

MYOCARDITIS

Cardiac Magnetic Resonance Appearance of Myocarditis Caused by High Dose IL-2: Similarities to Community-Acquired Myocarditis

W. Patricia Ingkanisorn, MD,^{1,*} D. Ian Paterson, MD,^{1,2,*} Katherine R. Calvo, MD, PhD,³ Douglas R. Rosing, MD,¹
Douglas J. Schwartzentruber, MD,³ Anthon R. Fuisz, MD,² and Andrew E. Arai, MD¹

National Heart, Lung and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA,¹
Washington Hospital Center, Washington, DC, USA,² National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA³

ABSTRACT

The purpose of this study was to describe and compare the cardiac magnetic resonance (CMR) characteristics of myocarditis caused by high dose interleukin-2 (7 patients) with community-acquired myocarditis (14 patients). A total of 21 patients with suspected myocarditis and elevated cardiac enzymes underwent cine CMR followed by delayed enhancement. The mean ejection fraction was mildly decreased in both groups. The location, pattern, and extent of DE were similar in both groups of patients. The CMR similarities between these two populations suggest that cytokine-mediated cytotoxicity may play an important role in community-acquired myocarditis.

INTRODUCTION

Myocarditis is an acute inflammatory condition of the myocardium that can mimic a myocardial infarction (MI) and is a cause of dilated cardiomyopathy. Most commonly, myocarditis results from a viral infection, although other causes include immunotherapy, radiotherapy and autoimmune diseases. Myocarditis is an uncommon complication of high-dose IL-2 therapy (1–4), affecting 3–5% of those undergoing therapy.

The diagnosis of myocarditis is often made on clinical grounds after the exclusion of an acute coronary syndrome or in the evaluation of cardiomyopathy. Endomyocardial biopsy can be used to make a diagnosis but is invasive and of low sensitivity (5–7, 21). Gadolinium delayed enhancement (DE) cardiac magnetic resonance (CMR) imaging has been validated in the diagnosis of myocarditis (8, 9). This technique reveals delayed enhancement abnormalities predominating in the subepicardial portion of the ventricular free wall (9). The reason for this distribution of myocardial necrosis is unclear.

The purpose of this study was to describe and compare the CMR characteristics of myocarditis caused by high dose interleukin-2 with community-acquired myocarditis.

METHODS

Study population

The study population consisted of two groups of patients with suspected myocarditis and no history of MI seen over a 33-month period (June 2002–March 2005). Written informed consent was obtained from all patients before undergoing CMR. Patients received high dose IL-2 immunotherapy for metastatic melanoma as part of a research protocol at the National Institutes of Health. Possible myocarditis in patients receiving IL-2

Keywords: Myocarditis, Magnetic Resonance Imaging, Interleukin-2, Gadolinium, Troponin

**These authors contributed equally to this work and share 1st-authorship.*

Funded by the intramural program of the National Heart, Lung, and Blood Institute. There are no conflicts of interest with regard to this manuscript.

*Correspondence to: Andrew E. Arai, MD
Laboratory of Cardiac Energetics
National Heart, Lung, and Blood Institute
National Institutes of Health
10 Center Dr., MSC 1061
Building 10, Room B1D-416
Bethesda, MD 20892-1061
email: arai@nih.gov
telephone: (301) 496-0248 fax: (301) 402-2389*

therapy was identified based on abnormally elevated troponin I (Tn-I) and creatine kinase on serial blood tests drawn as part of their research safety monitoring of the IL-2 therapy. Nine IL-2 patients were prospectively recruited after identifying the index case. Two patients were excluded from the analysis because they were unable to be imaged within a window of two weeks from the elevation in troponin. A total of 7 IL-2 patients were included in the analysis.

The second group was derived from a retrospective review of consecutive patients at 2 tertiary care hospitals presenting with chest discomfort, elevated Tn-I, and no significant coronary artery disease on conventional coronary angiography who were undergoing CMR for suspected viral myocarditis. A chart review was performed in all patients in order to collect the following data: clinical history, electrocardiography, cardiac enzymes, and coronary angiography. Of the 16 patients identified, 2 were excluded from the analysis because they did not undergo coronary angiography. Thus, a total of 14 patients with community-acquired myocarditis were included in the analysis.

Patients with standard contraindications to CMR such as pacemakers and defibrillators were also excluded.

Imaging protocol

For the IL-2 group and 3 patients of the community-acquired group, CMR was performed on a 1.5 T CV/i scanner (General Electric, Waukesha, WI, USA). Cardiac images were ECG-gated. We used a 4-channel phased array surface coil, performed during short breath-holds. LV function was assessed with steady state free precession cine CMR in long and short axis planes. Imaging parameters included a slice thickness of 8 mm with a skip of 3 mm, an in-plane resolution of 1.5×1.7 mm/pixel, TR of 3.7 ms, TE of 1.6 ms, a flip angle of 45° and 30 images per cardiac cycle. Delayed enhancement imaging was performed 15–20 minutes after administration of 0.2 mmol/kg of gadopentetate dimeglumine (Berlex Laboratories, Wayne, NJ, USA) through a peripheral intravenous line. A fast gradient recalled echo inversion recovery sequence was run with slice locations identical to the functional imaging. Inversion time was adjusted to null normal myocardium on a patient-by-patient basis. Parameters included a slice thickness of 8 mm with a skip of 3 mm, an in-plane resolution of 1.4×2.2 mm/pixel, inversion time 300 ms, TR 7 ms, TE 3.1 ms and a flip angle of 20° .

The remaining 11 cases of community-acquired myocarditis cases were imaged using a 1.5 T scanner Intera CV (Philips, Best, The Netherlands). Images were acquired using a 5-channel phased array coil and acquisitions times were shortened using a SENSE factor of 2. Steady state free precession cine CMR used imaging parameters including a slice thickness of 6 mm with a skip of 4 mm, a reconstructed in-plane resolution of 1.4×1.4 mm/pixel, TR of 3.2 ms, TE of 1.6 ms, a flip angle of 55° and 25 phases/cardiac cycle. Delayed enhancement imaging was performed 10 minutes after administration of 0.15–0.2 mmol/kg of gadodiamide (Amersham Health, Princeton, NJ, USA) through

a peripheral intravenous line. A balanced fast field echo inversion recovery sequence was run with slice locations identical to the functional imaging. Inversion time was also adjusted to null normal myocardium on a patient-by-patient basis. Parameters included a slice thickness of 5 mm with a skip of 5 mm, a reconstructed in-plane resolution of 0.8×0.8 mm/pixel, inversion time 200 ms, TR 4.0 ms, TE 1.2 ms and a flip angle of 15° .

Qualitative and quantitative MRI analysis

Volumetric and linear measures were performed using Cine 2.1 (General Electric) and Easy Vision (Philips). LV measures included LV ejection fraction (EF), stroke volume, end-diastolic volume, end-diastolic dimension, mass, septal thickness and left atrial size. The presence of pericardial effusions was also noted on cine and delayed enhancement imaging.

The presence and pattern (subendocardial, midmyocardial or subepicardial) of DE was characterized by consensus of 2 cardiologists blinded to the clinical details. Using a standardized 17-segment model of the heart (10), the transmural extent was noted and the severity was assessed by a scoring system. If a segment had no DE, then it received a score of 0. Segments with DE $< 25\%$ received a score of 1; those with DE 26–50% were scored 2; those with DE 51–75% were scored 3; and those with DE 76–100% were scored 4. Thus, for the 17-segment model, DE scores could range from 0 to 68.

Quantitative analysis was performed on a patient-by-patient basis to confirm that regions of delayed enhancement identified were brighter than normal myocardium. A region of interest was drawn within an area interpreted as having increased signal intensity, and a region of interest was drawn within an area of remote, normal-appearing myocardium. Significant delayed enhancement was defined as a signal intensity increase of greater than two standard deviations above the mean value of remote normal myocardium.

Pathologic correlation

One patient with IL-2 myocarditis died, and an autopsy was performed. The heart was cut in the LV short axis plane, and transmural samples of LV myocardium were selected based on the in vivo DE images. The tissue was stained with hematoxylin and eosin as well as Masson's trichrome.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation. Data were analyzed statistically using SigmaStat software (SPSS, Chicago, Illinois, USA). Comparisons between the IL-2 group and the community-acquired group were compared using an unpaired, two-tailed Student t-test. For data that were not normal, a Mann-Whitney Rank Sum Test was performed rather than a t-test. $P \leq .05$ was considered a significant result.

RESULTS

Clinical parameters (Table 1)

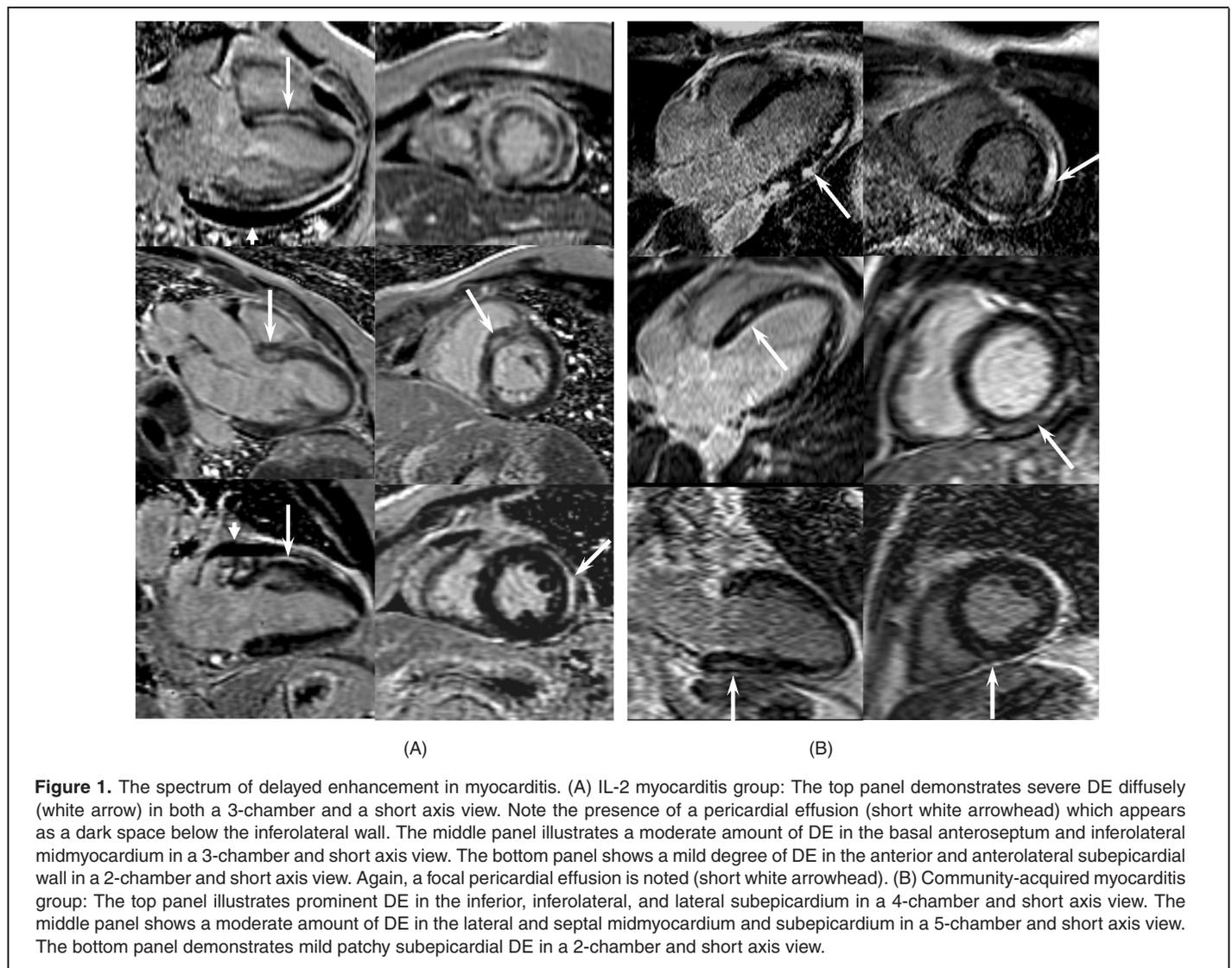
The IL-2 myocarditis group was older than the community-acquired group (mean age of 46 ± 5 years vs. 38 ± 12 years respectively), but this did not reach statistical significance ($p = .11$). All patients had 0-1 risk factors for coronary atherosclerosis except for two of the community-acquired patients who had 2 risk factors. Each patient from the IL-2 group had a negative stress test prior to undergoing immunotherapy. In the community-acquired group, 6 patients gave a history of recent viral infection, and all but 2 experienced chest discomfort upon arrival to the emergency room.

ECG abnormalities were observed in all but 3 patients. Significant ST elevation (≥ 1 mm) was present in 8 patients with community-acquired myocarditis and 1 patient with IL-2 induced injury consistent with either pericarditis or ST segment elevation MI.

Table 1. Demographics and clinical characteristics

	IL-2 (n = 7)	Community- Acquired (n = 14)	p value
Age (years)	46 ± 5	38 ± 12	0.11
Male	4 of 7	13 of 14	0.20
Caucasian	7	10 of 14	0.31
0-1 CAD risk factors	100%	12 of 14	0.18
Preceding viral illness	0%	6 of 14	0.12
Chest Pain	0%	12 of 14	0.002
Non-sustained V-T	4 of 7	0 of 14	0.04
ST segment elevation 1 mm	1 of 7	8 of 14	0.09
CK total (ng/mL)	845 ± 561	NA	
CK-mb (ng/mL)	173 ± 157	55 ± 127	0.06
Peak Tn-I (ng/mL)	382 ± 274	24 ± 54	<0.001

Peak Tn-I levels were significantly higher in the IL-2 group. The mean Tn-I for the IL-2 group was 382 ± 274 ng/mL (range 32–852). The mean Tn-I for the community-acquired group was 24 ± 54 ng/mL (range 0.8–224) ($p < .001$). Cardiac



catheterization was performed in all patients in the community-acquired group, and normal coronary arteries were found in each case. Endomyocardial biopsy was performed in one patient, and results are discussed below.

Three patients presented with cardiac decompensation. Two patients, 1 in the IL-2 group and one in the community-acquired group, experienced acute pulmonary edema that promptly responded to diuresis. The third patient (from the community-acquired group) required 24-hour intra-aortic balloon pump support for cardiogenic shock. All survived to discharge, but 1 patient in the IL-2 group died 10 months after the myocarditis diagnosis. The cause of death was hemoperitoneum from a metastatic lesion that had eroded through the capsule of the liver. An autopsy was performed, and the findings in the heart are discussed below.

CMR characteristics

Delayed enhancement (Fig. 1 and Table 2)

During initial hospitalization, all 21 patients underwent CMR. All patients exhibited abnormal DE of the myocardium after administration of gadolinium. A majority of patients in both groups had some septal involvement, 6 of 7 in the IL-2 group vs. 9 of 14 in the community-acquired group. In the IL-2 group, 3 had midmyocardial enhancement, 1 had subepicardial enhancement, and 3 had both midmyocardial and subepicardial enhancement. In the community-acquired group, 4 had midmyocardial enhancement, 6 had subepicardial enhancement, and 4 had both midmyocardial and subepicardial enhancement. None

Table 2. CMR characteristics

	IL-2 group (n = 7)	Community Acquired (n = 14)	p value
Days after Peak Tn-I	6 ± 5	1 ± 1	0.009
DE present	100%	100%	
DE pattern	Midwall and subepicardial	Midwall and subepicardial	
DE score	22 ± 12	14 ± 9	0.12
EF (%)	52 ± 8	53 ± 12	0.97
LVEDD (mm)	55 ± 4	57 ± 6	0.62
LVEDV (mL)	187 ± 42	191 ± 41	0.82
LV mass (g)	130 ± 30	159 ± 39	0.11
IVS (mm)	8 ± 2	10 ± 1	0.03
LA (mm)	37 ± 7	36 ± 6	0.73
Pericardial effusion	6 of 7	5 of 14	0.07

****LVEDD = left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, IVS = interventricular septum, LA = left atrium

of the patients had subendocardial involvement. The overall distribution in the myocardium was patchy, and in no cases did the affected segments follow a coronary distribution. The extent of DE trended toward higher in the IL-2 group (DE mean score for the IL-2 group 22 ± 12 vs. 14 ± 9 for the community-acquired group, p = .12).

LV measures (Table 2 and Fig. 2)

LV systolic function was depressed (<55%) in 10 of 21 patients. Calculated EF ranged from 41–59% for the IL-2

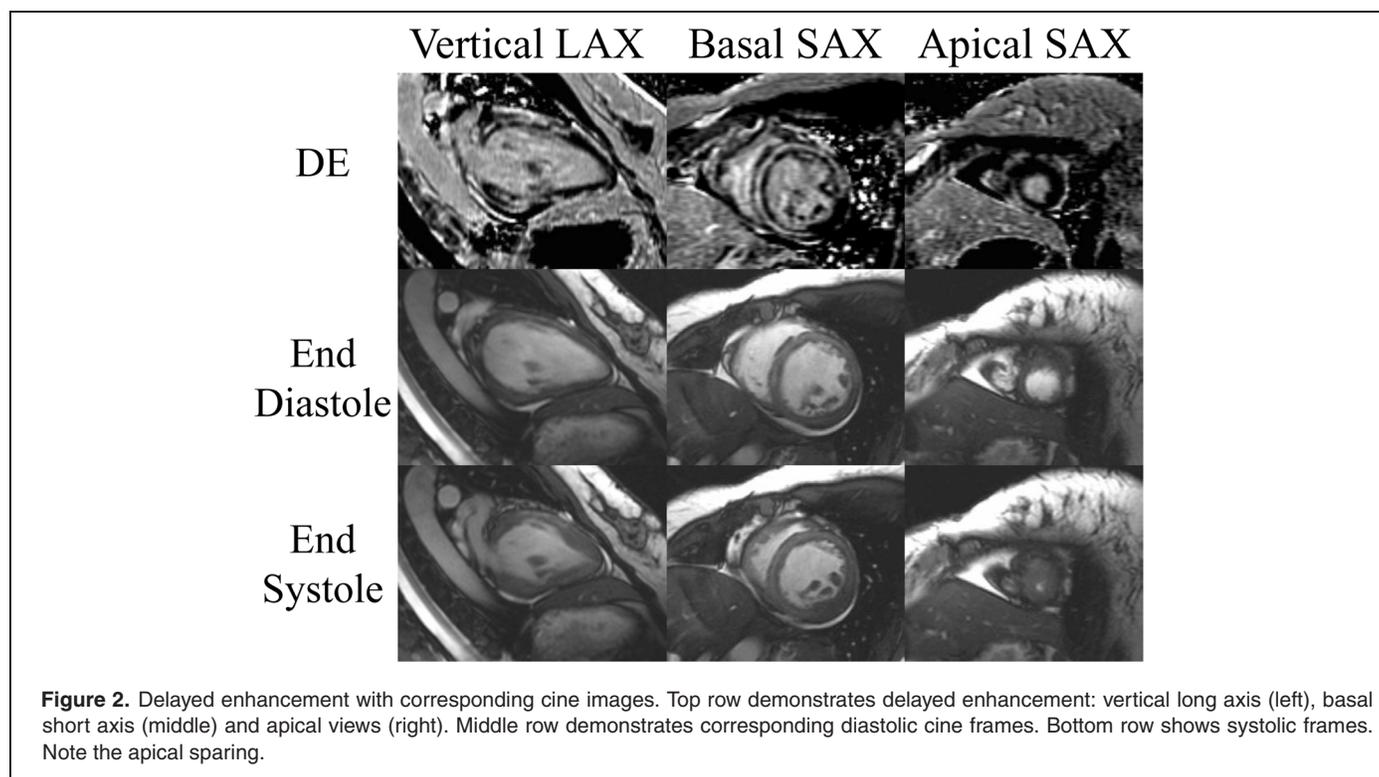
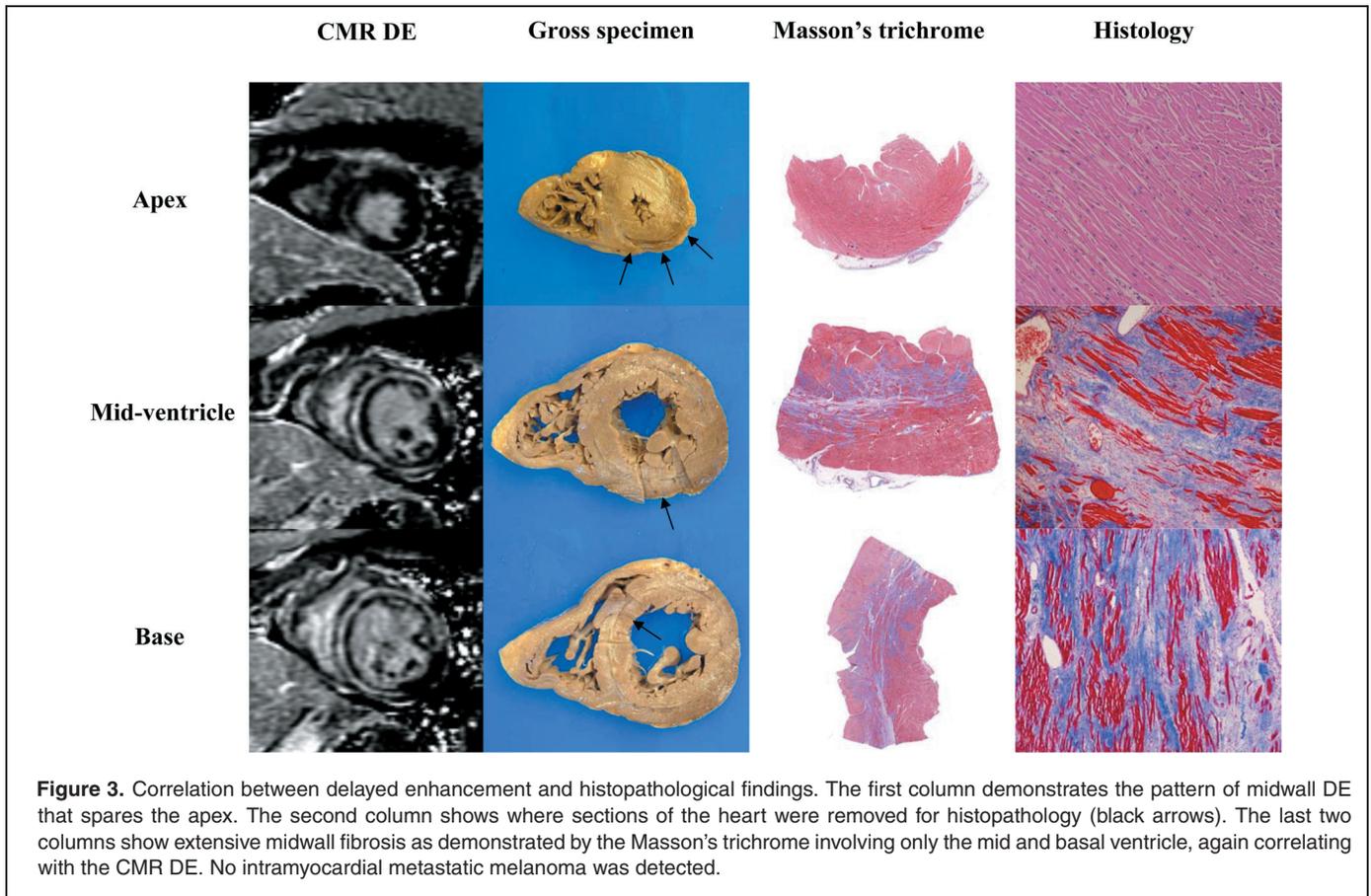


Figure 2. Delayed enhancement with corresponding cine images. Top row demonstrates delayed enhancement: vertical long axis (left), basal short axis (middle) and apical views (right). Middle row demonstrates corresponding diastolic cine frames. Bottom row shows systolic frames. Note the apical sparing.



myocarditis patients and 29–69% for the community-acquired group. On average, the LV end diastolic volume was at the upper limit of normal in both groups. Both ventricular mass and septal thickness were normal. Pericardial effusion was present in 6 patients with IL-2 myocarditis and 5 patients with community-acquired myocarditis.

Autopsy and biopsy results (Figs. 3–5)

One patient with IL-2 myocarditis died of non-cardiac causes 10 months after initial presentation. Short axis cross sections of the heart revealed mid wall myocardial scar in the basal and mid septum and inferior segments and absent scar in the apex. There was agreement between the distribution of scar of these specimens and the findings on CMR imaging. Histological inspection revealed myocardial fibrosis as well as focal areas of myocyte necrosis with surrounding lymphocytes. These findings were diagnostic for myocarditis according to the Dallas criteria (11). No coronary atherosclerotic plaques were detected. There was no evidence for metastatic melanoma in the heart.

One patient with community-acquired myocarditis underwent endomyocardial biopsy; however, he had a probable false negative biopsy (Fig. 5).

DISCUSSION

The pattern, extent and location of abnormal delayed enhancement CMR are similar between patients with IL-2

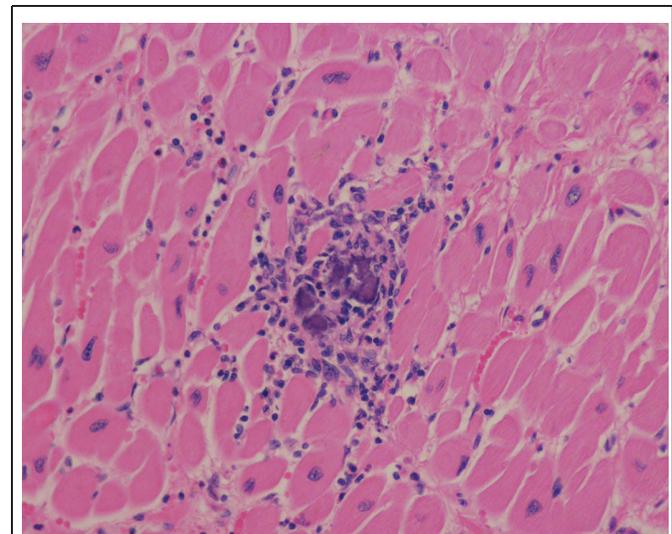


Figure 4. Necrotic myocytes with surrounding lymphocytes. From the same patient displayed in Figure 5, the histopathological findings are consistent with myocarditis.

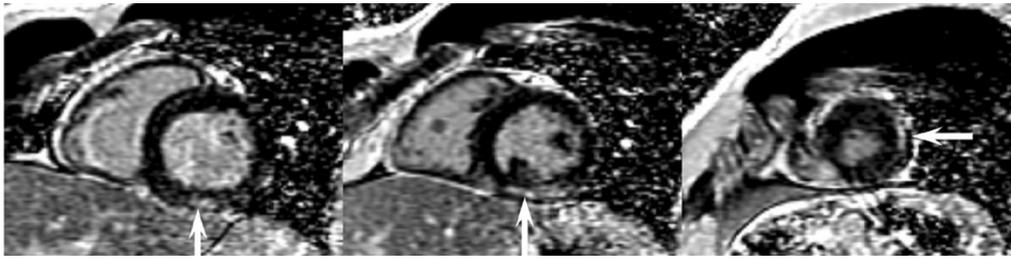


Figure 5. Patient who underwent probable false negative percutaneous endomyocardial biopsy of the RV septum. Twenty-eight year-old male with community-acquired myocarditis whose right heart biopsy yielded negative results. Note that the DE (white arrows) is located along the inferior and lateral walls and not in the septum (the sampling area).

myocarditis and community-acquired myocarditis. In both conditions, it appears as subepicardial or midmyocardial uptake in a non-coronary distribution. In contrast to previous reports (8, 9), we found that the septum was often involved. These similarities between IL-2 myocarditis and community-acquired myocarditis may suggest a common pathogenesis in both disease states.

We are confident that the myocardial delayed enhancement seen in the IL-2 patients represents myocarditis and not myocardial infarction or metastatic melanoma. Several studies in animal and humans have demonstrated the ability of IL-2 to cause myocarditis (1–3, 12). Furthermore, the pretest probability of significant coronary artery disease in each of the IL-2 patients was low, and each underwent negative exercise stress testing prior to receiving the immunotherapy. Myocardial infarction has a predilection for the subendocardium—a pattern not seen in these patients. The one patient who died was shown to have myocarditis at autopsy in areas that matched the delayed enhancement and no evidence of myocardial metastasis despite widespread metastatic disease elsewhere. Published reports in metastatic melanoma to the heart usually include large masses that occupy cardiac chambers (13, 20).

High dose IL-2 immunotherapy has been reported to cause myocarditis (1–4); thus, the midwall and epicardial predilection for fibrosis does not require viral factors. Zhang et al have proposed the following mechanism: “1) activation of lymphocytes to differentiate into LAK (lymphokine-activated killer) cells, 2) activation of endothelial cells leading to the expression of endothelial-cell-leukocyte adhesion molecules, 3) interaction between activated lymphocytes and activated endothelial cells resulting in increased adherence of lymphocytes to endothelium, particularly in capillaries and post capillary venules, 4) progressive but focal damage to the microcirculation, with disruption of endothelial junctions, capillary leaks and plugging of vessels with lymphocytes, 5) migration of lymphocytes and other inflammatory cells into myocardial interstitium, and 6) contacts between lymphocytes and cardiac myocytes, resulting in cytotoxic damage and necrosis of myocytes” (22) (pg. 1349).

In their study, Mahrholdt et al used current DE CMR techniques in a group of 32 patients meeting clinical criteria for myocarditis (9). DE was found in 28 patients, predominantly in the subepicardial portion of the lateral free wall. Given their

findings, it has since been postulated that myocarditis occurs as a direct extension of pericarditis into the subepicardium. However, in our study, we found a significant number (71%) of patients had midmyocardial septal involvement. Also only 9 of 21 patients had evidence of acute pericarditis on ECG (Fig. 6). Our results, therefore, suggest other mechanisms of early myocardial injury in community-acquired myocarditis, such as cytokine-mediated cytotoxicity.

There is evidence to support a central role for cytokine-mediated injury in viral myocarditis in animal models. Zhang et al were the first to show the cytolytic effects of IL-2 activated T cells on endothelial cells and myocytes (22). More recently, Okura et al have shown that IL-2 and IL-12 act synergistically to enhance the pathogenicity of cardiac myosin-specific lymphocytes (14). Miyamoto et al found that in mice with acute viral myocarditis, the immunosuppressor FTY720 is associated with decreased circulating IL-2 and IL-12 and improved survival (15). However, autoimmune myocarditis has also been induced in IL-2 deficient mice (12). Therefore, IL-2 is not prerequisite for myocarditis induction. Its more likely role in viral myocarditis is as a disease facilitator. Clinical immunotherapy studies reveal that if subjects are exposed to high enough doses then IL-2 can become a disease initiator (1–4).

In addition to aiding in the diagnosis and understanding the pathogenesis of myocarditis, CMR may also play a role in monitoring the effects of agents known to potentially cause myocarditis. The ability to monitor both left ventricular systolic function and the DE pattern over time offers a clinically useful tool for patients who require continued treatment with IL-2 immunotherapy.

Of note, other disease processes, besides myocarditis, have demonstrated unusual patterns on gadolinium DE. McCrohon et al reported that patchy or longitudinal patterns of midwall DE were seen in patients with dilated cardiomyopathy without coronary artery disease (16). These cases may represent prior myocarditis. Smedema et al reported a patchy DE pattern in patients with cardiac sarcoidosis (17). Choudhuru et al have shown heterogeneous DE in patients with hypertrophic cardiomyopathy (18). Although the two conditions should be easily distinguishable, it is apparent that the finding of midmyocardial DE is not unique to myocarditis. In fact, Mahrholdt et al did find biopsy evidence for hypertrophic cardiomyopathy on two of 32

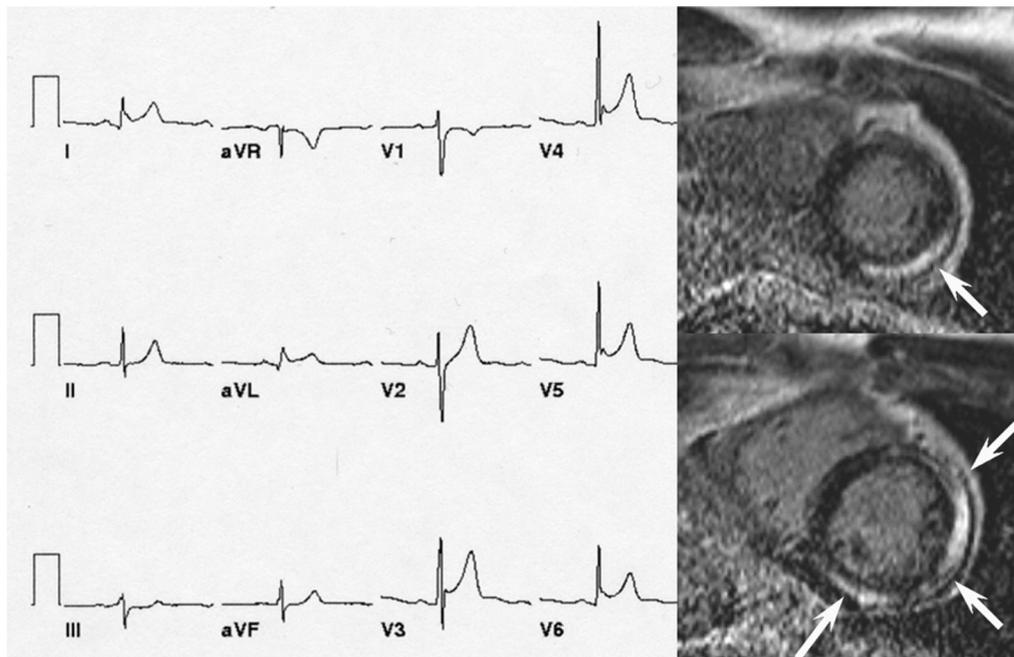


Figure 6. ST segment elevation in a patient with chest pain. ECG demonstrates lateral ST segment elevation. This 35 year-old patient presented with chest pain and was treated with thrombolytics. Coronary angiography subsequently revealed normal coronary arteries. CMR short axis views demonstrate extensive inferior, inferolateral and lateral subepicardial DE, which is atypical for MI and more consistent with myocarditis.

patients whose clinical picture and CMR suggested myocarditis (9).

CONCLUSION

Delayed enhancement CMR techniques have shown that patients with IL-2 myocarditis have a similar pattern of enhancement as those with community-acquired myocarditis. In contrast with previous delayed enhancement CMR reports of myocarditis, we found that a majority of patients had interventricular septal involvement, and 2 even had ventricular free wall sparing. The similarities between these 2 distinct types of myocarditis suggest that cytokine-mediated cytotoxicity may play a role in the pathogenesis of both forms of myocarditis.

ABBREVIATIONS

CMR = Cardiac Magnetic Resonance
 DE = Delayed Enhancement
 EF = Ejection Fraction
 IL-2 = Interleukin-2
 LV = Left Ventricle or Left Ventricular
 MI = Myocardial Infarction
 Tn-I = Troponin-I

REFERENCES

1. Kragel AH, Travis WD, Steis RG, Rosenberg SA, Roberts WC. Myocarditis or acute myocardial infarction associated with interleukin-2 therapy for cancer. *Cancer* 1990;66:1513-6.
2. Kruit WH, Punt KJ, Goey SH, de Mulder PH, van Hoogenhuyze DC, Henzen-Logmans SC, Stoter G. Cardiotoxicity as a dose-limiting factor in a schedule of high dose bolus therapy with interleukin-2 and alpha interferon. *Cancer* 1994;74:2850-6.
3. White RL, Schwartzentruber DJ, Guleria A, MacFarlane MP, White DE, Tucker E, Rosenberg SA. Cardiopulmonary Toxicity of Treatment with High Dose Interleukin-2 in 199 Consecutive Patients with Metastatic Melanoma or Renal Cell Carcinoma. *Cancer* 1994;74:3212-22.
4. Eisner RM, Husian A, Clark JI. Case report and brief review: IL-2 induced myocarditis. *Cancer Invest* 2004;22:401-4.
5. Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, Hare J, Bricker JT, Bowles KR, Towbin JA. Detection of viruses in myocardial tissue by polymerase chain reaction: Evidence of adenovirus as a common cause of myocarditis on children and adults. *J Am Coll Cardiol* 2003;42:466-72.
6. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, Moon TE. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:269-75.
7. Chow, LH. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. *J Am Coll Cardiol* 1989;14:915-20.
8. Abdel Aty H, Boye P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. *J Am Coll Cardiol* 2005;45:1815-22.
9. Mahrholdt H, Goecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation* 2004;109:1250-8.
10. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS,

- American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. *Circulation* 2002;105:539–42.
11. Aretz HT. Myocarditis: the Dallas criteria. *Hum Pathol* 1987;18:619–24.
 12. Grässl G, Pummerer CL, Horak I, Neu N. Induction of Autoimmune Myocarditis in Interleukin-2-Deficient Mice. *Circulation* 1997;95:1773–76.
 13. Gibbs P, Cebon JS, Calafiore P, Robinson WA. Metastases from malignant melanoma. *Cancer* 1999;85:78–84.
 14. Okura Y, Takeda K, Honda S, Hanawa H, Watanabe H, Kodama M, Izumi T, Aizawa Y, Seki S, Abo T. Recombinant murine interleukin-12 facilitates induction of cardiac myosin-specific type 1 helper T cells in rats. *Circ Res* 1998;82:1035–42.
 15. Miyamoto T, Matsumori A, Hwang MW, Nishio R, Ito H, Sasayama S. Therapeutic effects of FTY720, a new immunosuppressive agent, in a murine model of acute viral myocarditis. *J Am Coll Cardiol* 2001;37:1713–8.
 16. McCrohon JA, Moon JCC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ. Differentiation of Heart Failure Related to Dilated Cardiomyopathy and Coronary Artery Disease Using Gadolinium-Enhanced Cardiovascular Magnetic Resonance. *Circulation* 2003;108:54–9.
 17. Smedema J-P, Snoep G, van Kroonenburge MPG, van Geuns RJ, Dassen WR, Gorgels AP, Crijns HJ. Evaluation of the Accuracy of Gadolinium-Enhanced Cardiovascular Magnetic Resonance in the Diagnosis of Cardiac Sarcoidosis. *J Am Coll Cardiol* 2005;45:1683–90.
 18. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, Bonow RO, Judd RM, Kim RJ. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;40:2156–64.
 19. Hauk AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc* 1989;64:1235–45.
 20. Premkumar A, Marincola F, Taubenberger J, Chow C, Venzon D, Schwartzentruber D. Metastatic melanoma: correlation of MRI characteristics and histopathology. *J Magn Reson Imaging* 1997;6:190–4.
 21. Shirani J, Freant LJ, Roberts WC. Gross and semi-quantitative histological findings in mononuclear cell myocarditis causing death, and implications for endomyocardial biopsy. *Am J Cardiol* 1993;72:952–57.
 22. Zhang J, Yu ZX, Hilbert SL, Yamaguchi M, Chadwick DP, Herman EH, Ferrans VJ. Cardiotoxicity of human recombinant Interleukin-2 in rats: a morphological study. *Circulation* 1993;87:1340–53.