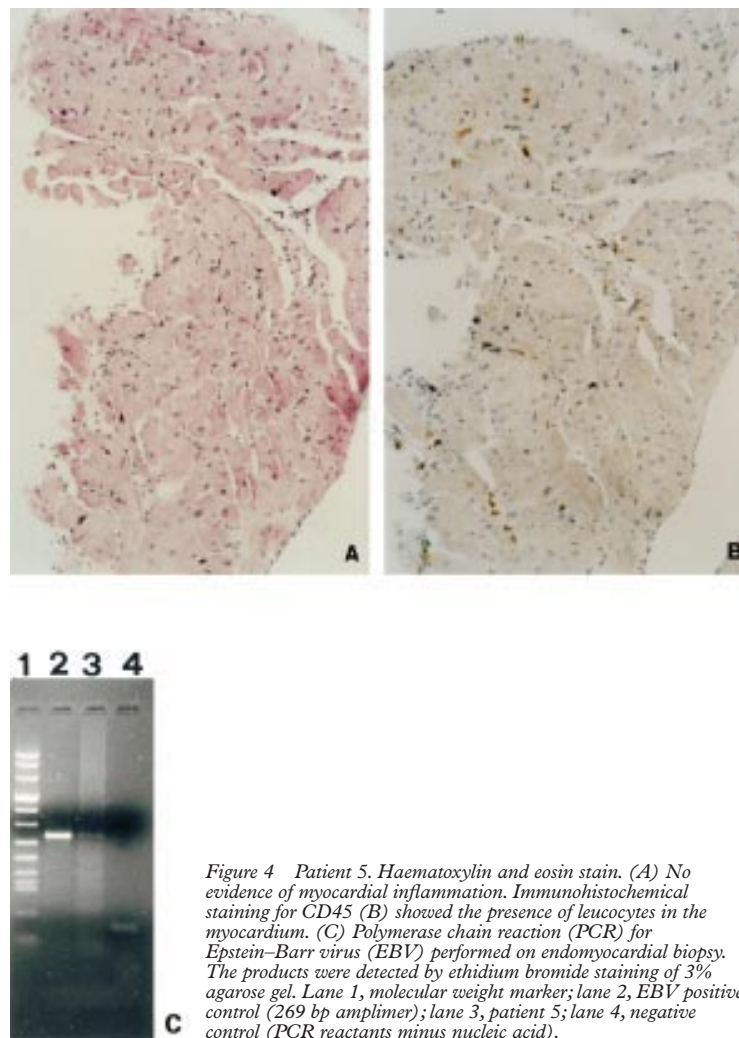


Figure 3 Patient 9: active lymphocytic myocarditis. Haematoxylin and eosin stain. (A) Inflammatory infiltrate surrounding a few necrotic myocytes. Immunohistochemical staining for CD45 (leucocytes) (B), for CD43 (lymphocytes) (C), and for CD 68 (macrophages) (D) confirmed the presence of inflammatory cells within the myocardium.





**Figure 4** Patient 5. Haematoxylin and eosin stain. (A) No evidence of myocardial inflammation. Immunohistochemical staining for CD45 (B) showed the presence of leucocytes in the myocardium. (C) Polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) performed on endomyocardial biopsy. The products were detected by ethidium bromide staining of 3% agarose gel. Lane 1, molecular weight marker; lane 2, EBV positive control (269 bp amplicon); lane 3, patient 5; lane 4, negative control (PCR reactants minus nucleic acid).

care unit with chest pain, ECG abnormalities compatible with acute myocardial infarction, creatine kinase elevation, and a normal coronary angiogram, all of whom underwent endomyocardial biopsy. In such cases it is essential to consider the differential diagnosis between myocardial infarction and other causes of chest pain. Myocarditis is often neglected in this regard, but it needs to be taken into account owing to its heterogeneous presentation. It is known that such cases may mimic acute myocardial infarction in their clinical and ECG pattern.<sup>8-10</sup> To test the hypothesis that our patients could have been suffering from myocarditis, we performed endomyocardial biopsies in all of them, using the Dallas criteria<sup>4</sup> for evaluation. On this basis myocarditis could be detected in only seven of the 12 patients—active in six and borderline in one. The sensitivity of the Dallas criteria has often been questioned.<sup>7</sup> Thus our next diagnostic step was to use immunohistochemical techniques to allow more sensitive detection and characterisation of inflammatory infiltrates.<sup>15 16 22</sup> In four of the five patients who did not fulfil the Dallas criteria, immunohistochemistry showed the presence of an inflammatory infiltrate in the myocardium characterised by T lymphocytes and macrophages, thus

excluding the possibility of acute ischaemia, which is characterised by a polymorphonuclear neutrophil infiltrate. In our study we tried to increase the diagnostic accuracy further by performing PCR for viruses<sup>23 24</sup> in the biopsy samples from seven of the patients. Two of these turned out to be positive for EBV. Even though EBV infection is common in the general population, cardiac involvement is infrequent and most cases follow an uncomplicated course.

Although the number of our cases was small, the detection of the EBV genome in two of them is of some interest. Previous studies have stressed the frequent non-specific ECG abnormalities found in patients with infectious mononucleosis.<sup>25 26</sup> To our knowledge, only four cases of EBV related myocarditis have been reported so far.<sup>27-29</sup> An aberrant immune response rather than a direct severe viral cytotoxic effect—as suggested by some investigators—could be responsible for an imbalance of inflammatory cytokines.<sup>20</sup>

We cannot exclude the possibility that the two patients with positive influenza virus serology had myocarditis caused by this virus. Unfortunately, in one of these cases PCR for RNA viruses was unsuccessful, and in the other, PCR was not performed owing to lack of adequate biopsy material. This highlights the need to obtain sufficient biopsy material at the time of the endomyocardial biopsy to investigate all the cardiotropic viruses.

The presence of an inflammatory infiltrate on immunohistochemical analysis, together with a positive PCR for myocardial virus genome, increases the diagnostic accuracy of endomyocardial biopsy in cases where the Dallas criteria would otherwise have failed to detect and characterise an inflammatory disease. Myocarditis was excluded in only one of our cases, on the basis that it was negative on both immunohistochemical and molecular analysis.

Our patients showed symptoms and ECG signs which made it necessary for the clinicians to consider the differential diagnosis between myocarditis and ischaemic heart disease. The non-specific character of the presentation was confirmed by the fact that even in the seven patients with a histological diagnosis of myocarditis based on the Dallas criteria no clinical features suggesting the correct diagnosis could be identified retrospectively. For example, the ECG abnormalities were not diffusely present in the precordial leads but were regionally distributed, even though haemodynamic studies showed global involvement of the heart.

Miklozek and colleagues reported 10 patients with acute myocarditis and apparent clinical signs of acute myocardial infarction.<sup>9</sup> Dec and associates described 34 patients presenting symptoms of acute myocardial infarction and normal coronary arteries<sup>8</sup>; they reported a 33% incidence of myocarditis diagnosed by endomyocardial biopsy using the Dallas criteria. Both groups stressed the need for an endomyocardial biopsy in pursuing the differential diagnosis. In the recent international myocarditis treatment trial,<sup>30</sup> only 200 of 2000 endomyocardial biopsies performed on

the basis of the clinical diagnosis of myocarditis were positive by the Dallas criteria. In this international trial, the patients were enrolled in the study if they had had symptoms in the two previous years, while in our study the biopsy was done at a mean of 3.5 (3.9) days from the onset of symptoms. The timing of the biopsy might well influence its sensitivity. One would expect that it would be better to perform it in the early phase of the disease, at the onset of symptoms, when viral invasion produces local myocardial damage with an inflammatory response accompanied by recruitment of cytolytic T lymphocytes and cytokine production. In fact, Friedrich and colleagues, using contrast medium enhanced magnetic resonance, showed that acute myocarditis evolves from a focal to a disseminated process during the first two weeks after the onset of symptoms, thus potentially increasing the sensitivity of endomyocardial biopsy performed in the earlier phase of the disease.<sup>31</sup>

As clinical, angiographic, and ECG criteria are insufficient for a definitive diagnosis of myocarditis, endomyocardial biopsy is of crucial importance and may influence the clinical management of these patients. Myocarditis resulting in mild left ventricular dysfunction does not require any specific treatment, but if the diagnosis is established, the chronic inappropriate use of drugs for the management of unusual forms of ischaemic heart disease—such as coronary artery vasospasm or occult coronary artery disease—can be avoided. Moreover the risk of complications from the endomyocardial biopsy procedure is very low. In our centre there have been no fatal complications and only 0.06% non-fatal complications in nearly 1300 biopsies performed. Our experience indicates that a combined approach which includes assessment of the Dallas criteria, immunohistochemistry for the characterisation of the inflammatory infiltrates, and PCR for virus detection represents the new gold standard.

#### LIMITATIONS

This was a retrospective study carried out on a selected population, in which we evaluated only those patients admitted to the coronary care unit with suspected myocardial infarction but normal coronary angiography, who then underwent endomyocardial biopsy.

#### CONCLUSIONS

Myocarditis in young patients with suspected myocardial infarction and normal coronary arteries may be more common than previously thought and has a good prognosis. Endomyocardial biopsy is strongly recommended for the detection of myocarditis, and its sensitivity may be further increased by the application of immunohistochemical and molecular biological techniques.

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