cin-C biology. *Cell Mol Life Sci* 2011; **68:** 3175–3199.
9. Orend G, Chiquet-Ehrismann R. Tenascin-C induced signaling in cancer. *Cancer Lett* 2006; **244:** 143–163.
10. Midwood KS, Orend G. The role of tenascin-C in tissue injury and tumorigenesis. *J Cell Commun Signal* 2009; **3:** 287–310.
11. Chiquet-Ehrismann R, Chiquet M. Tenascins: Regulation and putative functions during pathological stress. *J Pathol* 2003; **200:** 488–499.
12. Jones FS, Jones PL. The tenascin family of ECM glycoproteins: Structure, function, and regulation during embryonic development and tissue remodeling. *Dev Dyn* 2000; **218:** 235–259.
13. Udalova IA, Ruhmann M, Thomson SJ, Midwood KS. Expression and immune function of tenascin-C. *Crit Rev Immunol* 2011; **31:** 115–145.
14. Tavazoie SF, Alarcon C, Oskarsson T, Padua D, Wang Q, Bos PD, et al. Endogenous human microRNAs that suppress breast cancer metastasis. *Nature* 2008; **451:** 147–152.
15. Chen C, Wu CQ, Zhang ZQ, Yao DK, Zhu L. Loss of expression of miR-335 is implicated in hepatic stellate cell migration and activation. *Exp Cell Res* 2011; **317:** 1714–1725.
16. Saga Y, Yagi T, Ikawa Y, Sakakura T, Aizawa S. Mice develop normally without tenascin. *Genes Dev* 1992; **6:** 1821–1831.
17. Forsberg E, Hirsch E, Frohlich L, Meyer M, Ekblom P, Aszodi A, et al. Skin wounds and severed nerves heal normally in mice lacking tenascin-C. *Proc Natl Acad Sci USA* 1996; **93:** 6594–6599.
18. Roth-Kleiner M, Hirsch E, Schittny JC. Fetal lungs of tenascin-C-deficient mice grow well, but branch poorly in organ culture. *Am J Respir Cell Mol Biol* 2004; **30:** 360–366.
19. Ishii K, Imanaka-Yoshida K, Yoshida T, Sugimura Y. Role of stromal tenascin-C in mouse prostatic development and epithelial cell differentiation. *Dev Biol* 2008; **324:** 310–319.
20. Tamaoki M, Imanaka-Yoshida K, Yokoyama K, Nishioka T, Inada H, Hiroe M, et al. Tenascin-C regulates recruitment of myofibroblasts during tissue repair after myocardial injury. *Am J Pathol* 2005; **167:** 71–80.
21. Sawada Y, Onoda K, Imanaka-Yoshida K, Maruyama J, Yamamoto K, Yoshida T, et al. Tenascin-C synthesized in both donor grafts and recipients accelerates artery graft stenosis. *Cardiovasc Res* 2007; **74:** 366–376.
22. Yamamoto K, Onoda K, Sawada Y, Fujinaga K, Imanaka-Yoshida K, Shimpo H, et al. Tenascin-C is an essential factor for neointimal hyperplasia after aortotomy in mice. *Cardiovasc Res* 2005; **65:** 737–742.
23. Nakahara H, Gabazza EC, Fujimoto H, Nishii Y, D'Alessandro-Gabazza CN, Bruno NE, et al. Deficiency of tenascin C attenuates allergen-induced bronchial asthma in the mouse. *Eur J Immunol* 2006; **36:** 3334–3345.
24. El-Karef A, Yoshida T, Gabazza EC, Nishioka T, Inada H, Sakakura T, et al. Deficiency of tenascin-C attenuates liver fibrosis in immune-mediated chronic hepatitis in mice. *J Pathol* 2007; **211:** 86–94.
25. Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, et al. Tenascin-C is an endogenous activator of toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. *Nat Med* 2009; **15:** 774–780.
26. Nishioka T, Onishi K, Shimojo N, Nagano Y, Matsusaka H, Ikeuchi M, et al. Tenascin-C may aggravate left ventricular remodeling and function after myocardial infarction in mice. *Am J Physiol Heart Circ Physiol* 2010; **298:** H1072–H1078.
27. Imanaka-Yoshida K, Matsumoto K, Hara M, Sakakura T, Yoshida T. The dynamic expression of tenascin-C and tenascin-X during early heart development in the mouse. *Differentiation* 2003; **71:** 291–298.
28. Snarr BS, Kern CB, Wessels A. Origin and fate of cardiac mesenchyme. *Dev Dyn* 2008; **237:** 2804–2819.
29. Perez-Pomares JM, de la Pompa JL. Signaling during epicardium and coronary vessel development. *Circ Res* 2011; **109:** 1429–1442.
30. Ando K, Takahashi M, Yamagishi T, Miyagawa-Tomita S, Imanaka-Yoshida K, Yoshida T, et al. Tenascin C may regulate the recruitment of smooth muscle cells during coronary artery development. *Differentiation* 2011; **81:** 299–306.
31. Ishigaki T, Imanaka-Yoshida K, Shimojo N, Matsushima S, Taki W, Yoshida T. Tenascin-C enhances crosstalk signaling of integrin alphavbeta3/PDGFR-beta complex by SRC recruitment promoting PDGF-induced proliferation and migration in smooth muscle cells. *J Cell Physiol* 2011; **226:** 2617–2624.
32. Willems IE, Arends JW, Daemen MJ. Tenascin and fibronectin expression in healing human myocardial scars. *J Pathol* 1996; **179:** 321–325.
33. Imanaka-Yoshida K, Hiroe M, Nishikawa T, Ishiyama S, Shimojo T, Ohta Y, et al. Tenascin-C modulates adhesion of cardiomyocytes to extracellular matrix during tissue remodeling after myocardial infarction. *Lab Invest* 2001; **81:** 1015–1024.
34. Sato A, Aonuma K, Imanaka-Yoshida K, Yoshida T, Isobe M, Kawase D, et al. Serum tenascin-C might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol* 2006; **47:** 2319–2325.
35. Odaka K, Uehara T, Arano Y, Adachi S, Tadokoro H, Yoshida K, et al. Noninvasive detection of cardiac repair after acute myocardial infarction in rats by 111 In Fab fragment of monoclonal antibody specific for tenascin-C. *Int Heart J* 2008; **49:** 481–492.
36. Imanaka-Yoshida K, Hiroe M, Yasutomi Y, Toyozaki T, Tsuchiya T, Noda N, et al. Tenascin-C is a useful marker for disease activity in myocarditis. *J Pathol* 2002; **197:** 388–394.
37. Sato M, Toyozaki T, Odaka K, Uehara T, Arano Y, Hasegawa H, et al. Detection of experimental autoimmune myocarditis in rats by 111In monoclonal antibody specific for tenascin-C. *Circulation* 2002; **106:** 1397–1402.
38. Morimoto S, Imanaka-Yoshida K, Hiramitsu S, Kato S, Ohtsuki M, Uemura A, et al. Diagnostic utility of tenascin-C for evaluation of the activity of human acute myocarditis. *J Pathol* 2005; **205:** 460–467.
39. Frangogiannis NG, Shimoni S, Chang SM, Ren G, Dewald O, Gersch C, et al. Active interstitial remodeling: An important process in the hibernating human myocardium. *J Am Coll Cardiol* 2002; **39:** 1468–1474.
40. Taki J, Inaki A, Wakabayashi H, Imanaka-Yoshida K, Ogawa K, Hiroe M, et al. Dynamic expression of tenascin-C after myocardial ischemia and reperfusion: Assessment by 125I-anti-tenascin-C antibody imaging. *J Nucl Med* 2010; **51:** 1116–1122.
41. Nishioka T, Suzuki M, Onishi K, Takakura N, Inada H, Yoshida T, et al. Eplerenone attenuates myocardial fibrosis in the angiotensin II-induced hypertensive mouse: Involvement of tenascin-C induced by aldosterone-mediated inflammation. *J Cardiovasc Pharmacol* 2007; **49:** 261–268.
42. Franz M, Grun K, Richter P, Brehm BR, Fritzenwanger M, Hekmat K, et al. Extra cellular matrix remodelling after heterotopic rat heart transplantation: Gene expression profiling and involvement of ED-A+ fibronectin, alpha-smooth muscle actin and B+ tenascin-C in chronic cardiac allograft rejection. *Histochem Cell Biol* 2010; **134:** 503–517.
43. Tamura A, Kusachi S, Nogami K, Yamanishi A, Kajikawa Y, Hirohata S, et al. Tenascin expression in endomyocardial biopsy specimens in patients with dilated cardiomyopathy: Distribution along margin of fibrotic lesions. *Heart* 1996; **75:** 291–294.
44. Tsukada B, Terasaki F, Shimomura H, Otsuka K, Katashima T, Fujita S, et al. High prevalence of chronic myocarditis in dilated cardiomyopathy referred for left ventriculoplasty: Expression of tenascin C as a possible marker for inflammation. *Hum Pathol* 2009; **40:** 1015–1022.
45. Goh FG, Piccinini AM, Krausgruber T, Udalova IA, Midwood KS. Transcriptional regulation of the endogenous danger signal tenascin-C: A novel autocrine loop in inflammation. *J Immunol* 2010; **184:** 2655–2662.
46. Kanayama M, Morimoto J, Matsui Y, Ikesue M, Danzaki K, Kurotaki D, et al. Alpha9beta1 integrin-mediated signaling serves as an intrinsic regulator of pathogenic Th17 cell generation. *J Immunol* 2011; **187:** 5851–5864.
47. Frangogiannis NG. The immune system and cardiac repair. *Pharmacol Res* 2008; **58:** 88–111.
48. Dobaczewski M, Gonzalez-Quesada C, Frangogiannis NG. The extracellular matrix as a modulator of the inflammatory and reparative response following myocardial infarction. *J Mol Cell Cardiol* 2010; **48:** 504–511.
49. Imanaka-Yoshida K, Hiroe M, Yoshida T. Interaction between cell and extracellular matrix in heart disease: Multiple roles of tenascin-C in tissue remodeling. *Histol Hisopathol* 2004; **19:** 517–525.
50. Collins AR, Schnee J, Wang W, Kim S, Fishbein MC, Bruemmer D, et al. Osteopontin modulates angiotensin II-induced fibrosis in the intact murine heart. *J Am Coll Cardiol* 2004; **43:** 1698–1705.
51. Lenga Y, Koh A, Perera AS, McCulloch CA, Sodek J, Zohar R. Osteopontin expression is required for myofibroblast differentiation. *Circ Res* 2008; **102:** 319–327.
52. Chablais F, Jazwinska A. The regenerative capacity of the zebrafish heart is dependent on TGFbeta signaling. *Development* 2012; **139:** 1921–1930.
53. Hinz B, Phan SH, Thannickal VJ, Galli A, Bochaton-Piallat ML, Gabbiani G. The myofibroblast: One function, multiple origins. *Am J Pathol* 2007; **170:** 1807–1816.
54. Ballard VL, Sharma A, Duignan I, Holm JM, Chin A, Choi R, et al. Vascular tenascin-C regulates cardiac endothelial phenotype and neovascularization. *FASEB J* 2006; **20:** 717–719.
55. Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M,

et al. Prognostic impact of myocardial interstitial fibrosis in non-ischemic heart failure: Comparison between preserved and reduced ejection fraction heart failure. *Circ J* 2011; **75:** 2605–2613.
56. Kii I, Nishiyama T, Li M, Matsumoto K, Saito M, Amizuka N, et al. Incorporation of tenascin-C into the extracellular matrix by periostin underlies an extracellular meshwork architecture. *J Biol Chem* 2010; **285:** 2028–2039.
57. Manabe I. Chronic inflammation links cardiovascular, metabolic and renal diseases. *Circ J* 2011; **75:** 2739–2748.
58. Lange K, Kammerer M, Hegi ME, Grotegut S, Dittmann A, Huang W, et al. Endothelin receptor type B counteracts tenascin-C-induced endothelin receptor type A-dependent focal adhesion and actin stress fiber disorganization. *Cancer Res* 2007; **67:** 6163–6173.
59. Nagaharu K, Zhang X, Yoshida T, Katoh D, Hanamura N, Kozuka Y, et al. Tenascin C induces epithelial-mesenchymal transition-like change accompanied by SRC activation and focal adhesion kinase phosphorylation in human breast cancer cells. *Am J Pathol* 2011; **178:** 754–763.
60. Sato A, Hiroe M, Akiyama D, Hikita H, Nozato T, Hoshi T, et al. Prognostic value of serum tenascin-C levels on long-term outcome after acute myocardial infarction. *J Card Fail* 2012; **18:** 480–486.
61. Terasaki F, Okamoto H, Onishi K, Sato A, Shimomura H, Tsukada B, et al. Higher serum tenascin-C levels reflect the severity of heart failure, left ventricular dysfunction and remodeling in patients with dilated cardiomyopathy. *Circ J* 2007; **71:** 327–330.
62. Fujimoto N, Onishi K, Sato A, Terasaki F, Tsukada B, Nozato T, et al. Incremental prognostic values of serum tenascin-C levels with blood B-type natriuretic peptide testing at discharge in patients with dilated cardiomyopathy and decompensated heart failure. *J Card Fail* 2009; **15:** 898–905.
63. Franz M, Berndt A, Altendorf-Hofmann A, Fiedler N, Richter P, Schumm J, et al. Serum levels of large tenascin-C variants, matrix metalloproteinase-9, and tissue inhibitors of matrix metalloproteinases in concentric versus eccentric left ventricular hypertrophy. *Eur J Heart Fail* 2009; **11:** 1057–1062.
64. Hessel M, Steendijk P, den Adel B, Schutte C, van der Laarse A. Pressure overload-induced right ventricular failure is associated with re-expression of myocardial tenascin-C and elevated plasma tenascin-C levels. *Cell Physiol Biochem* 2009; **24:** 201–210.
65. Milting H, Ellinghaus P, Seewald M, Cakar H, Bohms B, Kassner A, et al. Plasma biomarkers of myocardial fibrosis and remodeling in terminal heart failure patients supported by mechanical circulatory support devices. *J Heart Lung Transplant* 2008; **27:** 589–596.
66. Kitaoka H, Kubo T, Baba Y, Yamasaki N, Matsumura Y, Furuno T, et al. Serum tenascin-C levels as a prognostic biomarker of heart failure events in patients with hypertrophic cardiomyopathy. *J Cardiol* 2012; **59:** 209–214.
67. Niebroj-Dobosz I, Madej-Pilarczyk A, Marchel M, Sokolowska B, Hausmanowa-Petrusewicz I. Circulating tenascin-C levels in patients with dilated cardiomyopathy in the course of Emery-Dreifuss muscular dystrophy. *Clin Chim Acta* 2011; **412:** 1533–1538.
68. Liabeuf S, Barreto DV, Kretschmer A, Barreto FC, Renard C, Andrejak M, et al. High circulating levels of large splice variants of tenascin-C is associated with mortality and cardiovascular disease in chronic kidney disease patients. *Atherosclerosis* 2011; **215:** 116–124.
69. Kobayashi N, Odaka K, Uehara T, Imanaka-Yoshida K, Kato Y, Oyama H, et al. Toward in vivo imaging of heart disease using a radiolabeled single-chain Fv fragment targeting tenascin-C. *Anal Chem* 2011; **83:** 9123–9130.
70. Golledge J, Clancy P, Maguire J, Lincz L, Koblar S. The role of tenascin C in cardiovascular disease. *Cardiovasc Res* 2011; **92:** 19–28.
71. Hedin U, Holm J, Hansson GK. Induction of tenascin in rat arterial injury: Relationship to altered smooth muscle cell phenotype. *Am J Pathol* 1991; **139:** 649–656.
72. Wallner K, Shah PK, Sharifi BG. Balloon catheterization induces arterial expression of new tenascin-C isoform. *Atherosclerosis* 2002; **161:** 75–83.
73. Imanaka-Yoshida K, Matsuura R, Isaka N, Nakano T, Sakakura T, Yoshida T. Serial extracellular matrix changes in neointimal lesions of human coronary artery after percutaneous transluminal coronary angioplasty: Clinical significance of early tenascin-C expression. *Virchows Arch* 2001; **439:** 185–190.
74. Wang M, Ihida-Stansbury K, Kothapalli D, Tamby MC, Yu Z, Chen L, et al. Microsomal prostaglandin E2 synthase-1 modulates the response to vascular injury. *Circulation* 2011; **123:** 631–639.
75. Fujinaga K, Onoda K, Yamamoto K, Imanaka-Yoshida K, Takao M, Shimono T, et al. Locally applied cilostazol suppresses neointimal hyperplasia by inhibiting tenascin-C synthesis and smooth muscle cell proliferation in free artery grafts. *J Thorac Cardiovasc Surg* 2004; **128:** 357–363.
76. Yamamoto K, Onoda K, Sawada Y, Fujinaga K, Imanaka-Yoshida K, Yoshida T, et al. Locally applied cilostazol suppresses neointimal hyperplasia and medial thickening in a vein graft model. *Ann Thorac Cardiovasc Surg* 2007; **13:** 322–330.
77. Jin L, Hastings NE, Blackman BR, Somlyo AV. Mechanical properties of the extracellular matrix alter expression of smooth muscle protein LPP and its partner palladin; relationship to early atherosclerosis and vascular injury. *J Muscle Res Cell Motil* 2009; **30:** 41–55.
78. Wallner K, Sharifi BG, Shah PK, Noguchi S, DeLeon H, Wilcox JN. Adventitial remodeling after angioplasty is associated with expression of tenascin mRNA by adventitial myofibroblasts. *J Am Coll Cardiol* 2001; **37:** 655–661.
79. Iso Y, Suzuki H, Sato T, Shoji M, Shibata M, Shimizu N, et al. The mechanism of in-stent restenosis in radius stent: An experimental porcine study. *Circ J* 2005; **69:** 481–487.
80. Wallner K, Li C, Shah PK, Fishbein MC, Forrester JS, Kaul S, et al. Tenascin-C is expressed in macrophage-rich human coronary atherosclerotic plaque. *Circulation* 1999; **99:** 1284–1289.
81. Kenji K, Hironori U, Hideya Y, Michinori I, Yasuhiko H, Nobuoki K. Tenascin-C is associated with coronary plaque instability in patients with acute coronary syndromes. *Circ J* 2004; **68:** 198–203.
82. Jones PL, Rabinovitch M. Tenascin-C is induced with progressive pulmonary vascular disease in rats and is functionally related to increased smooth muscle cell proliferation. *Circ Res* 1996; **79:** 1131–1142.
83. Jones PL, Cowan KN, Rabinovitch M. Tenascin-C, proliferation and subendothelial fibronectin in progressive pulmonary vascular disease. *Am J Pathol* 1997; **150:** 1349–1360.
84. Ihida-Stansbury K, McKean DM, Lane KB, Loyd JE, Wheeler LA, Morrell NW, et al. Tenascin-C is induced by mutated BMP type II receptors in familial forms of pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol* 2006; **291:** L694–L702.
85. Satta J, Soini Y, Pollanen R, Paakko P, Juvonen T. Tenascin expression is associated with a chronic inflammatory process in abdominal aortic aneurysms. *J Vasc Surg* 1997; **26:** 670–675.
86. Kimura T, Yoshimura K, Aoki H, Imanaka-Yoshida K, Yoshida T, Ikeda Y, et al. Tenascin-C is expressed in abdominal aortic aneurysm tissue with an active degradation process. *Pathol Int* 2011; **61:** 559–564.
87. Didangelos A, Yin X, Mandal K, Saje A, Smith A, Xu Q, et al. Extracellular matrix composition and remodeling in human abdominal aortic aneurysms: A proteomics approach. *Mol Cell Proteomics* 2011; **10:** M111.008128.
88. Shiba M, Suzuki H, Fujimoto M, Shimojo N, Imanaka-Yoshida K, Yoshida T, et al. Imatinib mesylate prevents cerebral vasospasm after subarachnoid hemorrhage via inhibiting tenascin-C expression in rats. *Neurobiol Dis* 2012; **46:** 172–179.
89. Suzuki H, Kanamaru K, Shiba M, Fujimoto M, Imanaka-Yoshida K, Yoshida T, et al. Cerebrospinal fluid tenascin-C in cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 2011; **23:** 310–317.
90. Suzuki H, Kanamaru K, Suzuki Y, Aimi Y, Matsubara N, Araki T, et al. Tenascin-C is induced in cerebral vasospasm after subarachnoid hemorrhage in rats and humans: A pilot study. *Neurol Res* 2010; **32:** 179–184.
91. Suzuki H, Kinoshita N, Imanaka-Yoshida K, Yoshida T, Taki W. Cerebrospinal fluid tenascin-C increases preceding the development of chronic shunt-dependent hydrocephalus after subarachnoid hemorrhage. *Stroke* 2008; **39:** 1610–1612.
92. Cowan KN, Jones PL, Rabinovitch M. Regression of hypertrophied rat pulmonary arteries in organ culture is associated with suppression of proteolytic activity, inhibition of tenascin-C, and smooth muscle cell apoptosis. *Circ Res* 1999; **84:** 1223–1233.
93. Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, et al. Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54:** S20–S31.
94. Minear MA, Crosslin DR, Sutton BS, Connelly JJ, Nelson SC, Gadson-Watson S, et al. Polymorphic variants in tenascin-C (TNC) are associated with atherosclerosis and coronary artery disease. *Hum Genet* 2011; **129:** 641–654.
95. Hao H, Ishibashi-Ueda H, Tsujimoto M, Ueda Y, Shite J, Gabbiani G, et al. Drug-eluting stent: Importance of clinico-pathological correlations. *Circ J* 2011; **75:** 1548–1558.
96. von Lukowicz T, Silacci M, Wyss MT, Trachsel E, Lohmann C, Buck A, et al. Human antibody against C domain of tenascin-C visualizes murine atherosclerotic plaques ex vivo. *J Nucl Med* 2007; **48:** 582–587.
97. Toma N, Imanaka-Yoshida K, Takeuchi T, Matsushima S, Iwata H, Yoshida T, et al. Tenascin-C-coated platinum coils for acceleration of organization of cavities and reduction of lumen size in a rat aneurysm model. *J Neurosurg* 2005; **103:** 681–686.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Temporal Changes in Echocardiographic Findings in Cardiac and Non-Cardiac Sarcoidosis Patients

Kunihiro Teramoto[1], Shinsaku Shimamoto[1], Fumio Terasaki[1], Yumiko Kanzaki[1], Manabu Tamaya[2], Isao Goto[2] and Nobukazu Ishizaka[1]

Abstract

Objective Echocardiography is used for the detection of cardiac sarcoid involvement in patients with non-cardiac sarcoidosis. Little information is available regarding temporal changes in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVDd) in non-cardiac sarcoidosis patients.

Methods and Results Fifty-four sarcoidosis patients who received periodic follow-up with echocardiography at our institute were enrolled in this study. At the time of initial ultrasonography, 13 patients were diagnosed with cardiac sarcoid involvement. All of the remaining 41 patients with extra-cardiac sarcoidosis only had a LVEF of >50%. During the median follow-up period of 39 months, two (4.9%) of the non-cardiac sarcoidosis patients were diagnosed with cardiac sarcoid involvement; one patient showed a progressive decline in the LVEF over a short period of time. It was also found that two of 41 non-cardiac sarcoidosis patients showed declines in the LVEF of >10% per year; however, they were not diagnosed with cardiac sarcoidosis during the follow-up period.

Conclusion Rapid deterioration of left ventricular function may increase the suspicion of sarcoid involvement of the heart in non-cardiac sarcoidosis patients; however, we must be aware that a certain subfraction of patients may not demonstrate significant abnormalities in LVEF or LVDd on periodic echocardiographic follow-up.

Key words: cardiac sarcoidosis, echocardiography, left ventricular function

(Intern Med 51: 3001-3007, 2012)
(DOI: 10.2169/internalmedicine.51.8396)

Introduction

Sarcoidosis is a disease that may tend to heal naturally; nevertheless, <5% of patients die of the disease (1). Pathological studies have shown that cardiac sarcoid involvement occurs in 25% to nearly 60% of cases of systemic sarcoidosis (2-4). Although cardiac sarcoid formation often involves only a small portion of the myocardium and is thus clinically silent (2, 5), it represents a major cause of death in patients with sarcoidosis (3), with mortality ranging from 10% to 40% over 5 years (6, 7). Although many efforts have been made to diagnose cardiac sarcoid involvement in the early phase for the purpose of providing prompt treatment (8, 9), early diagnosis of cardiac sarcoidosis remains challenging. In addition to endomyocardial biopsy (10), several less invasive diagnostic modalities have become available. These include cardiac magnetic resonance (CMR) and radionuclide-based examinations such as fluorodeoxyglucose positron emission tomography (FDG-PET) (4, 11, 12). However, the repetitive performance of such examinations may be limited due to cost, the time-consuming nature of the examination or irradiation exposure. In their diagnostic algorithm for cardiac sarcoidosis in patients with extra-cardiac sarcoidosis, Youssef et al. proposed that 12-lead and Holter electrocardiogram (ECG) and echocardiography should be performed and, when certain abnormal findings, such as a left ventricular ejection fraction (LVEF) of <50%, are present, the use of advanced cardiac imaging using CMR or FDG-PET should be considered (13).

Information seems to be limited regarding temporal changes in echocardiographic findings among patients with

[1]Department of Cardiology, Osaka Medical College, Japan and [2]Department of Respiratory Medicine, Osaka Medical College, Japan
Received for publication June 17, 2012; Accepted for publication July 26, 2012
Correspondence to Dr. Fumio Terasaki, in3012@poh.osaka-med.ac.jp

non-cardiac sarcoidosis. At our institute, patients with non-cardiac sarcoidosis undergo annual echocardiographic follow-up. In the current study, we retrospectively analyzed temporal changes in echocardiographic findings among patients diagnosed with cardiac sarcoidosis and in those diagnosed with non-cardiac sarcoidosis who eventually develop cardiac sarcoid involvement.

Materials and Methods

Study patients

This study was approved by the Ethics Committee of Osaka Medical College, Osaka, Japan. Between 2002 and 2011, 83 patients with sarcoidosis attended our hospital. Of these 83 patients, 54 underwent multiple echocardiography at our institute and were enrolled in the current study. For cardiac and non-cardiac sarcoidosis patients, the interval from the time of clinical diagnosis to the first echocardiography at our institute was a median of 31 months (range: 0-125 months) and 34 months (range: 0-168 months), respectively.

Echocardiography

Echocardiography was performed at least twice in our study population. In non-cardiac sarcoidosis patients, echocardiography was, in general, performed once a year; however, if certain abnormalities suggestive of cardiac involvement emerged, the frequency of ultrasonography increased according to the discretion of the cardiologists. For cardiac and non-cardiac sarcoidosis patients, echocardiography was performed a median of five times (range: 2-9 times) and four times (range: 2-11 times) during a median period of 42 months (range: 5-94 months) and 39 months (range: 5-117 months), respectively. The right ventricular systolic pressure (RVSP) was evaluated using Doppler gradient in a fraction of patients only (six cardiac and 12 non-cardiac sarcoidosis patients). The primary reason for this was the absence of tricuspid regurgitation for the estimation of RVSP.

The difference in the LVEF and left ventricular end-diastolic dimension (LVDd) between the first and latest echocardiography were calculated on a per-year basis using the following equations:

Change in LVEF (percent per year)={('the latest LVEF'-'the first LVEF')/'the first LVEF'×100}/'interval of the latest and the first echocardiography'. Change in LVDd (percent per year)={('the latest LVDd'-'the first LVDd')/'the first LVDd'×100}/'interval of the latest and the first echocardiography'.

Diagnosis of systemic sarcoidosis and cardiac involvement

The diagnosis of systemic sarcoidosis was made according to the Diagnostic Standard and Guideline for Sarcoidosis 2006 advocated by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (14). At the time of first echocardiography, 13 patients and 41 patients were considered to have cardiac and non-cardiac sarcoidosis, respectively. All but one patient with cardiac sarcoidosis showed sarcoid involvement in other organs (Table). The one patient diagnosed to have cardiac-restricted sarcoid involvement was diagnosed using a histological analysis of an excised myocardium specimen obtained by volume reduction left ventriculoplasty.

Statistical analysis

The data are expressed as the mean ± SD, unless otherwise described. Paired and unpaired t-tests were used for intragroup and intergroup comparison using the software SPSS. A p value <0.05 was considered to be statistically significant.

Results

Baseline characteristics at the time of first echocardiography

The mean age and prevalence of men did not significantly differ between patients with cardiac sarcoidosis and those with non-cardiac sarcoidosis (Table). The use of corticosteroid therapy was more frequent in the cardiac sarcoidosis patients (10/13, 77%) than in the non-cardiac sarcoidosis patients (7/41, 17%, $p<0.01$). The values of LVEF were significantly lower and the values of both LVDd and end-systolic dimension (LVDs) were significantly higher in the patients with cardiac sarcoidosis than in those with non-cardiac sarcoidosis. The LVEF was >50% in all non-cardiac sarcoidosis patients and in only seven (54%) of the patients with cardiac sarcoidosis.

Temporal changes in parameters of echocardiography

The values of LVEF did not significantly differ between the first (mean: 67.5±6.1%) and latest (mean: 65.7±10.1%) echocardiography in the non-cardiac sarcoidosis patients (Fig. 1). On the other hand, the values of LVEF decreased, albeit borderline significantly ($p=0.088$), in the cardiac sarcoidosis patients. Two patients in the non-cardiac sarcoidosis group were diagnosed with cardiac involvement during the follow-up period. One of these patients showed the greatest decline in LVEF (34%) and the greatest enlargement of LVDd (16 mm).

As the interval between the first and latest echocardiography differed substantially, the difference in LVEF between the first and latest echocardiography was calculated on a per-year basis (Fig. 2). Substantial variations were found in the per-year-base changes in LVEF and LVDd in both the non-cardiac and cardiac sarcoidosis patients: three (7.3%) non-cardiac sarcoidosis patients (one of which is case 1) and two (15%) cardiac sarcoidosis patients experienced decline in LVEF of ≥10% per year and two of 41 non-cardiac sarcoidosis patients showed LVEF declines of ≥10% per year

Table. Baseline Characteristics

Characteristics	Overall (n=54)	Cardiac involvement (-) (n=41)	Cardiac involvement (+) (n=13)	P
Age, y	57.7 ± 12.5	57.4 ± 12.9	58.7 ± 11.9	ns
Male sex, n (%)	20 (37)	17 (41)	3 (23)	ns
Exracardiac sacroidosis, n (%)				
Clinical organ involvement, n (%)				
Lung	29 (54)	24 (59)	5 (38)	ns
Lymphonode	26 (48)	18 (44)	8 (62)	ns
Skin	11 (20)	9 (22)	2 (15)	ns
Eye	18 (33)	15 (37)	3 (23)	ns
Skeletal muscle	2 (4)	2 (5)	0 (0)	ns
Liver	1 (2)	1 (2)	0 (0)	ns
Kidney	1 (2)	1 (2)	0 (0)	ns
Positive biospy site, n (%)				
Lung (biopsy and/or BAL)	28 (52)	23 (56)	5 (38)	ns
Biopsy	21 (39)	16 (39)	5 (38)	ns
BAL	8 (15)	8 (20)	0 (0)	ns
Lymphonode	8 (15)	3 (7)	5 (38)	0.01
Skin	9 (17)	7 (17)	2 (15)	ns
Eye	0 (0)	0 (0)	0 (0)	ns
Skeletal muscle	2 (4)	2 (5)	0 (0)	ns
Liver	1 (2)	1 (2)	0 (0)	ns
Kidney	1 (2)	1 (2)	0 (0)	ns
Medications				
Corticosteroid	17 (31)	7 (17)	10 (77)	<0.01
Immuno-suppressive therapy	0 (0)	0 (0)	0 (0)	-
ACEI/ARB	13 (24)	9 (22)	4 (31)	ns
Beta blockers	7 (13)	3 (7)	4 (31)	<0.05
Diuretics	6 (11)	1 (2)	5 (38)	<0.01
Aldosterone antagonists	1 (2)	0 (0)	1 (8)	<0.05
Amiodaron	3 (6)	1 (2)	2 (15)	ns

but were not diagnosed with cardiac sarcoid involvement during the follow-up period. The follow-up periods in these two patients were 13 months and 15 months. In both patients, the latest echocardiography showed no abnormal findings, including reduced LVEF (<50%). Therefore, further cardiac examinations with other modalities, including CMR and FDG-PET, were not performed. Two patients (5%) with non-cardiac sarcoidosis and one patient (7.7%) with cardiac sarcoidosis experienced enlargements of LVDd of ≥10% per year.

The temporal changes in left ventricular end-diastolic interventricular septum thickness (IVSd) and end-diastolic posterior wall thickness (PWd) were also analyzed. The values of IVSd did not significantly differ between the first and latest echocardiography in either the non-cardiac (mean: 8.8±1.2 and 9.0±1.4 mm, p=0.41) or cardiac (mean: 8.8±2.1 and 8.2±1.7 mm, p=0.22) sarcoidosis patients. The IVSd/PWd ratios showed no significant differences between the first and latest echocardiography in the non-cardiac sarcoidosis patients (mean: 1.03±0.09 and 1.00±0.12, p=0.30). In the cardiac sarcoidosis patients, the IVSd/PWd ratios at the latest echocardiography were smaller than those measured at the first echocardiography (mean: 0.99±0.26 and 0.86±0.21, p=0.048).

On the other hand, at the time of the first echocardiography, abnormal septal thinning localized at the basal portion, which is thought to be characteristic of cardiac sarcoidosis, was recognized in eight (62%) of the 13 cardiac sarcoidosis patients and in none of the 41 non-cardiac sarcoidosis patients. However, abnormal septal thinning was not observed in the two patients who developed cardiac sarcoid involvement during the study period.

Patients who developed cardiac sarcoid involvement during the study period

Two patients who had been diagnosed with non-cardiac sarcoidosis at the time of first echocardiography were diagnosed with cardiac involvement during the follow-up period. These patients were categorized in the non-cardiac sarcoidosis group in the Figs. 1, 2 according to the diagnosis made at the time of first echocardiography. The characteristics and clinical courses of these two cases were as follows.

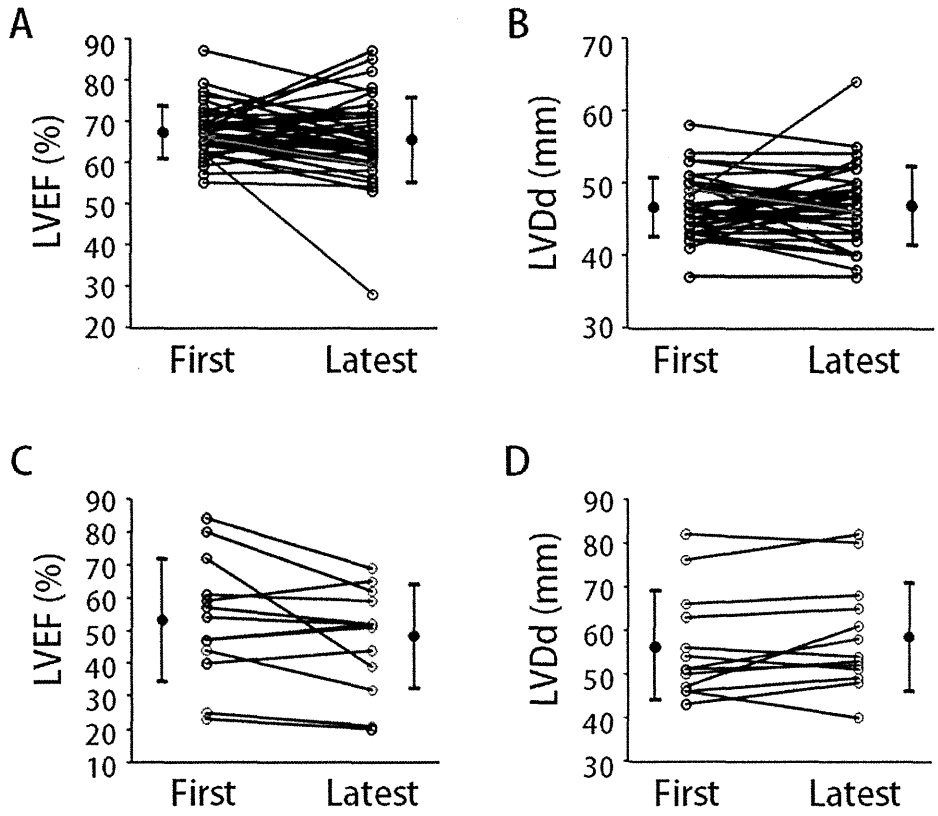

Figure 1. Left ventricular ejection fraction (LVEF) and end-diastolic dimension (LVDd) at the first and latest echocardiography. A, B. The values of LVEF (A) and LVDd (B) in the non-cardiac sarcoidosis patients. The red open circles (case 1) and blue circles (case 2) indicate the data of the patients who were diagnosed with cardiac sarcoid involvement during the follow-up period. C, D. The values of LVEF (C) and LVDd (D) in the cardiac sarcoidosis patients.

The first case (case 1) is a 69-year-old man who had been diagnosed with systemic sarcoidosis on a lymph node biopsy. The first echocardiographic screening was performed at the time of the diagnosis of systemic sarcoidosis and demonstrated no apparent abnormal findings: LVDd: 48 mm; LVEF: 62%; and estimated RVSP: 29 mmHg (Fig. 3A, B). 12-lead ECG showed a right bundle branch block. Thirty months after the first echocardiography was performed, rapidly progressing enlargement of LVDd and reduction of LVEF emerged (Fig. 3C, D, E arrow). 12-lead ECG showed a complete right bundle branch block and a left axis deviation. Under the suspicion of cardiac sarcoid involvement, further examinations were performed: FDG-PET showed abnormal cardiac FDG uptake, CMR showed late gadolinium enhancement (data not shown), coronary artery angiography showed no flow-limiting coronary stenosis and an endomyocardial biopsy showed loss of cardiomyocytes and fibrotic degeneration with infiltration of CD45-positive lymphocytic cells and CD68-positive monocytes and macrophages (Fig. 3F-I). These findings confirmed cardiac sarcoid involvement. During hospitalization, sustained ventricular tachyarrythmia occurred. Corticosteroid therapy was started and the patient underwent implantation of a cardiac resynchronization therapy-defibrillator.

The second case (case 2) is a 40-year-old man with systemic sarcoidosis involving the liver, which had been diagnosed histologically, and eyes and lungs, which had been diagnosed clinically. Thirteen years after the diagnosis of systemic sarcoidosis, ambulatory ECG showed non-sustained ventricular tachyarrythmias. The first echocardiographic screening performed at our institute showed no apparent abnormal findings (Fig. 4A). Forty-one months after the first echocardiography, 12-lead ECG showed Q waves in lead III. Echocardiography showed a mildly decreased LVEF, although the global left ventricular function was preserved (Fig. 4A, arrow). CMR showed late gadolinium enhancement (Fig. 4B) and technetium-99m based single photon emission computed tomography (SPECT) (data not shown) showed abnormal cardiac uptake. Although an endomyocardial biopsy specimen did not demonstrate histologic findings specifically suggestive of cardiac sarcoid involvement (Fig. 4C), corticosteroid therapy was started under the diagnosis of cardiac sarcoidosis.

Discussion

In the current study, we analyzed the data of 54 sarcoidosis patients who received follow-up with echocardiography. At the time of first ultrasonography, 13 patients were diagnosed with cardiac sarcoid involvement. The remaining 41 patients were diagnosed with extra-cardiac sarcoidosis only, and all of these patients had an LVEF of >50%. During the

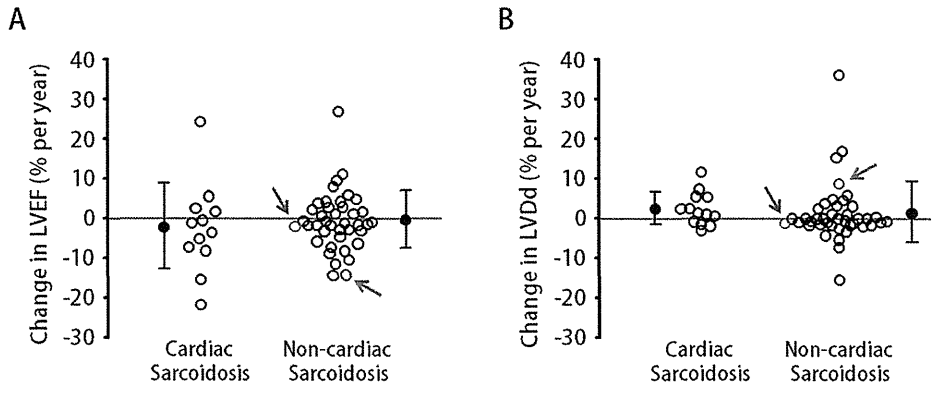

Figure 2. The percent changes in left ventricular ejection fraction (LVEF) and end-diastolic dimension (LVDd) on a per-year basis. A. The percent change in LVEF per year. B. The percent change in LVDd per year. The red open circles (case 1) and blue circles (case 2) pointed by the arrows indicate the data of the patients who were diagnosed with cardiac sarcoid involvement during the follow-up period.

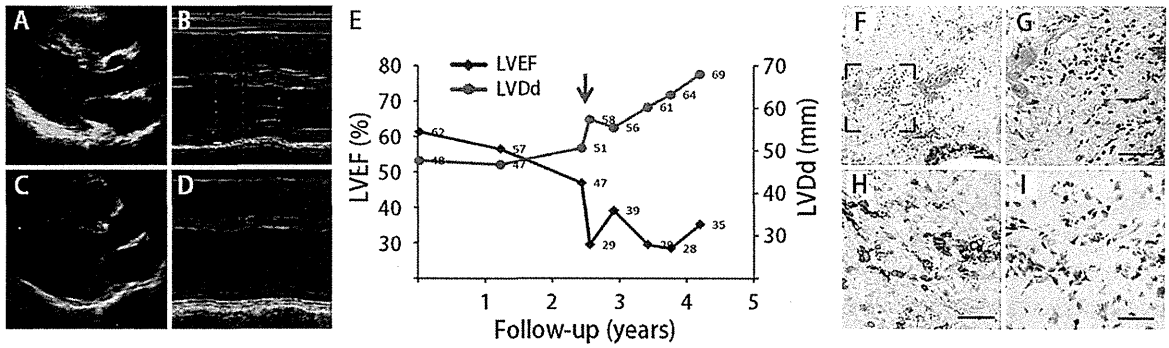

Figure 3. The findings of echocardiography and an endomyocardial biopsy in case 1. A-D. Two dimensional longitudinal axis (A, C) and M-mode (B, D) echocardiography. The findings of the first echocardiography (A, B) and that obtained 30 months afterward (C, D) are demonstrated. Thirty months after the first echocardiography was performed, a rapidly progressing enlargement of left ventricular end-diastolic dimension (LVDd) and a reduction of left ventricular ejection fraction (LVEF) emerged. E. Temporal changes in LVEF and LVDd on echocardiography. The arrow indicates the point of the diagnosis of cardiac sarcoid involvement. F-I. The histologic and immunohistochemical analyses of the biopsy specimens. Loss of cardiomyocytes and fibrotic degeneration with infiltration of CD45-positive lymphocytic cells and CD68-positive monocytes and macrophages are observed. No multinucleated giant cells are observed. F, G. Hematoxylin and Eosin staining. G is a high-power image of the bracketed area in F. H. CD45 staining. I. CD68 staining. The scale bars indicate 50 μm.

median follow-up period of 39 months, two (4.9%) of the 41 non-cardiac sarcoidosis patients developed cardiac manifestations, leading to a diagnosis of cardiac sarcoid involvement (10). One of these patients (case 1) showed a progressive decline in the LVEF over a short period of time (Fig. 3). On the other hand, the cardiac function of the other patient (case 2) was preserved both at the time of diagnosis and after diagnosis of cardiac sarcoid involvement (Fig. 4).

The current study showed that the per-year base percent changes in LVEF did not significantly differ, although there were substantial variations in this parameter in both groups and two (4.9%) patients without cardiac involvement showed LVEF reductions of >10% per year (Fig. 2). Considering that only a subfraction of the sarcoidosis patients who were diagnosed with cardiac involvement at necropsy had clinical evidence of cardiac involvement (2), it is possible that the non-cardiac sarcoidosis patients who showed LVEF reductions might have had subclinical cardiac sarcoid involvement. Together with the ability of LVEF reductions to predict clinically significant cardiac involvement in non-cardiac sarcoidosis patients, this point should be clarified in further investigations.

The abnormal septal thinning localized at the basal portion that strongly suggests cardiac sarcoid involvement was not documented in the two patients who developed cardiac sarcoid involvement during the study period.

When cardiac manifestations occur in patients with systemic sarcoidosis, cardiac involvement is strongly suspected,

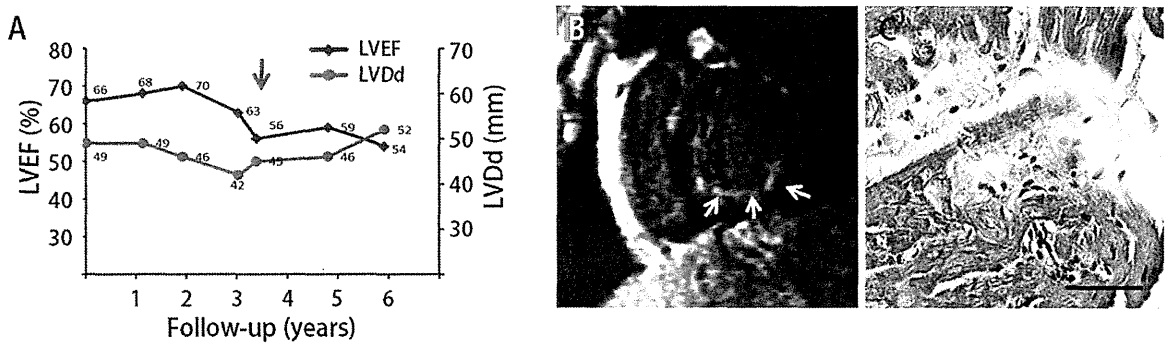

Figure 4. The findings of echocardiography, cardiac magnetic resonance (CMR) imaging and an endomyocardial biopsy in case 2. A. Temporal changes in left ventricular ejection fraction (LVEF) and end-diastolic dimension (LVDd) on echocardiography in case 2. The arrow indicates the point of the diagnosis of cardiac sarcoid involvement. B. CMR performed at the time of Q wave appearance on 12-lead ECG (arrow in A). Late gadolinium enhancement is recognized (arrows). C. Hematoxylin and Eosin staining of the biopsy specimen. Interstitial fibrosis and fatty infiltration are observed; however, no sarcoid granulomas are seen. The scale bar indicates 50 μm.

although evidence is circumstantial (15). For such situations, several non-invasive diagnostic modalities, such as FDG-PET and CMR, have become available. Indeed, CMR with gadolinium enhancement and radionuclide examination helped to diagnose cardiac sarcoid involvement in the two patients who had not been diagnosed with cardiac sarcoidosis at the time of first echocardiography. However, several issues should be considered when using these modalities, including time, cost, irradiation exposure and certain contraindications (16). In this sense, both echocardiography and ECG, although they may be less sensitive than CMR (17, 18), are practical and useful modalities that can be performed repeatedly. We must be aware, however, that such ultrasonographic follow-up may not be able to identify ongoing cardiac sarcoid involvement in a certain subfraction of non-cardiac sarcoidosis patients, as in case 2 in the current study.

There are several limitations to the current study. First, diagnostic modalities that are more sensitive for making an early diagnosis of cardiac involvement (19), such as gallium-67 citrate scintigram, CMR (18) and FDG-PET, were not performed in all non-cardiac sarcoidosis patients. Therefore, the true rate of cardiac involvement might have been greater than that reported in the current study (3). Second, two patients developed cardiac involvement more than two years after the start of echocardiographic follow-up. Therefore, with a longer follow-up period, more patients may manifest signs and symptoms of cardiac involvement. Third, ultrasonography was performed by multiple physicians and medical laboratory technicians, occasionally using different machines; however, this condition may reflect the situation of daily clinical practice, and non-cardiac sarcoidosis patients, in particular, should receive follow-up for years. We focused primarily on LVEF and LVDd and not on other findings potentially associated with cardiac sarcoidosis such as regional wall thinning, left ventricular regional wall motion abnormalities (20-22) and diastolic dysfunction (23).

In conclusion, among the 41 patients with sarcoidosis without cardiac involvement, two (4.9%) were diagnosed with cardiac involvement during the median follow-up period of 39 months according to Japanese criteria (10). Although one of these patients (case 1) showed a progressive decline in the LVEF over a short period of time, the other (case 2) showed only a mild decline in the LVEF with a preserved global left ventricular function. Therefore, rapid deterioration of left ventricular function may increase the suspicion of cardiac involvement in patients with extracardiac sarcoidosis; however, we must be aware that periodic screening of LVEF and LVDd may not detect a certain subfraction of patients who develop cardiac sarcoid involvement.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare (Investigation of Idiopathic Cardiomyopathy) and Research Grants from the Osaka Heart Club and the Meiji Yasuda Life Foundation of Health and Welfare.

References

1. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA **305**: 391-399, 2011.
2. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation **58**: 1204-1211, 1978.
3. Matsui Y, Iwai K, Tachibana T, et al. Clinicopathological study of fatal myocardial sarcoidosis. Ann N Y Acad Sci **278**: 455-469, 1976.
4. Habersberger J, Manins V, Taylor AJ. Cardiac sarcoidosis. Intern Med J **38**: 270-277, 2008.
5. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis **16**:

149-173, 1999.
6. Yazaki Y, Isobe M, Hiramitsu S, et al. Comparison of clinical features and prognosis of cardiac sarcoidosis and idiopathic dilated cardiomyopathy. Am J Cardiol **82**: 537-540, 1998.
7. Ardehali H, Howard DL, Hariri A, et al. A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. Am Heart J **150**: 459-463, 2005.
8. Bargout R, Kelly RF. Sarcoid heart disease: clinical course and treatment. Int J Cardiol **97**: 173-182, 2004.
9. Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. Circ Arrhythm Electrophysiol **4**: 43-48, 2011.
10. Guidelines for diagnosis and treatment of myocarditis (JCS 2009): digest version. Circ J **75**: 734-743, 2011.
11. Sharma S. Cardiac imaging in myocardial sarcoidosis and other cardiomyopathies. Curr Opin Pulm Med **15**: 507-512, 2009.
12. Nomura S, Funabashi N, Tsubura M, et al. Cardiac sarcoidosis evaluated by multimodality imaging. Int J Cardiol **150**: e81-e84, 2011.
13. Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. Heart **97**: 2078-2087, 2011.
14. Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. J Cardiovasc Electrophysiol **20**: 578-583, 2009.
15. Sekhri V, Sanal S, Delorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. Arch Med Sci **7**: 546-554, 2011.
16. Yeboah J, Lee C, Sharma OP. Cardiac sarcoidosis: a review 2011. Curr Opin Pulm Med **17**: 308-315, 2011.
17. Smedema JP, Snoep G, van Kroonenburgh MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol **45**: 1683-1690, 2005.
18. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation **120**: 1969-1977, 2009.
19. Tadamura E, Yamamuro M, Kubo S, et al. Effectiveness of delayed enhanced MRI for identification of cardiac sarcoidosis: comparison with radionuclide imaging. AJR Am J Roentgenol **185**: 110-115, 2005.
20. Lewin RF, Mor R, Spitzer S, Arditti A, Hellman C, Agmon J. Echocardiographic evaluation of patients with systemic sarcoidosis. Am Heart J **110**: 116-122, 1985.
21. Valantine H, McKenna WJ, Nihoyannopoulos P, et al. Sarcoidosis: a pattern of clinical and morphological presentation. Br Heart J **57**: 256-263, 1987.
22. Uemura A, Morimoto S, Kato Y, et al. Relationship between basal thinning of the interventricular septum and atrioventricular block in patients with cardiac sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis **22**: 63-65, 2005.
23. Aydin Kaderli A, Gullulu S, Coskun F, Yilmaz D, Uzaslan E. Impaired left ventricular systolic and diastolic functions in patients with early grade pulmonary sarcoidosis. Eur J Echocardiogr **11**: 809-813, 2010.

6 心筋生検

国立循環器病研究センター臨床検査部臨床病理科 松山高明
同 部長 植田初江

はじめに

心内膜心筋生検（心筋生検）の大きな目的は二次性心筋症の鑑別診断である．しかし，心筋生検は，CTやエコーなどによる正確な病変部位のガイドもなく，X線透視下でカテーテルを用いて盲目的に採取されるため，サンプリングエラーも多く，心筋生検のみで確定診断に至る疾患は少ない．そのため，疾患に特異的な所見を認めない場合は心筋細胞肥大や線維化の程度の報告にとどまることも多い．しかし，心筋生検での光学および電子顕微鏡による観察は，細胞レベルから超微細形態に至り，その解像度はいまもなお，臨床で用いられている画像装置をはるかに超えており，特徴的な所見が得られる場合は，治療や予後を左右する重要な情報を提供することのできる有用なモダリティである．

ここでは心筋生検で確定診断することのできる疾患と，必ずしも確定診断までは至らないが日々よく経験する代表的な心筋症の典型的な組織所見を紹介する．

確定診断される代表的心疾患

1．炎症性疾患

標本内に炎症細胞（特にリンパ球）を認める場合は，心筋炎やサルコイドーシスを疑う．典型的な組織像は以下に示すとおりであるが，リンパ球浸潤が消退した時期に検体が採取される症例も多く，実際には判断が難しいことも多い．

心筋炎

心筋炎は発症経過などから，臨床診断がついてから生検されることも多い．急性期で重症であるほど炎症細胞浸潤が高度で，診断は容易であるが，出現する炎症細胞の種類をよく見極めることが重要で，現在の日本のガイドラインでは，組織学的にはリンパ球性，好酸球性，巨細胞性などに分類されている[1]．リンパ球性はTリンパ球を主体とする炎症細胞が主体で，ウイルス性であることが多い（**図1-A**）．また，リンパ球とともに好酸球を伴う症例も多く，顕著な場合は好酸球性心筋炎と診断し，ステロイドの投与などを検討する必要がある（**図1-B, C**）．また，巨細胞を含む場合は巨細胞性心筋炎として報告し，次に述べるサルコイドーシスとの鑑別が重要である．巨細胞性心筋炎は心筋壊死が強く，巨細胞は一般にサルコイドーシスの巨細胞より小型のものが多く，残存する心筋線維の配列に一致する巨細胞の配列を認めることもある．また，好酸球を周囲に伴っていることも多い（**図2**）[2]．

サルコイドーシス

壊死を伴わない類上皮肉芽腫（epithelioid granuloma）を形成する．巨細胞はLanghans型が多いが，時にTouton型巨細胞のこともある（**図3**）．病変は心外膜側を主体に，飛び石状に分布することが多いので，他の画像検査でサルコイドーシスと診断されていても，サンプリングエラーにより実際に診断の決め手となる肉芽腫病変が採取される確率は低い．当センターでも，サルコイドーシスの臨床診断で心筋生検において肉芽腫を認めた症例は約30%にすぎない．しかし，時に臨床的に拡張型心筋症として，診断・治療中に心筋生検で肉芽腫を認め，実際はサルコイドーシスであった症例もみられるため，

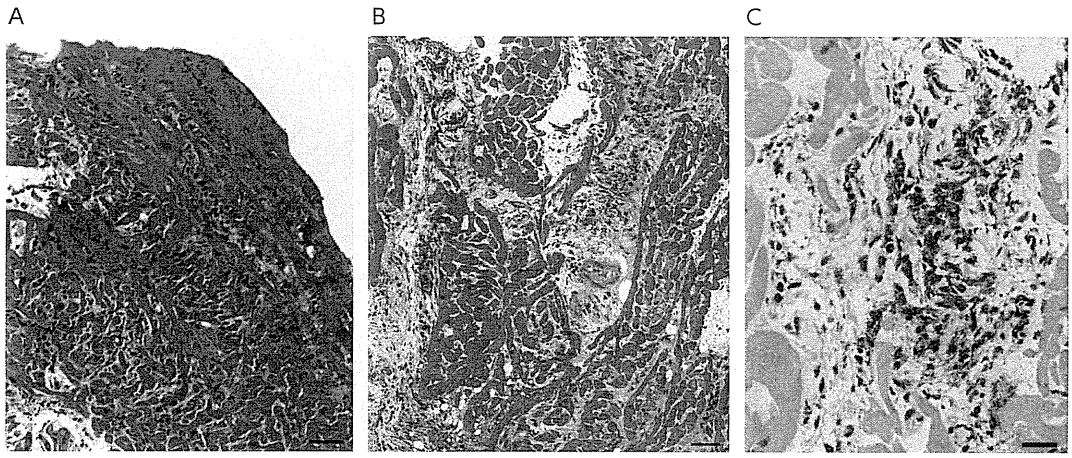

図1　急性心筋炎

A：リンパ球性心筋炎．浸潤細胞はリンパ球性が主体である．
B：好酸球性心筋炎．
C：Bの強拡大像．赤い好酸球の脱顆粒がみられる．
H&E染色，Scale bars＝50μm．

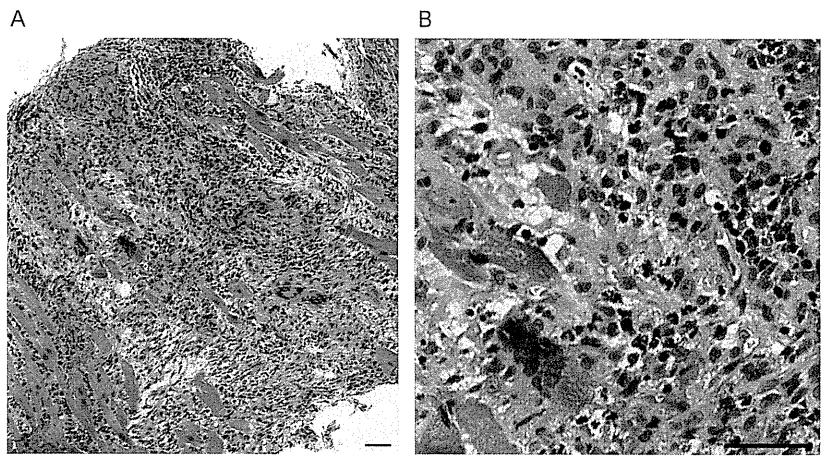

図2　巨細胞性心筋炎

A：びまん性の炎症細胞浸潤がみられ，巨細胞は心筋の配列方向に準じている．心筋壊死も目立つ．
B：強拡大像．巨細胞とともに好酸球の浸潤もみられる．
H&E染色，Scale bars＝50μm．

診断価値がないとは言えない．このようにサルコイドーシスの病変一つひとつは限局性であり，病変部以外の心筋はほぼ正常であることも特徴である．また，肉芽腫はしばしば線維化巣の辺縁部に存在する．

先述のように巨細胞は巨細胞性心筋炎のそれより大型で，特異的所見ではないが，細胞質内にasteroid bodyと呼ばれる小封入体を有することがある．また，好酸球を伴わないことが多い（図3-B）．

2．代謝性疾患

代謝性疾患はびまん性に病変が広がることが多く，サンプリングエラーは比較的少ないが，細胞質の変性や線維化などの非特異的な変化と類似した所

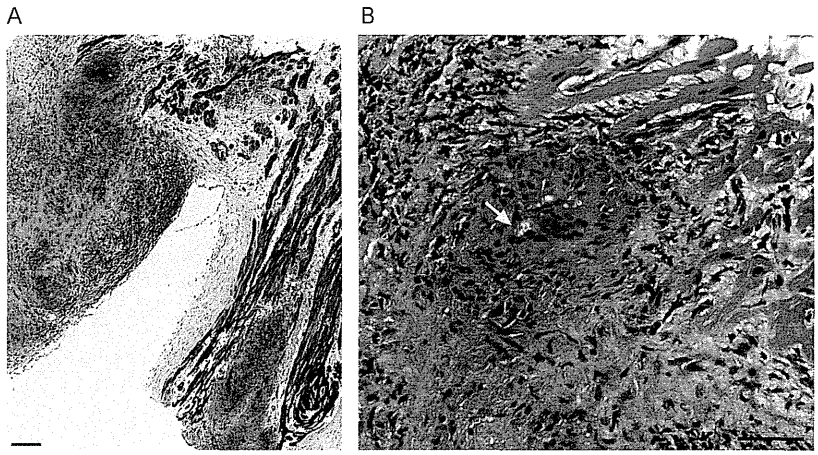

図3　心サルコイドーシス

A：巨細胞を含む胞巣状のリンパ球やマクロファージの浸潤（肉芽腫の形成）を認める．Masson-trichrome 染色，Scale bar＝100 μm.
B：巨細胞の細胞質内には asteroid body を認める（矢印）．H&E 染色，Scale bar＝50 μm.

見も多く，見逃さないように注意を要する．

アミロイドーシス

アミロイドーシスは，小動脈壁や間質にびまん性にアミロイド物質が沈着するため，心筋生検での診断率も高い．アミロイドの沈着量が増加すると，H＆E 染色でエオジン好性の無構造なアミロイド線維が心筋細胞一つひとつを取り囲むように沈着する（**図 4-A**）．特異的にアミロイドを判別する染色としてはコンゴーレッド染色やダイレクトファストスカーレット（DFS）染色が有用で，アミロイドの沈着部位は橙色に染色される．これらを偏光顕微鏡で観察すれば，アミロイド沈着部位は緑色の複屈折を呈することも特徴である（**図 4-B**）．また，過マンガン酸カリウム（$KMnO_4$）処理後のコンゴーレッド染色でも，橙色の染色性が維持されれば非 AA アミロイドであることが示唆される．免疫染色による原因検索も有用で，AL（κ，λ），二次性の AA，トランスサイレチン由来の ATTR（老人性，家族性トランスサイレチンアミロイドーシス）の区別も可能であるが，アミロイド蛋白は構造的に多様性を示すこともあり，必ずしも免疫染色で明瞭に区別できるとは限らない．また，電子顕微鏡によるアミロイド細線維の観察も有用である（**図 4-C**）．

Fabry 病

Fabry 病は，糖脂質（セラミドトリヘキソシド）の心筋細胞質への蓄積により，H＆E 染色では空砲化～レース様に変性した細胞質が特徴的である（**図 5-A**）．また，X 連鎖劣性遺伝で，男性では組織所見が高度であるが，ヘテロ接合体の女性でも発症することがあり，この場合は細胞質の変性が部分的であることも多い．細胞質の空胞化は，不全心におけるミトコンドリアの増加の際やミトコンドリア心筋症でも類似の所見を認めるため，Fabry 病の空胞化と区別が困難なこともある．より正確な診断には，電子顕微鏡で渦巻き状のミエリン様沈着物を確認する必要がある（**図 5-B**）．

確定診断には至らない疾患

特発性心筋症は，典型例でも組織学的には心筋細胞肥大や配列異常，間質の線維化など非特異的な所

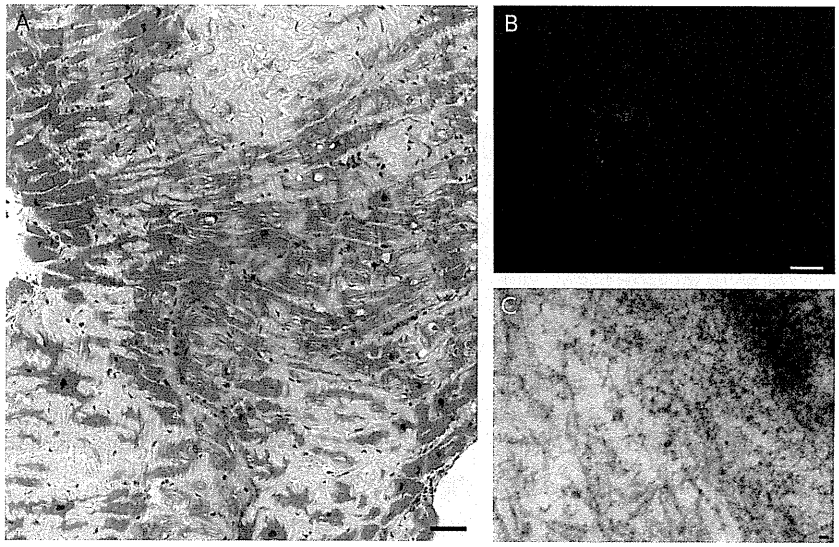

図4　心アミロイドーシス（AL-λ型）

A：心筋間にエオジン淡染のアミロイド物質が沈着し，心筋細胞は萎縮している．
H&E 染色，Scale bar＝50 μm.
B：Congo-red 染色の偏光顕微鏡像．アミロイド沈着部分は緑色を示す．Scale bar＝20 μm.
C：アミロイド細線維の電子顕微鏡像．径 10 nm 前後の細かい線維を無数に認める．
Scale bar＝20 nm.

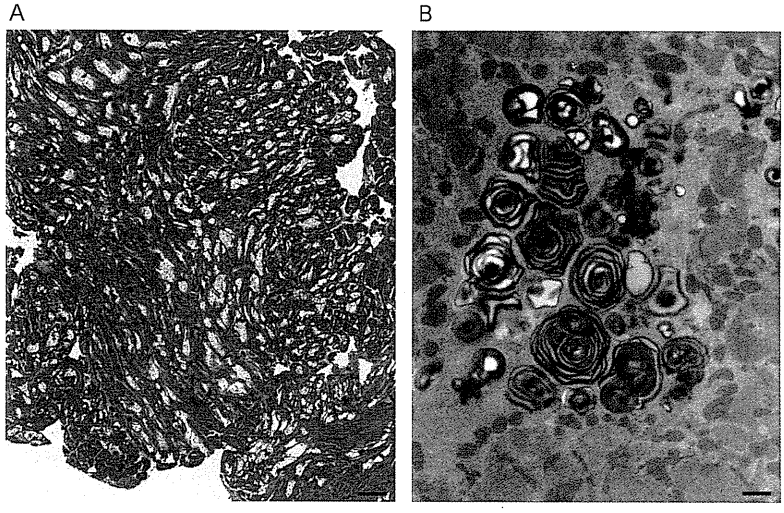

図5　心Fabry病

A：心筋細胞の細胞質はレース状の空胞変性を示している．H&E 染色，Scale bar＝50 μm.
B：電子顕微鏡では空胞部分に渦巻き状のミエリン様構造物が沈着している．Scale bar＝1 μm.

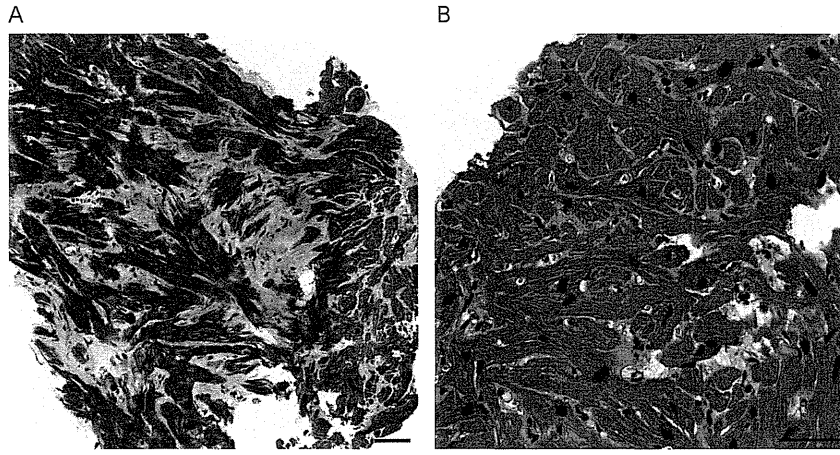

図6　肥大型心筋症

A：心筋細胞の配列は乱れ，錯綜配列を示している．線維化も高度で置換性の線維化を示している．Masson-trichrome 染色．
B：心筋細胞は肥大し，核の腫大・変形も目立つ．H&E 染色，Scale bars＝50μm.

見が主体であり，確定診断は困難であるが，臨床情報と照らし合わせることにより，臨床的な病態を組織学的に支持することもできる．

1．特発性心筋症

肥大型心筋症（hypertrophic cardiomyopathy：HCM）

教科書的には心筋細胞肥大，錯綜配列，変形・腫大した核が典型的な所見とされる．錯綜配列は生検で採取される中隔部分では生理的にも存在するため，判定が困難なことは多い．しかし，**図6**のように錯綜配列が標本全体に目立つ場合は，他の画像検査で壁肥厚などの特徴を確認した上で，HCM として矛盾しないとコメントすべきである．線維化は錯綜配列部位周囲に高度にみられる傾向があり，置換性の線維化が典型的である．線維化が高度である場合は拡張相へ移行している可能性も考慮される．

拡張型心筋症（dilated cardiomyopathy：DCM）

DCM の線維化は，一つひとつの心筋細胞周囲にびまん性に広がる間質線維化が典型的な線維化であるが（**図7**），置換性の線維化も認められる．病初期の症例では，細胞肥大や線維化が目立たないものもあり，組織所見が軽度だからといって疾患を否定することはできない．また，慢性炎症が関与するものも inflammatory DCM（DCMI）として提唱されており，そのような症例では慢性心筋炎の範疇に入るようなわずかなリンパ球浸潤や置換性の線維化を示す症例もある[3]．

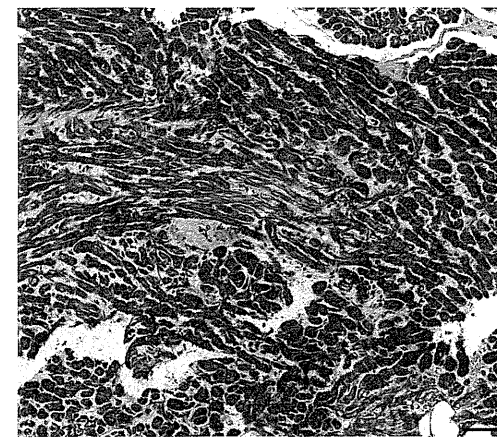

図7　拡張型心筋症

間質は心筋細胞一つひとつの周囲にびまん性に広がっている．Masson-trichrome 染色，Scale bar＝50μm.

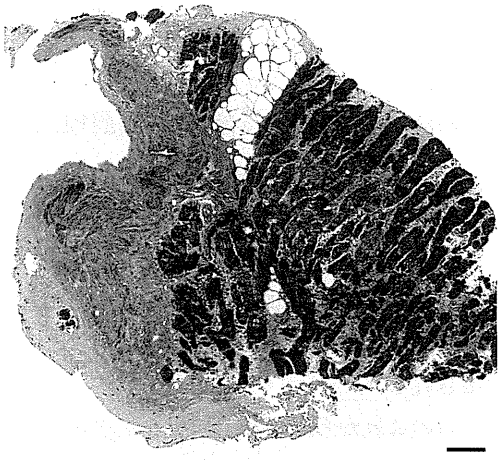

図8　不整脈源性右室心筋症

心筋細胞肥大，間質線維化とともに脂肪浸潤を認める．
Masson-trichrome 染色，Scale bar＝100 μm.

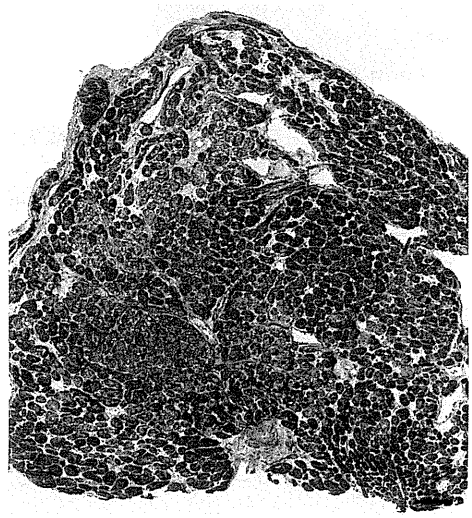

図9　高血圧性心疾患

高度の心筋肥大と小動脈を中心に放射状に広がる，血管周囲性の線維化が典型的である．
Masson-trichrome 染色，Scale bar＝100 μm.

不整脈源性右室心筋症（arrhythmogenic right ventricular cardiomyopathy：ARVC）

ARVC は，線維脂肪化を標本に含むことが典型的であるが（**図8**），心筋生検で得られる所見として，脂肪浸潤の有無よりも線維化病変を認めることが重要視されてきている[4]．中年以降の女性では生理的に脂肪浸潤を右室壁内に認めることも多く，この場合は脂肪組織周囲の線維化や心筋細胞の変化が乏しい．

高血圧性心疾患（hypertensive heart disease：HHD）および弁膜症などによる圧負荷や容量負荷による変化

長期にわたる心負荷により，心筋細胞は高度に肥大する症例が多い．線維化は，小動脈または毛細血管から放射状に広がる血管周囲性線維化が典型的である（**図9**）．筋層内小動脈の壁肥厚もしばしば観察される．

おわりに

以上，よく経験することの多い疾患の心筋生検での典型的な所見を挙げてきたが，日常提出される標本は典型的所見を含まないものが大多数である．この非特異的所見が主体の判断の難しい検体から有意義な情報を得るには，臨床と病理が標本を供覧し検討することも必要であると考える．

● 参考文献

1) JCS Joint Working Group. Guidelines for diagnosis treatment of myocarditis (JCS 2009)：digest version. Circ J. 75 (3), 2011, 734-43.
2) Okura, Y. et al. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. J Am Coll Cardiol. 41 (2), 2003, 322-8.
3) Maisch, B. et al. Inflammatory dilated cardiomyopathy (DCMI). Herz. 30 (6), 2005, 535-44.
4) Marcus, FI. et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia：proposed modification of the task force criteria. Circulation. 121, 2010, 1533-41.

特集

不安定プラークを
どう見つけ，
どう治療する

2 診る

不安定プラークを
バイオマーカーからとらえる

Biomarkers of vulnerable atheromatous plaques

佐久間理吏，野出孝一（佐賀大学医学部循環器内科）

キーワード

プラーク破綻，急性冠症候群，
バイオマーカー

急性冠症候群のうち，特に急性心筋梗塞は心筋壊死とその後のリモデリングから心不全の経過をたどる。このため急性心筋梗塞発症前段階である動脈硬化プラークの不安定化をいかに診断し，迅速に治療介入できるかが，心筋梗塞ひいては心不全発症予防へとつながる。

近年各種デバイスの発達により，不安定プラークの診断は，イメージングがその中心を担っている。実際イメージングの発達によりプラーク破綻には，外膜におけるvasa vasorumからの新生血管の関与が証明された。またプラーク破綻しやすい病理学的特徴をイメージングデバイスでとらえることができるようになった。しかし不安定プラークのスクリーニングとなると，迅速で簡便かつ診断感度，特異度の高さが求められる。血液バイオマーカーによる不安定プラークの診断はこれらの要望に応えられる可能性を秘めている。

本稿ではプラーク破綻を予測しうるバイオマーカーに関する最新知見を概説する。

1342-6591/13/¥400/論文/JCOPY

ラーク破綻の特徴

破綻を起こすようなプラークの特徴としてNarulaらは，プラーク総面積はポジティブリモデリングにより拡大した血管における総断面積の50%以上であり，necrotic coreはプラークの25%を占める。vasa vasorumからプラーク内新生血管を通じて赤血球の漏出，マクロファージの浸潤を認め，線維性被膜の厚さは65μm以下と指摘している[1]（図1）。

また Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) 研究では，急性冠症候群697症例に対して，責任血管を含む3枝すべてに血管内超音波 (intravascular ultrasound；IVUS) や Virtual Histology™ (VH) IVUSを行い，有意狭窄を有さない非責任病変のその後のイベントをIVUS所見により予測できるか検討した[2]。その結果

①プラーク荷重(70%以上)
②VH-IVUSによる薄い線維性被膜をもつ粥腫
③病変部最小血管断面積4.0mm^{2}以下

の3つの指標が非責任病変によるイベントと相関した。

しかしここで注目すべき点はVH-IVUSを施行した623症例のうち313症例に薄い線維性被膜をもつ粥腫596病変を認めたが，3年間のフォローアップ期間で不安定狭心症や安定狭心症で入院が必要となった症例は69人(10.8%)，急性心筋梗塞発症症例はわずか6人(1%)であったことである。これは急性冠症候群の原因として薄い線維性被膜をもつ粥腫が関与しているが，すべての症例が急性冠症候群に至るわけではないことが示唆された。

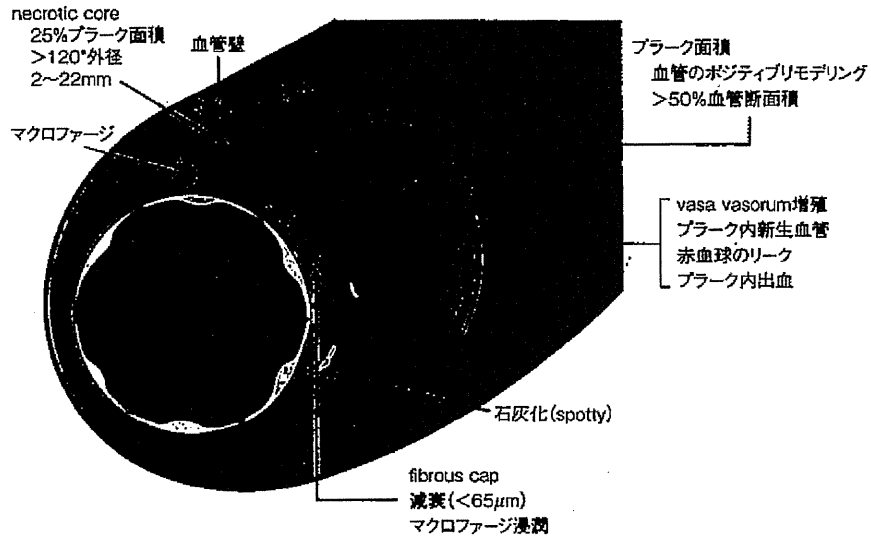

図1 破綻しやすいプラークの特徴(文献1より引用)
①プラークはポジティブリモデリングしている血管断面積の50%以上。
②necrotic coreはプラークの25%を占める。
③vaso vasorumの増殖によるプラーク内新生血管から赤血球のリーク。
④マクロファージの浸潤。
⑤線維性被膜の厚さは65μm以下。

Arbab-Zadehらは典型的な急性冠症候群発症は，動脈硬化プラーク破綻かerosion(浅い潰瘍)によって引き起こされるが，大多数の症例ではプラーク破綻かerosionは徴候なく病変が収束するか，狭窄病変へ進展すると報告している[3]（図2）。つまり薄い線維性被膜をもつ粥腫が存在しても，血管を閉塞するようなプラーク破綻は，プラーク荷重や急速に進展するプラーク，血栓を誘引しやすい環境が重要であり，これらを反映するバイオマーカーがプラーク破綻を予測しうるバイオマーカーになりうる可能性が高い。

イオマーカー

プラーク不安定化から破綻に至るまでの主要バイオマーカーを図3に示した。各バイオマーカーは病態を反映した生理活性を示し，各ステージの特異的マーカーや急性炎症を示すマーカーが報告されている。

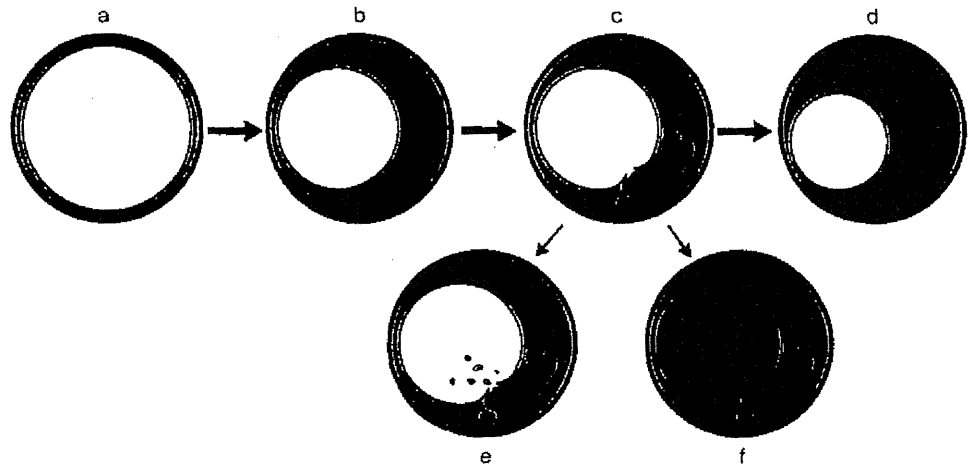

図2　冠動脈硬化病変の進展
(文献3より引用)
a：正常冠動脈断面イメージ。b：動脈硬化プラークの蓄積とポジティブリモデリング。c：プラーク内出血によるプラーク不安定化と破綻。d：多くの場合プラーク破綻やerosionは微候なく病変が収束するか，狭窄病変へ進展。e：症状を伴わない程度の末梢血栓閉塞。f：プラーク破綻やerosion部位での血栓閉塞による急性冠症候群発症。

しかし実際に臨床の現場で急性冠症候群の診断に応用されているバイオマーカーは急性心筋梗塞に際し細胞壊死を反映する，クレアチニンキナーゼ/クレアチニンキナーゼMB分画(CK/CKMB)，トロポニンI，トロポニンT，心臓型脂肪酸結合蛋白(heart-type fatty acid-binding protein；H-FABP)である。H-FABPは遊離脂肪酸の細胞内輸送に関与する低分子可溶性蛋白であり，心筋梗塞発症数時間以内に陽性として測定できる感度，特異度の高いマーカーであり臨床現場で使用されている。またトロポニンI，トロポニンTは筋原線維構造蛋白であり，発症数時間以内で陽性を示し高感度となったことで測定精度が高くなった[4]。このため2012年European Society of Cardiologyでも引き続き，心筋梗塞の世界共通定義として心筋梗塞診断バイオマーカーは心筋トロポニンI/Tが推奨されている[5]。一方プラーク破綻をとらえるバイオマーカーの報告は散見されているものの，実臨床現場で使用するまでには至っていない。以下にプラーク破綻を反映するバイオマーカー候補を概説する。

プラーク破綻反映バイオマーカー

(1)C反応性蛋白(C-reactive protein；CRP)

CRPは局所の炎症を反映してインターロイキン(interleukin；IL)-6の刺激により肝臓で産生されるが，筆者らは冠動脈狭窄病変(プラーク)遠位部

と近位部で高感度CRP(high sensitive CRP；hsCRP)を測定したところ，特に不安定狭心症において有意な遠位近位部間格差を認めた。このことからプラークからのhsCRP産生が示唆された[6]。Boukiらは急性冠症候群と労作性狭心症症例に光干渉断層法(optical coherence tomography：OCT)を施行し，責任病変とhsCRPを検討した[7]。労作性狭心症群と比較して，急性冠症候群ではOCT所見で明らかなプラーク破綻や薄い線維性被膜をもつ粥腫を80%に認め，これに相関しhsCRPは有意に高値を示したと報告した。

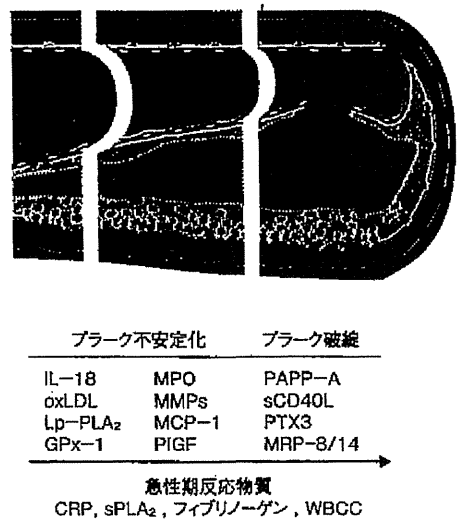

図3 プラーク破綻に至るまでのバイオマーカーカスケード(文献22，23より引用改変)

Lp-PLA2：lipoprotein associated phospholipase A2，MCP-1：monocyte chemoatractant protein-1，GPx-1：glutathione peroxidase，MMP：matrix metalloprotease，MPO：myeloperoxidase，PIGF：placental growth factor，PAPP-A：pregnancy-associated plasma protein-A，sCD40L：soluble CD40 ligand，sPLA2：secretory type Ⅱ phospholipase A2，SAA：serum amyloid A，WBCC：white blood cell count

(2) PTX3

ペントラキシン3(pentraxin；PTX3)はCRPと同じペントラキシンファミリーに属し，IL-1βや腫瘍壊死因子α(tumor necrosis factor α；TNFα)などの刺激により血管内皮細胞，血管平滑筋細胞，マクロファージ，樹状細胞，脂肪細胞や白血球特に好中球から産生される。また進行したプラーク内にもPTX3は認められている[8]。Inoueらは安定労作性狭心症ではPTX3の血中濃度の上昇は認められないが，不安定狭心症において上昇したと報告した[9]。また急性心筋梗塞症例において，血栓吸引カテーテルにより採取した血栓標本にPTX3の発現が認められている[10]。

(3) MRP8/14

急性心筋梗塞の原因がプラーク破綻とそれに引き続き生じる血栓閉塞によることから血栓の主要因子である血小板に着目し，筆者らはマイクロアレイを用いて，急性心筋梗塞患者群と安定労作性狭心症群から血小板(メガカリオサイト)の遺伝子をプロファイリングし解析した。すると安定労作性狭心症群よりも急性心筋梗塞群で発現が高い蛋白としてmyeloid-related protein(MRP)-14が同定された[11]。MRP-14はカルシウムイオン調節蛋白のS100蛋白に属しS100A9，カルグラニュリンBとして知られている。血中ではMRP-8/14ヘテロダイマーとして存在し，好中球，単球から産生されている。Altweggらは，胸痛を主訴とした心筋梗塞患者において，ほかの心筋壊死マーカーであるトロポニンT，ミオグロビン，CKMBより早期に血中MRP-8/14値上昇を認めたと報告した[12]。

(4) myeloperoxidase(MPO)

MPOは白血球に存在する酵素であり，生体防御にとって重要な働きをする。酸化ストレス関連因子であり，動脈硬化病変においてはプラーク破綻に関与する。実際，急性冠症候群の破綻したプラークには多数の好中球浸潤が認められたと報告されている[13]。またMPOはCRPの急性冠症候群予測能より優れ，トロポニンT陰性の胸痛症例においても，陽性症例と同等に急性冠

症候群の発症を予測した。このことから心筋壊死に至る前に心血管イベントを識別でき，胸痛患者のリスク層別化に役に立つと報告されている[14]。

(5) soluble CD40 ligand (sCD40L)

CD40リガンド(CD40L)は活性化CD4陽性ヘルパー細胞(Th2細胞)表面に発現し，単球・マクロファージや樹状細胞表面のCD40と結合することでこれら抗原提示細胞を活性化させる。CD40Lは動脈硬化症におけるプラークの進展や，不安定化にも重要な役割を担うと考えられており，そのsoluble form(sCD40L)が活性化リンパ球や血小板から放出され，マクロファージや平滑筋細胞上の組織因子発現を増強させ，炎症反応や凝固を更新させ血栓形成を促すと考えられる。実際動脈硬化病変にはCD40とそのリガンドであるCD40Lの発現が認められている[15]。

(6) pregnancy associated plasma protein A (PAPP-A)

元来PAPP-Aはダウン症のスクリーニングに最も優れたマーカーとして妊娠期間中に測定されていたが，最近PAPP-A抗原がinsulin-like growth factor-Iを特異的に活性化させることから動脈硬化促進的に働く可能性が示唆されている。PAPP-Aは安定プラークには発現しないが，不安定化プラークに発現を認める。また急性冠症候群患者で血中PAPP-A濃度が上昇しており，CRPやIGF-Iと有意な相関を示すのに対し，トロポニンIやCKMBとは相関を示さないことから，PAPP-Aの上昇はプラーク不安定化を反映していると考えられている[16]。

(7) matrix metalloproteinase-9 (MMP-9)

MMPは細胞外基質を分解する酵素の総称であり，マクロファージがMMPを産生する。MMPは線維性被膜の細胞外基質を分解することでプラークの不安定化を加速させ，ついにはプラーク破綻に至ることで，急性冠症候群が発症する。特にMMP-9は，急性冠症候群において安定狭心症と比べ有意な上昇が報告されている[17]。Kobayashiらの報告では発症4時間以内の急性冠症候群に関してトロポニンTよりも早期に血中濃度が上昇し高い診断精度を認めたと報告している[18]。

バイオマーカーと高感度トロポニンTとの比較研究

McCannらの報告では急性の胸痛患者415症例を対象に，心筋傷害マーカー〔H-FABP，glycogen phosphorylase-BB(GP-BB)〕，神経ホルモン活性マーカー(NT-proBNP)，凝固活性マーカー(Dダイマー)，血管炎症マーカー(hsCRP，MPO，MMP-9，PAPP-A，sCD40L)とトロポニンTで急性心筋梗塞診断精度を比較した[19]。**表1**に示すとおりROC曲線から得られたarea under the receiver operating curve(AUC)による診断精