Endomyocardial Biopsy

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Abbreviations and Acronyms

CMR	Cardiac magnetic resonance
CS	Cardiac sarcoidosis
DCM	Dilated cardiomyopathy
EMB	Endomyocardial biopsy
HSM	Hypersensitivity myocarditis
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
LVEDVi	Left ventricular end-diastolic volume index
LVEF	Left ventricular ejection fraction
PCR	Polymerase chain reaction
PET	Positron emission tomography
RV	Right ventricular

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9.1 Introduction

Endomyocardial biopsy (EMB) is a useful diagnostic tool for the investigation and treatment of myocardial diseases. The introduction of the transvascular endomyocardial bioptome by Konno and Sakakibara in 1962 [1] has been an important breakthrough in the EMB and in the in vivo diagnosis of heart muscle diseases. EMB has spread in subsequent years due to the availability of new and better devices, to the improved skill of the operators and to the development of new and more sophisticated methods of diagnosis.

In the first years, opinions on the use and on the usefulness of EMB in myocardial diseases were conflicting. Ferrans and Roberts [2], as early as 1978, concluded that in patients with suspected dilated cardiomyopathy (DCM), the technique is "informative" but of limited "diagnostic value". In spite of recurrent variations of opinions on the use and usefulness of EMB in myocardial diseases, its expansion gave the cardiologist the possibility of increasing the understanding about the histology of heart muscle disease, with an important role in the diagnosis of acute myocarditis.

The main use of EMB is the routine surveillance for rejection of a transplanted heart, but this scenario is outside the scope of this report.

9.2 Technique

Early EMBs were usually performed from the right ventricle (RV) and subsequently also from the left ventricle (LV). Although there are no clear recommendations, in our experience an approach based on the clinical question is preferred [3, 4], also considering the procedural feasibility in the individual patient (e.g. presence of left ventricular thrombosis, aortic valvular prosthesis or intra-aortic balloon pump).

In the largest head-to-head comparison study, complication rates for LV (0.33%) and RV (0.45%) EMB were comparable [5]. Actual techniques enable to perform multiple drawings of tissue samples from both ventricles with low incidence of procedural complications, but this is mostly dependent by the expertise of the operator.

Fluoroscopy is the most useful imaging modality and is often sufficient, but two-dimensional and three-dimensional echocardiography are increasingly being used to accurately direct biopsy forceps and reduce the likelihood of perforation or recurrent biopsy of the same area [6].

For the RV EMB, the right internal jugular vein is the most common access route. Alternative approaches include femoral vein, using longer bioptomes, and subclavian and brachial veins. Once in the right atrium, anticlockwise rotation might be needed to traverse the tricuspid valve, and then clockwise rotation will bring the tip with the open jaws into contact with the ventricular septum, the preferred site for EMB because of safety problems (direction of rotation should be reversed if approaching from the femoral vein). Going on in the ventricular chamber with open jaws reduces the perforation risk because it uses a greater contact surface. Confirmation of positioning on the septum can be made using contrast injection by the long sheath. Resistance can be appreciated by the operator and only gentle forward pressure is required. Ventricular ectopy or non-sustained ventricular

tachycardia is common while the bioptome is in contact with the ventricular myocardium. The forceps should be closed and pulled away from the heart carefully, at which point a small amount of tension might be felt as the sample is removed [6]. The LV can be reached in two ways, in a retrograde direction from the aorta or via trans-septal puncture (uncommon). Currently, the typical approach for EMB is still via the femoral artery, but transradial access is increasingly adopted, particularly in patients with a significant bleeding risk. General advice about steering the bioptome is as for the right ventricle. Crossing the aortic valve is performed in the routine way, using a pigtail catheter into the long sheath to enter the LV. A ventriculography in the left anterior oblique projection should allow positioning of the sheath in the midcavity so that the bioptome forceps can open free of the ventricular wall. Before the procedure i.v. heparin is given to target an activated clotting time of 250–300 s to reduce the risk of embolism [6]. Technique for sampling the myocardium itself is as per RV EMB, with particular care to avoid damaging mitral valve apparatus. The sheath should be aspirated and flushed between each sample as the risk and consequence of air or tissue embolism is ostensibly higher than in the RV [7]. The median number of bioptic samples per patient is 4 (minimum–maximum, 1–6).

False-negative results are possible, particularly with multifocal or microfocal localized diseases (Table 9.1) [8]. Conflicting data exist regarding the benefit of cardiac magnetic resonance (CMR)-guided targeting of areas of late gadolinium enhancement [6]. An analysis of 540 patients undergoing CMR and EMB demonstrated no additional diagnostic yield when targeting areas of late gadolinium enhancement [3, 7].

Table 9.1 Indications and pitfalls of endomyocardial biopsy

Indications for endomyocardial biopsy	Pitfalls of endomyocardial biopsy
• Suspected myocarditis in patients with high-risk syndromes (cardiogenic shock, refractory heart failure or left ventricular dysfunction with LVEF <40% despite conventional therapy, persistent life-threatening ventricular arrhythmias) • Suspected giant cell myocarditis or eosinophilic myocarditis • Suspected cardiac sarcoidosis[a] • Suspected end-stage HCM • Suspected infiltrative cardiomyopathy[b] • Out-of-hospital cardiac arrest without significant coronary artery disease • Monitoring cardiac transplant rejection status • Histological diagnosis of cardiac tumors[c]	Diagnostic accuracy of EMB depends on: • Expertise of operator who performs the procedure • Timing of the procedure related to beginning of patient symptoms • Biopsy site (RV or LV) • Number of bioptic samples • Expertise of pathologist who analyses the samples • Patchy diseases

[a]In cardiac sarcoidosis (CS), the EMB has low sensitivity due to the focal nature of the disease, revealing non-caseating granulomas in less than 25% of patients with CS [30]

[b]In cardiac amyloidosis, the role of EMB has been resized by the recent implementation of non-invasive diagnostic technique as CMR, positron emission tomography (PET) and single-photon emission computed tomography (SPECT)

[c]Following characterization of a cardiac tumour, our multidisciplinary care team, which include cardiologists, radiologists, oncologists and cardiac surgeons, sit down together to develop an individualized treatment plan in order to achieve the optimal outcome. In general, patients with a primary cardiac tumour require surgical resection

9.3 Complications

EMB is invariably characterized by a mild, but not negligible, rate of major complications (around 1%) even when performed by experienced operators [3, 5, 9]. Complications include vasovagal syncope, vascular damage, pneumothorax, supraventricular and ventricular arrhythmias, heart block, damage to the tricuspid valve, ventricular perforation, pericardial tamponade, coronary-cameral fistula formation, bleeding complications and pulmonary and systemic embolism [6]. The risks of EMB likely vary with the experience of the operator, clinical status of the patient, presence or absence of left bundle branch block, access site and possibly bioptome. An echocardiographic control and a low dose of heparin are useful to minimize the risk of systemic embolism during LV EMB [10].

The death associated with EMB is possible and can be the result of perforation with pericardial tamponade [11]. Patients with increased right ventricular systolic pressures, bleeding diathesis, recent receipt of heparin or right ventricular enlargement seem to be at higher risk in case of RV EMB.

9.4 Indications in DCM Scenarios

EMB is an invasive procedure, and for this reason it is fundamental a correct selection of patients to undergo this diagnostic technique. In addition to some particular clinical contexts as after heart transplantation or suspected infiltrative disorders with heart failure presentation such as amyloidosis, the most frequent indication to EMB is suspected acute myocarditis in patients with "major" symptoms (DCM with mildly dilated left ventricle, recent-onset heart failure with relevant left ventricular dysfunction, sustained ventricular arrhythmias) [Fig. 9.1; Case I–IV; Figs. 9.2, 9.3, 9.4 and 9.5] [4].

Myocarditis is an inflammatory process affecting the myocardium that can be caused by infectious agents like virus, bacteria, rickettsia, protozoa and fungi but can be caused also by other agents like toxins, medications and autoimmune phenomena. It is characterized by extreme variability in clinical presentation and ensuing evolution, including a presentation as DCM with severe systolic dysfunction. This variability necessitates patient-tailored diagnostic and therapeutic management in which the advanced and often costly testing and treatments are reserved for those with the most severe and threatening clinical presentation.

Histopathologic analysis of myocardial tissue samples collected with EMB is the only way to definitively diagnose myocarditis. International recommendations about EMB implementation in clinical practice are controversial. The American College of Cardiology/American Heart Association guidelines recommend EMB in patients with severe clinical presentation in terms of recent heart failure or life-threatening arrhythmias [10, 12]. Conversely, the position statement on the diagnosis and management of myocarditis by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases expanded the spectrum of EMB indications, recommending this test for all cases of clinically suspected myocarditis

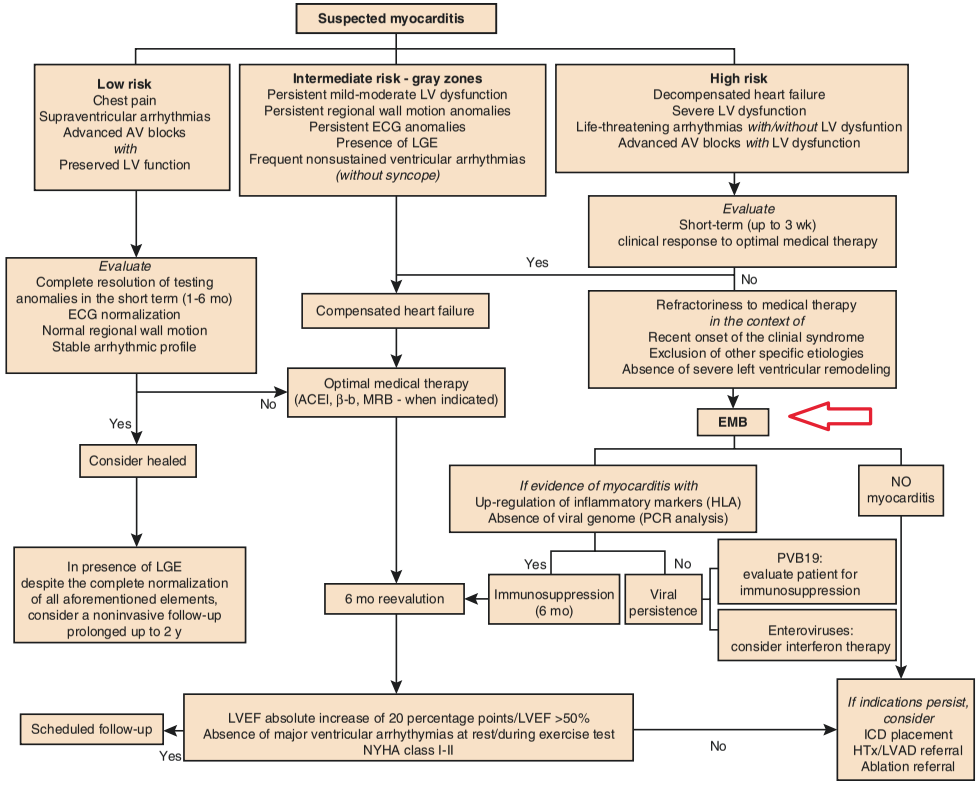

Fig. 9.1 Proposal for clinical management of patients with suspected myocarditis: the role of EMB. Modified from Sinagra G, et al. M. Myocarditis in Clinical Practice. Mayo Clin Proc. 2016 Sep;91(9):1256–66. *ACEI* angiotensin-converting enzyme inhibitor, *AV* atrioventricular, *b-b* b-blocker, *ECG* electrocardiographic, *EMB* endomyocardial biopsy, *HLA* HLA antigen, *HTx* heart transplant, *ICD* implantable cardioverter-defibrillator, *LGE* late gadolinium enhancement, *LV* left ventricular, *LVAD* LV assist device, *LVEF* LV ejection fraction, *MRB* mineralocorticoid receptor blocker, *NYHA* New York Heart Association, *PCR* polymerase chain reaction, *PVB19* parvovirus B19

regardless of the pattern and severity of clinical presentation [13]. In clinical practice, the value of EMB becomes crucial in detecting the specific histotype of the myocarditis and assessing the immunologic and virologic status of the myocardium through immunohistochemical and biomolecular PCR (polymerase chain reaction) analyses.

Hence, EMB should be performed for the in-depth evaluation of suspected myocarditis with recent-onset high-risk major clinical syndromes (heart failure and/or life-threatening arrhythmias, in particular when associated with severe left ventricular dysfunction), not responding to standard optimized medical therapy in the short term (from hours to 2 weeks after admission, on the basis of clinical status severity) [10]. The in-depth characterization of the myocardial substrate can provide the guide for a biopsy-driven therapeutic plan [14, 15]. Conversely, the value of EMB is questionable in patients presenting with low-risk syndromes and responding to standard care [8]. Finally, in the setting of intermediate-risk syndromes (presence of structural or functional abnormalities, such as mild-to-moderate ventricular dysfunction, persistent wall motion or ECG abnormalities, late gadolinium enhancement in the absence of severe left ventricular dysfunction and remodelling on cardiac magnetic resonance imaging or frequent non-sustained ventricular arrhythmias), EMB should be considered on a case-by-case basis according to the clinical status of the patient, the presence of extensive structured myocardial involvement and when findings on cardiac magnetic resonance imaging cannot be considered conclusive [4]. In particular, EMB could be useful in diagnosing cardiac sarcoidosis or giant cell myocarditis allowing to plan an appropriate therapeutic management [3, 16]. In this setting, unexplained heart failure of >3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree AV heart block, or failure to respond to usual care within 1–2 weeks can be the clinical presentation of cardiac sarcoidosis or idiopathic granulomatous myocarditis. EMB is reasonable in this clinical setting (class of recommendation 2a, level of evidence C) [10]. Interestingly, cardiac involvement is present in about 25% of patients with systemic sarcoidosis [17], but symptoms referable to cardiac sarcoidosis occur in only 5% of sarcoid patients [18, 19], and up to 50% of patients with granulomatous inflammation in the heart have no evidence of extracardiac disease. Patients with cardiac sarcoidosis sometimes may be distinguished from those with DCM by a high rate of heart block (8–67%) [4].

Suspected eosinophilic myocarditis can be another setting in which EMB can help to define the specific diagnosis. Eosinophilic myocarditis is associated with the hypereosinophilic syndrome and it typically evolves over weeks to months. The presentation is usually biventricular heart failure, although arrhythmias may lead to sudden death. Usually hypereosinophilia precedes or coincides with the onset of cardiac symptoms, but the eosinophilia may be delayed [20]. Eosinophilic myocarditis may also occur in the setting of hypersensitivity myocarditis (HSM), malignancy or parasite infection and early in the course of endocardial fibrosis. Early

suspicion and recognition of HSM may lead to withdrawal of offending medications and administration of high dosage of corticosteroids. The hallmark histological findings of HSM include an interstitial infiltrate with prominent eosinophils with little myocyte necrosis; however, granulomatous myocarditis, or necrotizing eosinophilic myocarditis, may also be a manifestation of drug hypersensitivity [21] and may be distinguished from common forms of HSM only by EMB.

Moreover, the degree of fibrosis seen on EMB can be correlated with a poorer prognosis in terms of major adverse cardiovascular events (defined as cardiovascular death, an arrhythmic event and heart failure-related hospital admission) [22].

In conclusion, while in the past EMB was used more extensively in DCM patients also only for the detection of a histological typical pattern like cell involutive aspects and fibrosis, without a direct gain in terms of therapy, now the indications in DCM are limited to some selected cases (Table 9.1).

9.5 Diagnosis of Myocarditis

EMB, using standardized histopathological [23] and immunohistochemical diagnostic criteria, is the current gold standard by which a diagnosis of myocarditis is made. The Dallas criteria define active myocarditis as an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes. The infiltrates are usually lymphocytic but might be neutrophilic or, occasionally, eosinophilic and almost always include macrophages [see Case I–IV]. "Borderline myocarditis" is the term used when the inflammatory infiltrate is too sparse or myocyte injury is not demonstrated [23]. The Dallas criteria are limited, however, by virtue of a high degree of interobserver variability in pathological interpretation and the inability to detect noncellular inflammatory processes and yield diagnostic information in only 10–20% of patients [24, 25]. Therefore, immunohistochemistry with the use of a large panel of monoclonal and polyclonal antibodies is now obligatory to differentiate the inflammatory components present and the immunological processes activated [13]. According to the WHO definition, active myocarditis is present with immunohistochemical detection of focal or diffuse mononuclear infiltrates (T lymphocytes and macrophages) using a cut-off of >14 cells per mm^2, in addition to increased expression of HLA class II molecules [26]. Molecular detection of viral genomic sequences in diseased myocardium is also feasible and, when coupled with immunohistochemical analysis, increases the diagnostic accuracy of EMB in addition to providing an aetiology and offering prognostic information [5, 27, 28]. Information about the safety of particular treatments can also be gleaned from data obtained via EMB. Detection of specific HLA markers on EMB tissue sections combined with the absence of infectious agents (PCR-negative for viral genome) suggests either primary or postinfectious immune-mediated myocarditis, at which point immunosuppression might be considered [29].

9.6 Examples of Endomyocardial Biopsy

9.6.1 Case I (J.D.)

EMB of patient (J.D., 30 years old, M) admitted with fulminant myocarditis with need of inotropes and intra-aortic balloon pump (IABP). Initial left ventricular ejection fraction (LVEF) 27%, left ventricular end-diastolic diameter (LVEDD) 56 mm and left ventricular end-diastolic volume index (LVEDVi) 39 mL/m^2. Discharged after 2 weeks with LVEF 65%. LVEF at 15 months of follow-up 62% (Fig. 9.2).

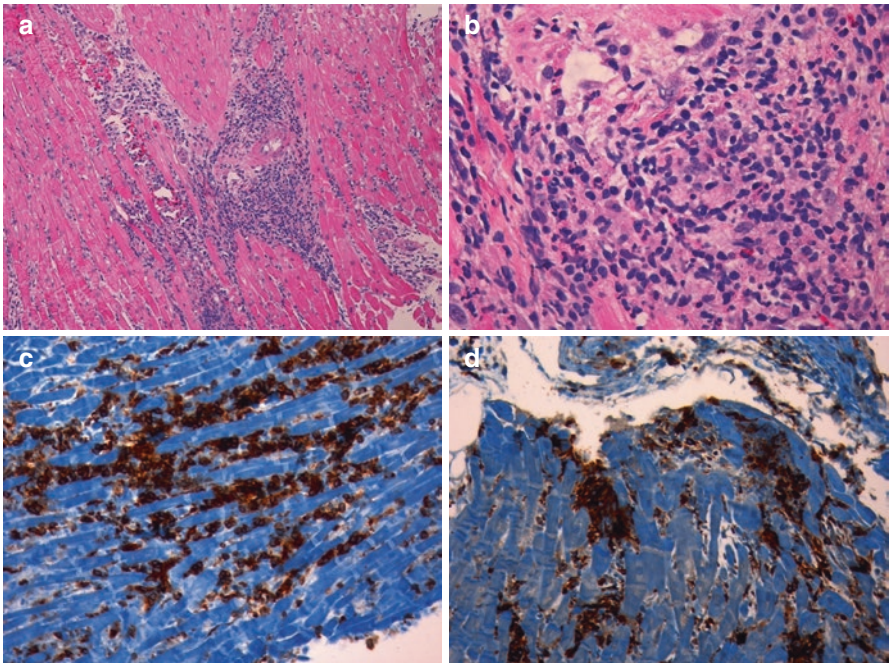

Fig. 9.2 (**a**, **b**) The haematoxylin-eosin (H&E) stain shows diffuse myocardial inflammatory infiltrates (lymphocytes, granulocytes, eosinophils) with some granulomatous pattern (**a**, H&E ×10; **b**, H&E ×40). (**c**) Myocardial interstitium with diffuse infiltrates of CD4-positive T cells (CD4 ×40). (**d**) High expression of HLA-DR by inflammatory elements (HLA-DR ×20)

9.6.2 Case II (C.P.)

EMB of patient (C.P., 52 years old, F) admitted with fulminant myocarditis with need of inotropes and non-invasive ventilation (NIV). Initial LVEF 36%, LVEDD 45 mm, LVEDVi 37 mL/m^2. Discharged after 2 weeks with LVEF 49%. LVEF at 2 years of follow-up 54% (Fig. 9.3).

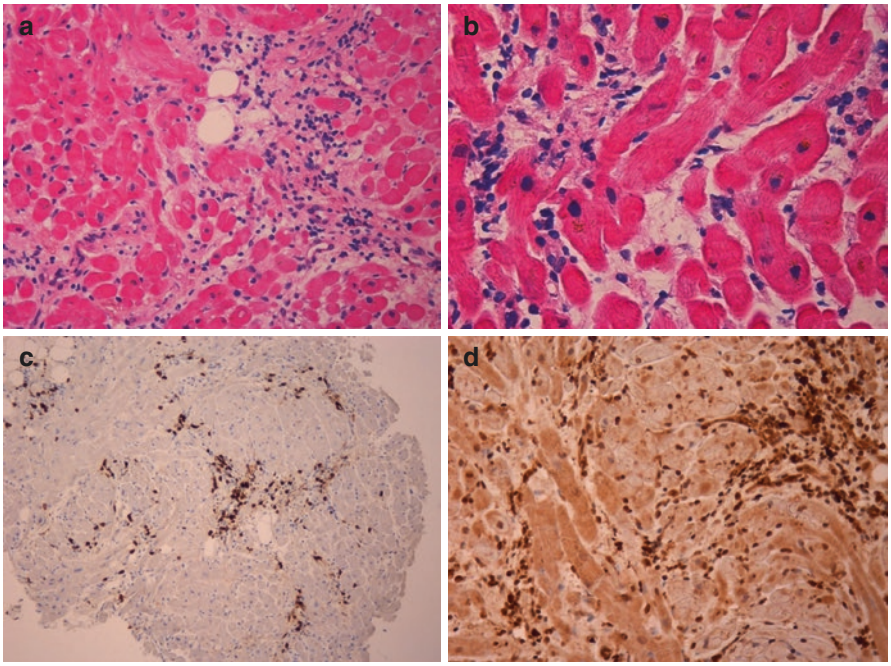

Fig. 9.3 (**a**, **b**) The haematoxylin-eosin (H&E) stain shows diffuse myocardial lympho-histiocytic infiltrates associated with myocyte degeneration, fraying and myocyte necrosis. The myocardial interstitium appears wide with abundant oedema and mild fibrosis (newly formed) (**a**, H&E ×20; **b**, H&E ×40). (**c**) Myocardial interstitium with diffuse infiltrates of CD8-positive suppressor cells (CD8 ×10). (**d**) High expression of HLA-DR by inflammatory elements, endothelium and myocytes (HLA-DR ×20)

9.6.3 Case III (C.S.)

EMB of patient (C.S., 51 years old, M) admitted with non-fulminant myocarditis. Initial LVEF 29%, LVEDD 62 mm, LVEDVi 80 mL/m^2. Discharged after 12 days with LVEF 28%, LVEDD 63 mm, LVEDVi 93 mL/m^2. LVEF at 3 years of follow-up 43% (Fig. 9.4).

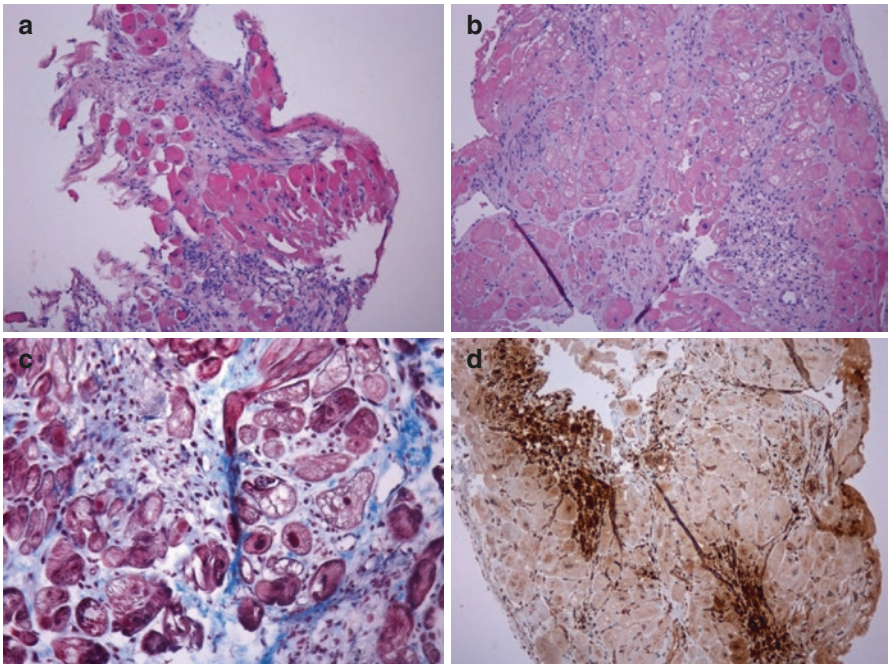

Fig. 9.4 (**a**, **b**) The haematoxylin-eosin (H&E) stain shows many myocardial lympho-histiocytic infiltrates, some of them localized in a wide fibrotic matrix. The EMB shows also cell involutive aspects (hypertrophic cells and/or cells with loss of contractile proteins) (**a**, H&E ×10; **b**, H&E ×10). (**c**) Mallory's trichrome stain shows interstitial fibrosis and severe involutive aspects of myocells (Mallory Trichrome ×20). (**d**) Diffuse myocardial lympho-histiocytic infiltrates (CD68 KP1 ×10)

9.6.4 Case IV (C.F.)

EMB of patient (C.F., 61 years old, M) admitted with non-fulminant myocarditis. Initial LVEF 27%, LVEDD 70 mm, LVEDVi 92 mL/m^2. Discharged after 21 days with LVEF 26%, LVEDD 71 mm, LVEDVi 97 mL/m^2. LVEF at 1 year of follow-up 49% (Fig. 9.5).

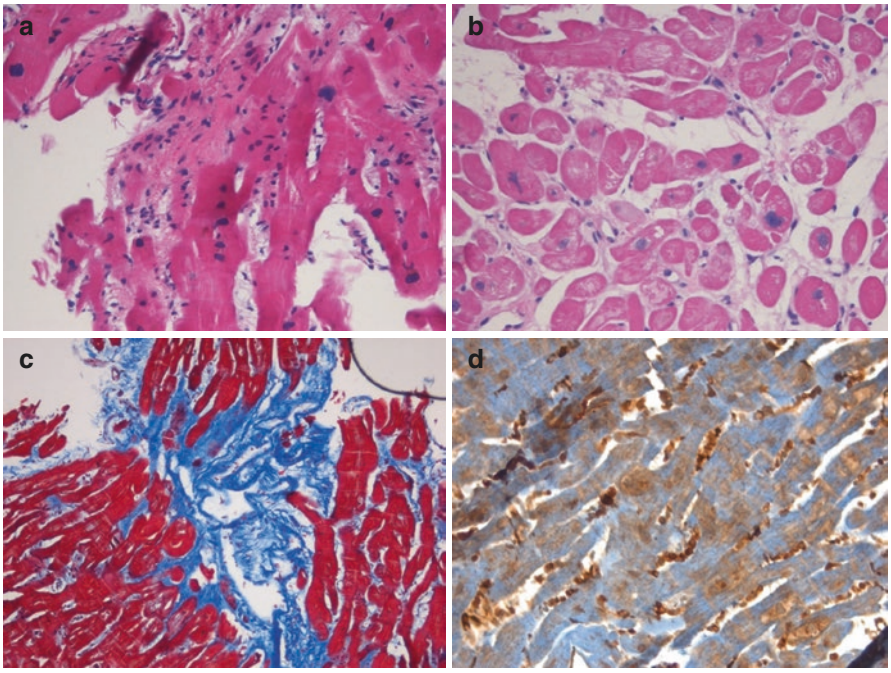

Fig. 9.5 (**a**) The haematoxylin-eosin (H&E) stain shows myocardial lympho-histiocytic infiltrate with replacement myocardial fibrosis (H&E ×20). (**b**) The EMB shows also hypertrophy, attenuation and involutive aspects of myocells with loss of contractile proteins (H&E ×20). (**c**) Mallory's trichrome stain shows interstitial and replacement fibrosis (Mallory trichrome ×10). (**d**) HLA-DR expression by interstitial inflammatory elements and by some myocells (HLA-DR ×20)

References

1. Sakakibara S, Konno S. Endomyocardial biopsy. Jpn Heart J. 1962;3:573–43.
2. Ferrans UJ, Roberts WC. Myocardial biopsy: a useful diagnostic procedure or only a research tool? Am J Cardiol. 1978;41:965–7.
3. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation. 2010;122:900–9.
4. Sinagra G, Anzini M, Pereira NL, Bussani R, Finocchiaro G, Bartunek J, et al. Myocarditis in clinical practice. Mayo Clin Proc. 2016;91(9):1256–66.
5. Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. Circulation. 2013;128:1531–41.
6. Francis R, Lewis C. Myocardial biopsy: techniques and indications. Heart. 2018;104(11):950–8.
7. Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation. 2004;109:1250–8.
8. Calabrese F, Thiene G. Myocarditis and inflammatory cardiomyopathy: microbiological and molecular biological aspects. Cardiovasc Res. 2003;60:11–25.
9. Bennett MK, Gilotra NA, Harrington C, Rao S, Dunn JM, Freitag TB, et al. Evaluation of the role of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. Circ Heart Fail. 2013;6(4):676–84.
10. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology; endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2007;28(24):3076–93.
11. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. J Am Coll Cardiol. 1992;19:43–7.
12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2013;128(16):e240–327.
13. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636–48.
14. Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, Wojciechowska C, Glanowska G, Wilczewski P, et al. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. Circulation. 2001;104(1):39–45.
15. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J. 2009;30(16):1995–2002.
16. Felker GM, Thompson RE, Hare JM, Glanowska G, Wilczewski P, Niklewski T, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342(15):1077–84.
17. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation. 1978;58:1204–11.
18. Okura Y, Dec GW, Hare JM, Berry GR, Tazelaar HD, Cooper LT. A multicentre registry comparison of cardiac sarcoidosis and idiopathic giantcell myocarditis. Circulation. 2000;102(18 Suppl II):II–788.

19. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic considerations. Cardiovasc Drugs Ther. 1996;10:495–510.
20. Morimoto S, Kato S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, et al. Narrowing of the left ventricular cavity associated with transient ventricular wall thickening reduces stroke volume in patients with acute myocarditis. Circ J. 2003;67:490–4.
21. Daniels PR, Berry GJ, Tazelaar HD, Cooper LT. Giant cell myocarditis as a manifestation of drug hypersensitivity. Cardiovasc Pathol. 2000;9:287–91.
22. Mueller KA, Mueller II, Eppler D, Zuern CS, Seizer P, Kramer U, et al. Clinical and histopathological features of patients with systemic sclerosis undergoing endomyocardial biopsy. PLoS One. 2015;10:e0126707.
23. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1:3–14.
24. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation. 2006;113:876–90.
25. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59:779–92.
26. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies. Circulation. 1996;93:841–2.
27. Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral myocarditis—diagnosis, treatment options, and current controversies. Nat Rev Cardiol. 2015;12(11):670–80.
28. Dennert R, Crijns HJ, Heymans S. Acute viral myocarditis. Eur Heart J. 2008;29:2073–82.
29. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol. 2012;21(4):245–74.
30. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11(7):1305–23.