Mesothelial / Monocytic Incidental Cardiac Excrescence: A New Theory of Pathogenesis
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Abstract
Mesothelial / monocytic incidental cardiac excrescence (Cardiac MICE) is a rare benign cardiac lesion. MICEs are usually incidental findings during cardiac surgery, but can also be identified in the endomyocardial biopsy setting. Grossly, MICEs mimic thrombus and microscopically, they contain mesothelial and monocytic cells with fibrin, and empty spaces. The pathogenesis of MICE remains unknown. We propose a new theory that the empty spaces are air microbubbles and these contribute to the formation of MICE. We present two cases of MICE: the first case was a previously formed MICE incidentally found in the left atrium of a patient during valve replacement. Histologically, many variable-sized empty spaces were lined by macrophages and these empty spaces probably represent air microbubbles. The second case was a recently formed MICE found in an endomyocardial biopsy which contained fresh air microbubbles without lining cells in the thrombus admixed with mesothelial cells.

INTRODUCTION
Mesothelial / monocytic incidental cardiac excrescence (Cardiac MICE) is an extremely rare benign cardiac lesion composed of mesothelial cells, macrophages / monocytic cells, fibrin, empty spaces, and other inflammatory cells without a vascular network and supporting stroma. MICE can be mistakenly confused with malignancy even for experienced pathologists. First termed MICE by Veinot et al in 1994,1 they usually are incidental findings during cardiac surgery, namely valve replacement surgery. Locations of MICE include cardiac chambers, cardiac valves, free floating in the pericardial sac, ascending aorta, pleural space, and mediastinum. Since 1979, there have been fewer than 50 cases of MICE reported in the English literature.1-9 The pathogenesis of MICE still remains unknown. Two hypotheses have been proposed. One theory postulates that these lesions might represent mesothelial hyperplasia, probably a reactive process due to previous cardiac catheterization.3 The other hypothesis suggests these lesions are artificially produced during cardiac surgery via suction.4 Apparently, neither hypothesis can fully explain the formation of MICE. Here, we report two cases of MICE and provide a third hypothesis that air microbubbles brought by instrumentation into intravascular spaces attract macrophages together with mesothelial cells and form the MICE lesion.

CASE REPORT
Case 1
A 64-year-old female was admitted to the emergency room due to significant peripheral edema. She had a previous history of a heart murmur since she was a child, but she denied any previous history of congestive heart failure. Physical examination revealed her blood pressure was 136/74 mm Hg. A grade 3/6 pansystolic murmur was heard at the apex and it radiated to her left axilla. Jugular vein pressure was increased at 3 to 4 cm above the sternal angle. S3 sound was present. Peripheral edema (2+) was seen. Her baseline electrocardiography revealed sinus rhythm with left ventricular hypertrophy and ST-T wave abnormalities, probably secondary to left ventricle strain. A diagnosis of congestive heart failure and New York Heart Association Class IV was made. She was found to have two different systolic murmurs consistent with mitral and aortic valve disease. She underwent an echocardiography two days later which revealed findings suggestive of rheumatic heart disease. There was severe aortic stenosis as well as severe aortic insufficiency, moderate mitral stenosis and moderate mitral regurgitation. She had undergone cardiac catheterization just before the cardiac surgery that showed normal coronary arteries.

Two weeks after admission, the patient underwent valve replacement of both aortic and mitral valves. During the
surgery, a transesophageal echocardiogram confirmed the preoperative findings of severe aortic stenosis and insufficiency with typical rheumatic morphology. A patent foramen ovale was noted and closed surgically. A ‘thrombus’ found on the endocardial surface of the left atrium was removed and submitted for pathologic evaluation.

Pathological Findings:
Grossly, the specimen was an irregular fragment of brown soft tissue measuring 1.0 x 0.6 x 0.2 cm; it was serially sectioned and entirely submitted for histopathologic evaluation.

Figure 1
A, MICE lesion contains mesothelial cells, macrophages, and fibrin (hematoxylin-eosin, original magnification x400). B, variable-sized empty spaces or vacuoles in the MICE (hematoxylin-eosin, original magnification x200). C, calretinin stain highlights the mesothelial cells (original magnification x400). D, Lining cells of empty spaces are immune-reactive to CD68 (original magnification x400). E, Recently formed MICE contains thrombus, mesothelial cells and empty spaces without cell lining (hematoxylin-eosin, original magnification x100). F, Mesothelial cells are calretinin positive (original magnification x100).

Microscopically, the lesion was composed of a central cellular component and peripheral loose acellular component. The cellular component mainly consisted of monocytes or macrophages with abundant cytoplasm, inconspicuous nucleoli, and indistinct cell borders, as well as lymphocytes, neutrophils, red blood cells, fibrin, rare hemosiderin-laden macrophages, and scattered single, chains, or glandular structures of polygonal or cuboidal cells with bland nuclei and dense cytoplasm (Figure 1A). Occasional mitotic figures were present. The peripheral acellular component mainly contained fibrin, neutrophils, red blood cells, and rare macrophages and appeared consistent with thrombus formation. In both the cellular and loose areas, there were scattered single or clusters of cuboidal cells and viable-sized, round, empty spaces reminiscent of mature adipocytes (Figure 1B). At immunohistochemistry, the polygonal or cuboidal cells were positive for calretinin (Figure 1C), WT-1, D2-40, CK7, and CK20 (data not shown), but negative for MOC31 and BerEP4 (data not shown), indicating these cells are mesothelial cell origin. The monocytes or macrophages are immunoreactive to CD68. The lining cells of the empty spaces are positive for CD68 (Figure 1D), but negative for S-100 (data not shown), indicating these cells are macrophages rather than adipocytes. Based on these features, a diagnosis of MICE was rendered.

Case 2
A 52-year-old male was admitted because of shortness of breath on exertion that was progressively getting worse and associated with extreme fatigue, low energy level, decreased oral intake, nausea, anorexia, and decreased urine output for 3 to 4 weeks. He had an abnormal electrocardiography outside of hospital and was considered query myocardial ischemia. He also had new onset of rapid atrial fibrillation, and his heart rate was increased up to 100 per minute. He was treated with aspirin, metoprolol, and warfarin for his likely coronary disease and rapid atrial fibrillation. He had worsening shortness of breath, dizziness, orthopnea, and a paroxysmal nocturnal dyspnea. After 3 days of admission, an echocardiogram showed moderate global hypokinesis of left ventricle, and the interventricular septum and inferior walls appeared severely hypokinetic to akinetic. The right ventricle was moderately dilated and the right ventricle systolic function was moderately to severely reduced. It also showed moderately reduced left ventricle function and detected moderate mitral regurgitation and tricuspid regurgitation as well. Initially, the patient was suspected to have massive pulmonary embolism, which was causing his right ventricle strain. However, an urgent ventilation / perfusion scan showed low probability of pulmonary embolism. After one week of admission, a coronary angiography (cardiac catheterization) was then performed.
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which demonstrated normal coronary arteries. In the same time, an endomyocardial biopsy was done.

Pathological Findings
Microscopically, the biopsy specimen was composed of fragments of myocardium and a thrombus admixed with scattered variable-sized empty spaces without cell lining, as well as strips and aggregates of mesothelial cells (Figure 1E). The myocardium showed mild myocyte hypertrophy, mild fatty infiltration, and mild interstitial fibrosis. The thrombus was relatively fresh consisting of fibrin, rare hemosiderin-laden macrophages, single or groups of mesothelial cells, and neutrophils. The mesothelial cells were immune-reactive to calretinin (Figure 1F), D2-40, and WT-1 (data not shown), but negative for CD31 and CD45. Rare macrophages (CD68 positive) were also present. The diagnosis of recently formed MICE was favored most likely caused by accidental biopsy at epicardial surface even though there was no clinical sign of cardiac perforation.

DISCUSSION
Cardiac MICE is a rare cardiac lesion composed of mesothelial cells, macrophages, fibrin, empty spaces mimicking mature adipocytes, and other inflammatory cells. In 1979, Rosai et al. described the first case in a review of histiocytoid hemangioma.2 Since then less than 50 cases of MICE have been reported in the English literature. Grossly, the lesion mimics thrombus and ranges from microscopic to 3.0 cm. We reviewed the cases reported in the literature and we found most of the images showed variable-sized empty spaces in the MICE lesions. However, these empty spaces were either ignored or described as adipocytes, lipid droplets, or round spaces. The possibilities for what these empty spaces represent include mature adipocytes, lipid droplets, or air microbubbles. We think the empty spaces probably are air microbubbles introduced into blood stream during a cardiac procedure such as catheterization or cardiac biopsy. Both of our cases had cardiac catheterization. The first case had cardiac catheterization before the cardiac surgery, and the other one had cardiac catheterization during the cardiac biopsy. The immunohistochemical study for CD68 and S100 in our cases showed many of these empty spaces were lined by CD68 positive cells and these cells were largely negative for S100, indicating these lining cells were macrophages, but not adipocytes. In the second case with recently formed MICE, the empty spaces were not lined with cells, most likely were fresh air microbubbles. Lipid droplets usually are very small vacuoles and they usually do not attract macrophages. Emphysematous changes in the vagina (vaginitis emphysematosa), gallbladder (emphysematous cystitis), gastrointestinal wall (pneumatosis intestinalis), and ovary (pneumatosis ovarii) have been well described in the literature. 10-13 The gas or air is produced by bacteria or introduced via procedures and these empty spaces are lined by macrophages, microscopically.

The incidence of gas microemboli and microbubbles is underrecognized and usually overlooked in daily practice. Almost every invasive procedure may cause the introduction of microbubbles into the blood stream.14 Gas or air microbubbles usually originate in extracorporeal tubing used to infuse fluids into the blood stream. Also, air microbubbles can be introduced into vascular spaces by instruments such as catheters.15 These air microbubbles travel to the heart, which probably is the organ at the highest position while patient is lying down. When there is a perforation through cardiac atria or ventricles, mesothelial cells are brought into cardiac chambers by the catheter from the epicardial surface, and the air microbubbles go to the perforation site where thrombus formation occurs. Air microbubbles, mesothelial cells, and thrombus meet together, and air microbubbles attract macrophages and eventually form a MICE lesion. In addition, air microbubbles affect clotting through both activating coagulation and inducing platelet aggregation and can cause thrombus formation by themselves.15 The CD68 positive macrophages lining the empty spaces in our case support our hypothesis.

In summary, we propose a new theory that air microbubbles contribute to the formation of the MICE lesion. And our cases also support the hypothesis that MICEs are probably a reactive process of previous cardiac catheterization.

References
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