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Differentiation of Acute Myocarditis and Acute Myocardial Infarction by the Regional Distribution of Myocardial Irreversible Injury Using Cardiovascular Magnetic Resonance Imaging

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Key words: *myocarditis; myocardial infarction; late gadolinium enhancement.*

Summary. *Background and Objective. In this study, we have sought for differences between cardiovascular magnetic resonance patterns of acute myocarditis and acute myocardial infarction.*

Material and Methods. A prospective analysis of 110 consecutive patients was performed. The presence, precise location, and pattern of late gadolinium enhancement (LGE) by cardiovascular magnetic resonance were investigated.

Results. The subendocardial LGE pattern was much more frequent in the myocardial infarction group (76.7%) than myocarditis group (10.0%) (P<0.001). Meanwhile, midmyocardial LGE was much more typical of myocarditis (65.0%) than acute myocardial infarction (1.1%) (P<0.001), and epicardial LGE was also much more typical of myocarditis (55.0%) than acute myocardial infarction (0.0%) (P<0.001). Midmyocardial and epicardial LGE patterns were defined as a nonischemic LGE pattern more typical of myocarditis. Logistic regression analysis revealed that the subendocardial and midmyocardial LGE locations played the greatest role in differentiation between acute myocarditis and acute myocardial infarction. A statistical model based on midmyocardial LGE distribution and age showed a sensitivity of 90% and a specificity of 93.3% in differentiating between acute myocarditis and acute myocardial infarction.

Conclusion. Our findings suggest that in clinical practice, differentiation between acute myocardial infarction and acute myocarditis can be done based on the subendocardial and midmyocardial LGE location. The presence of subendocardial LGE was found to be strongly associated with acute myocardial infarction; meanwhile, the presence of midmyocardial LGE indicated acute myocarditis. However, other clinical factors should also be taken into account when making the final diagnosis.

Introduction

Human myocarditis is an uncommon disease possessing a broad range of symptoms. It is defined by an inflammatory process of the myocardium, leading to the necrosis of myocytes. Spontaneous recovery is common (1), but this disease can occasionally result in sudden death. Viral infection accounts for most cases of myocarditis in previously healthy patients (1, 2); however, toxins, bacterial infection, ischemic or mechanical injury, drugs, transplant rejection reaction, and other immune reactions can cause myocardial inflammation.

It may be difficult to differentiate clinically between acute myocarditis and acute myocardial infarction (MI), because a patient can have the symptoms applicable to both. Chest pain, changes in ECG and biochemical markers, and hemodynamic instability can manifest in both cases (2). It is difficult to recognize myocarditis clinically, and current diagnostic methods leave room for improvement as most of the sudden death cases due to myocarditis are diagnosed postmortem (3). Endomyocardial biopsy was the "gold standard" for diagnosing acute myocarditis, but as the disease can be focal (4), endomyocardial biopsy lacks sensitivity (5). Friedrich et al. (6) introduced the idea of the use of contrast medium–enhanced cardiovascular magnetic resonance (CMR) imaging as a possible tool for diagnosing myocarditis, showing that the extent and localization of inflammation within the myocardium can be visualized by contrast-enhanced magnetic resonance imaging (MRI).

In 2009, the International Consensus Group

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on CMR Diagnosis of Myocarditis published recommendations for diagnostics of myocarditis (7). This paper introduced indications recommended for CMR in patients with suspected myocarditis and terminologies proposed for describing CMR findings and diagnostic CMR criteria.

CMR is also used as a tool to diagnose MI according to the pattern and location of late gadolinium enhancement (LGE). LGE presence and amount also can be used to determine acute MI severity, significance, and prognosis (8).

The aim of our study was to find the differences between the pathognomonic CMR patterns of acute myocarditis and acute MI and to evaluate the significance of these findings.

Material and Methods

A total of 110 patients with suspected acute MI or acute myocarditis underwent CMR in Vilnius University Hospital Santariškių Klinikos during 2009–2010, using a Siemens Avanto 1.5 T magnetic resonance system. Steady-state free precession cine cardiac MRI was performed during the breath holding in 4-, 3-, and 2-chamber views, and a short axis stack covering the left ventricle (LV) every 8 mm without a gap was acquired at rest (TE/TR/flip angle, 1.22 ms/63 ms/65 degrees; FOV, 250 mm; voxel size, 1.9×1.3×8 mm).

T2-weighted TIRM sequences were applied for the evaluation of myocardial edema before the injection of contrast media. Following 10–15 minutes after an infusion of 0.2-mmol/kg commercially available gadolinium-based contrast agent (gadopentetate dimeglumine or gadodiamide), an inversion recovery gradient-echo sequence (TE/TR/flip angle, 3.2 ms/700 ms/25 degrees; FOV, 400 mm) was performed in the same planes as cine images with inversion time (240 to 330 ms) chosen to null normal myocardium. Typical voxel size was 2.1×1.6×8 mm.

All 110 patients underwent a CMR scan. There were 75 men (68.2%) and 35 women (31.8%). The clinical diagnosis of acute MI for 90 patients (81.8%) was made according to the ESC/ACCF/AHA/WHF Universal Definition of Myocardial Infarction (9). All patients with acute MI underwent a successful primary percutaneous coronary intervention with TIMI flow grade 2 or 3 after the procedure. CMR was done for all patients during the hospital stay (within the period of 2 weeks after the onset of symptoms) due to other reasons, such as for the exclusion of suspected MI complications (apical thrombus, etc.) or suspected myocarditis, for the assessment of myocardial viability or microvascular obstruction (as part of other research protocol).

Relying on CMR findings according to the JACC White Paper on CMR in myocarditis (7), coronary angiograms with unobstructed epicardial coronary arteries, ECG, and clinical picture, the diagnosis of acute myocarditis was established in 20 patients (18.2%). Based on an improving and stable clinical scenario, no patient required or underwent myocardial tissue biopsy.

The readers of CMR scans were blinded to the clinical data. The study was approved by the Lithuanian Ethics Committee (No. 17, 06/21/2007), and informed written consent was obtained from each patient.

Statistical Analysis. Data were analyzed using the SPSS 17.0 (version for Windows) software. To compare continuous variables, the Man-Whitney test was employed. Comparisons of the categorical variables were made using the χ^2 test or the Fisher exact test. To find out commonly enhancing locations for each disorder, logistic regression with forward selection was applied. In certain cases, odds ratios from contingency tables were also calculated. Descriptive statistics for continuous variables was presented in a form of means and standard deviations. Frequencies were reported for the categorical variables. The level of significance was set at 0.05. All reported *P* values were two-sided.

Results

A total of 110 patients underwent a CMR scan. There were 75 men (68.2%) and 35 women (31.8%). Acute MI was diagnosed in 90 patients (81.8%) using the established MI diagnostic criteria (9). Patients in the MI group were aged from 53 to 77 years (mean age, 65.1 years). There were 70 men (77.8%) and 20 women (22.2%) in this group. Twenty patients (18.2%) were diagnosed with acute myocarditis according to the criteria based on clinical presentation, ECG, echocardiography, CMR, and angiography. Patients in the myocarditis group were aged from 14 to 48 years (mean age, 31.1 years). There were 5 men (25%) and 15 women (75%) in this group.

The groups significantly differed with respect to age (65.1 years [SD, 12.3] in the MI group vs. 31.1 years [SD, 17] in the myocarditis group, $P<0.001$), gender (22.2% of women in the MI group vs. 75.0% of women in the myocarditis group, $P<0.001$), and LV ejection fraction (42.2% [SD, 15.5%] in the MI group vs. 51.6% [SD, 14.3%] in the myocarditis group, $P=0.007$).

A hyperintense signal on T2-weighted TIRM sequences representing myocardial edema was reported in all patients with acute myocarditis and in 63% of patients with MI (presence of edema on T2 sequence could be not detected by CMR in the second week from the onset of MI). Locations of a hyperintense signal on T2 sequence in our patients' cohort corresponded well with LGE location on an inversion recovery sequence. Comparisons with respect to the location and patterns of LGE showed

Table 1. Comparison of Different Locations and Patterns of Late Gadolinium Enhancement According to the Established Diagnosis

	Subendocardial	Midmyocardial	Epicardial	Transmural	Focal	LV-RV junctions	RV
MI	69 (76.7)	1 (1.1)	0 (0.0)	35 (38.9)	2 (2.2)	2 (2.2)	8 (8.9)
Myocarditis	2 (10.0)	13 (65.0)	11 (55.0)	0 (0.0)	6 (30.0)	1 (5.0)	1 (5.0)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	0.456	0.566

Values are number (percentage). RV, right ventricle; RV-LV junctions, junctions between the right and left ventricles.

significant differences in the frequency of subendocardial, midmyocardial, and focal LGE between the 2 patients' groups. No differences were observed in LGE frequency of LV-RV (right ventricle) junctions and RV between the 2 patients' groups (Table 1).

Subendocardial LGE (Fig. 1) was much more frequent in the MI group than myocarditis group (76.7% vs. 10.0%, $P<0.001$). Meanwhile, midmyocardial LGE was more frequent in the acute myocarditis group than MI group (1.1% vs. 65.0%, $P<0.001$), and epicardial LGE was also much more typical of myocarditis than acute MI (55.0% vs. 0.0%, $P<0.001$). Midmyocardial and epicardial LGE patterns were defined as a nonischemic LGE pattern more typical of myocarditis (Figs. 2 and 3). The groups also significantly differed with respect to the frequencies of transmural and focal LGE; however, logistic regression analysis revealed that subendocardial and midmyocardial locations were most suitable to distinguish between the diseases.

Logistic regression with forward selection was applied (variable entered the model if its significance was less than 0.05) to find out which LGE locations are most important. Disorder type (acute MI or myocarditis) acted as a dependent variable (myocarditis treated as an "event"). The list of independent variables consisted of binary indicators, showing the presence or absence of enhancement at particular location: subendocardial (yes/no), midmyocardial (yes/no), and RV (yes/no). The obtained model had 2 significant independent varia-

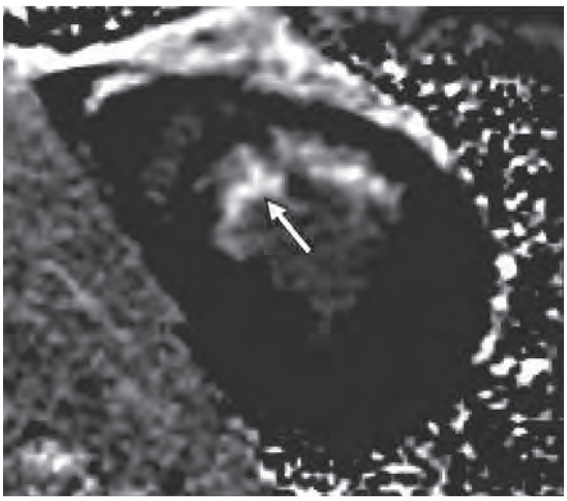
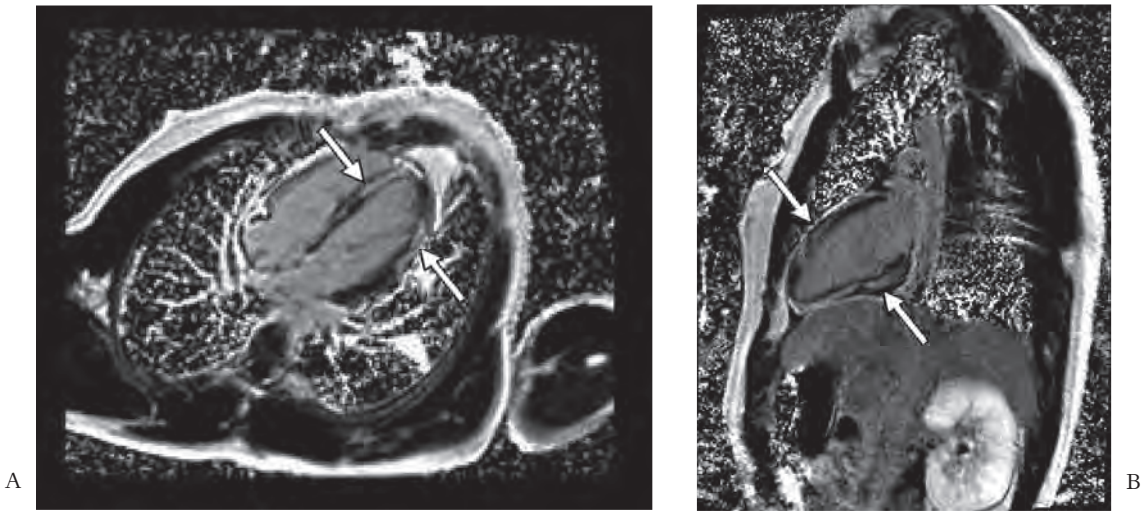


Fig. 1. Subendocardial late gadolinium enhancement in the midventricular segments of the anteroseptal and anterior walls (arrow), a typical LGE pattern and segmental location for acute myocardial infarction



A B

Fig. 2. Four-chamber heart view (A) and two-chamber heart view (B)

Please note epicardial and midmyocardial late gadolinium enhancement in the interventricular septum, anterior, inferior and lateral walls of the left ventricle (arrows), a typical late gadolinium enhancement pattern for acute myocarditis.

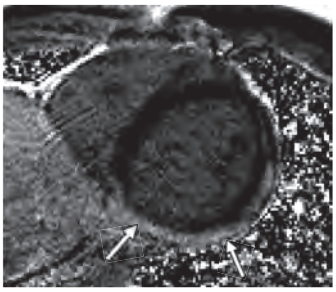


Fig. 3. Epicardial and midmyocardial late gadolinium enhancement in the midventricular segment of the inferior and lateral walls of the left ventricle (arrows), a typical late gadolinium enhancement pattern for acute myocarditis

Table 2. Odds Ratio for Myocarditis in the Presence of Late Gadolinium Enhancement at a Particular Location*

Location	*P*	OR (95% CI)
Subendocardial	<0.001	0.034 (0.007; 0.158)
Midmyocardial	<0.001	165.286 (18.785; 1454.298)

*Reported OR = (odds to have myocarditis if LGE at location is present)/ (odds to have myocarditis if LGE at location is absent).

bles. Those were subendocardial and midmyocardial LGE. However, this model had one drawback. The confidence intervals for odds ratios were very wide. Therefore, odds ratios for each of two independent variables separately employing a usual technique of estimation based on 2×2 cross table were calculated (results are presented in Table 2). In addition, the model was rebuilt. This time instead of 2 binary variables (subendocardial LGE [yes/no] and midmyocardial LGE [yes/no]), 2 dummy variables (location 1 and location 2) were used. The correspondence between the values of new and old variables was as follows: location 1=0, location 2 = 1 ~ subendocardial = yes, midmyocardial = yes or subendocardial = no, midmyocardial = yes; location 1=1, location 2 = 0 ~ subendocardial = yes, midmyocardial = no; location 1=0, location 2 = 0 ~ subendocardial = no, midmyocardial = no.

The results of this model are presented in Table 3. Taking into account other clinical data, logistic regression analysis revealed only 2 significant variables: age and midmyocardial LGE. The predictive ability of this model was rather good since at optimal cut-point, sensitivity and specificity were 95% and 93.3%, respectively (optimal cut-point, 0.158). The selection of optimal classification cut-point was based on the Youden index (Se+Spe-1) of the corresponding model ROC, i.e., the cut-point that maximized the Youden's index was reported. However, this model also suffered because of the same problem as the one described previously. It is presented in Table 4.

Simple cross-validation by means of "leave-one-out" produced a usual slight decrease in the predictive ability: sensitivity decreased to 90.0%, whereas specificity remained the same.

Discussion

MRI offers safety, anatomical clarity, interobserver consistency, quantitative accuracy, and a broad spectrum of diagnostic targets. The first description of T2-weighted CMR findings in children with myocarditis (10) prompted the studies of non-contrast and contrast-enhanced CMR in patients with myocardial inflammation (Fig. 4). Gagliardi et al. (10) published the first case series on CMR for the noninvasive diagnosis of acute myocarditis in 11 infants and children. Compared with endomyocardial biopsy (Dallas criteria), T2-weighted spin echo CMR sequences were found to have a specificity

Table 3. Logistic Regression Model for the Prediction of Myocarditis/Myocardial Infarction: Final Model With Two Dummy Variables*

Independent variable	Regression coefficient (SE)	*P*	OR (95% CI)
Location 1	–2.967 (1.109)	0.007	0.051 (0.006; 0.452)
Location 2	5.034 (1.1383)	0.001	45.500 (4.907; 421.933)
Constant	–1.253 (0.463)	0.007	–

*Nagelkerke R^2=0.669; area under ROC (95% CI) = 0.927 (0.885; 0.997); dummy variable coding: location 1=0, location 2 = 1 ~ subendocardial = yes, midmyocardial = yes or subendocardial = no, midmyocardial = yes; location 1=1, location 2 = 0 ~ subendocardial = yes, midmyocardial = no; location 1=0, location 2 = 0 ~ subendocardial = no, midmyocardial = no; "myocarditis" was treated as an "event."

Table 4. Logistic Regression Model for the Prediction of Myocarditis/Myocardial Infarction: Model With Age and Midmyocardial Late Gadolinium Enhancement*

Independent variable	Regression coefficient (SE)	*P*	OR (95% CI)
Age	–0.128 (0.034)	<0.001	0.880 (0.822; 0.941)
Midmyocardial	5.402 (1.608)	0.001	221.854 (9.488; 5187.342)
Constant	3.779 (1.548)	0.015	–

*Nagelkerke R^2=0.818; area under ROC (95% CI) = 0.962 (0.897; 1.000); "myocarditis" was treated as an "event."

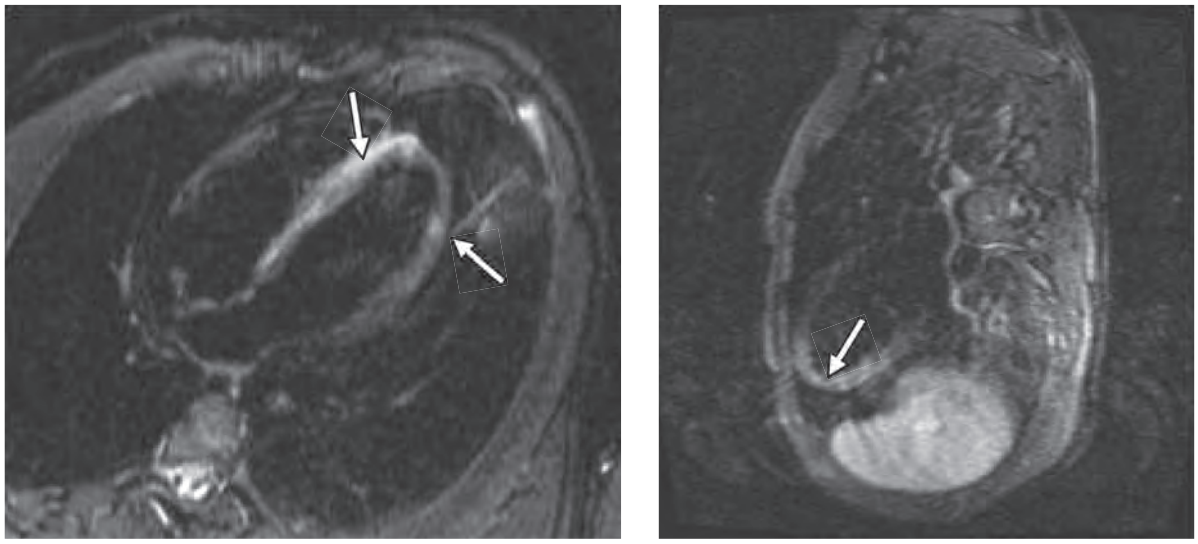


Fig. 4. T2-weight TIRM sequence in a 4-chamber heart view (A) showing a moderately hyperintense signal because of edema (arrows) in the interventricular septum and lateral wall and T2-weight TIRM sequence in a 2-chamber heart view (B) showing edema in the apex and the inferior wall of left ventricular myocardium (arrow)

of 100% and a sensitivity of 100%. Sensitivity and specificity of CMR remained high during subsequent evolution of the disease (11). In our study, a T2-weighted TIRM sequence was applied for the evaluation of myocardial edema before the injection of contract medium. In all 20 cases of acute myocarditis, myocardial edema was evident (Fig. 4). In 2008, during a study conducted by Gutberlet et al. (12), CMR findings were compared to histological and immunohistological criteria (reference standard). The findings have shown that CMR was a sufficiently sensitive tool for diagnosing inflammation in the myocardium as compared with endomyocardial biopsy (12).

Published data suggest that there is enough solid evidence of CMR as a sensitive tool for the diagnosis of myocarditis. However, most of these studies are single-center reports with a small sample size, variable inclusion criteria, and nonuniform patient populations. Studies were performed at variable time points after disease onset, used different imaging diagnostic criteria, and not all of them used biopsy for confirmation. Endomyocardial biopsy is the most specific examination, and it is considered as the method of reference for the diagnosis of myocarditis. In clinical practice, it is often skipped because of its invasive nature and the risk of false-negative results due to the patchy and heterogeneous distribution of myocardial tissue damage. Indeed, its sensitivity is low, and it is estimated to be in the range of 50%–65%. Therefore, the need for reliable diagnostic tools is of great importance.

It is well known that acute myocarditis can masquerade as acute MI. In the setting of acute chest pain with concomitant ST-segment elevation on at least 2 contiguous ECG leads, guidelines for the management of ST-segment elevation MI should be applied. When patients have a low-risk profile for CAD and particularly if they have a recent history of fever or flu, invasive coronary angiography should be a preferred method (if it is available) in order to avoid potentially inappropriate thrombolytic therapy. CMR should play an important role when coronary angiography rules out a significant coronary stenosis in these cases and has the potential to confirm the diagnosis of myocarditis. On the other hand, in the setting of acute chest pain without ST-segment elevation, CMR, if available, may become a first-line imaging modality, especially in those patients with a low cardiovascular risk profile and/or a recent history of flu.

In 2009, the International Consensus Group on CMR Diagnosis of Myocarditis published the recommendations for diagnostics of myocarditis. The recommended indications for CMR in patients with suspected myocarditis, proposed terminology for describing CMR findings, and proposed diagnostic CMR criteria were introduced. These criteria included focal or regional edema, hyperemia/capillary leak appearing in early gadolinium enhancement, and irreversible cell injury appearing in LGE. Supportive CMR findings included regional/global systolic dysfunction and small-to-large pericardial effusion (7).

Our data show that CMR can be used as a tool to diagnose acute MI and to differentiate it from other ailments, such as myocarditis. Clear distinction among LGE patterns is observed, as subendocardial and transmural enhancement appears mostly in MI patients, and midmyocardial and epicardial

enhancement affects patients with myocarditis. Furthermore, patients in myocarditis group tend to be younger and with a less pronounced impairment of LV ejection fraction. As a potential limitation of all myocarditis studies by CMR, LGE shows a variable sensitivity to detect an active or chronic inflammation, depending on the selection of patients (7). One reason may be that active myocarditis may not always lead to large-enough regions of necrotic myocytes to be visually detectable, given the pixel size in CMR images. This contrasts with the situation in ischemic necrosis for which LGE has been shown to be highly sensitive. Therefore, LGE may be insensitive for the detection of symptomatic myocarditis with limited or nonfocal irreversible injury. More studies are needed to address this issue.

Myocardial edema may be depicted by T2-weighted CMR during the acute phase of MI. Although the distribution of myocardial edema is theoretically different, it is often difficult to distinguish between myocarditis and acute MI based on T2-weighted CMR images. Thus, as previously described, the patterns of LGE are very distinct and help discriminate between acute MI and acute myocarditis.

The abovementioned findings are not in conflict with other published data mentioned in the discussion. We recommend using a CMR-based evaluation algorithm for patients with suspected acute coronary syndrome without a significant coronary stenosis on coronary angiography, especially in those with a low cardiovascular risk profile and/or a recent history of fever or flu.

Conclusions

Cardiovascular magnetic resonance imaging is being used to differentiate between acute myocardial infarction and acute myocarditis. Our data indicate that in patients with irreversible myocardial injury, the regional distribution patterns may differentiate a primarily inflammatory process from a primarily ischemic injury. Our study shows that attention should be paid to the presence/absence of subendocardial and midmyocardial late gadolinium enhancement: subendocardial late gadolinium enhancement is associated with acute myocardial infarction, while midmyocardial late gadolinium enhancement is associated with acute myocarditis.

Statement of Conflict of Interest

The authors state no conflict of interest.

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