Microvascular Angina: An Underappreciated Cause of SLE Chest Pain

To the Editor:

Data are accumulating that microvascular dysfunction is an unrecognized source of anginal chest pain in patients with autoimmune diseases such as systemic lupus erythematosus (SLE)[1,2,3]. Studies show that microvascular impairment contributes to cardiovascular disease in other autoimmune conditions such as systemic sclerosis[1,2,4]. Patients with SLE presenting with anginal chest pain pose a diagnostic challenge. Evaluating the role of microvascular impairment as a cause of chest pain may lead to earlier and improved management of these patients.

Chest pain and discomfort are frequently reported by patients with SLE[5], the origin of which can be attributed to multiple causes, including valvular disease, conduction abnormalities, pericardial disease (pericarditis, pericardial effusion), myocarditis, pulmonary hypertension, coronary artery disease (CAD), esophageal disease, musculoskeletal manifestations (costochondritis, myofascial pain, muscle spasm), and even psychiatric illness. However, upon clinical examination, diagnostic testing is often generally negative or minimally abnormal. Normal or minimally abnormal cardiovascular findings on coronary angiography are particularly frustrating to interpret, leaving the physician puzzled about the reported chest pain[6].

Anginal chest pain without flow-limiting stenosis on coronary angiography is often referred to as cardiac syndrome X (CSX)[6,7,8]. Patients with CSX are predominantly older women and exhibit a classic triad of angina, evidence of myocardial ischemia, and normal coronary arteries[7,8]. Causal mechanisms that have been ascribed to CSX include microvascular coronary dysfunction (MCD), diffuse atherosclerosis, hematologic dysfunction, chronic systemic inflammation, diffuse conduit vessel vasoconstriction, myocardial ischemia, estrogen deficiency, and abnormal pain perception[7]. CSX is not necessarily a benign condition[8]. It has been reported that in these women with signs and symptoms of ischemia, the risk is elevated for cardiovascular events such as myocardial infarction, stroke, or hospitalization for unstable angina or heart failure, despite the absence of obstructive CAD compared to asymptomatic control women[9,10].

The prevalence of CSX is roughly 42% in women with cardiac chest pain in the absence of obstructive CAD, and at least 1 estimate suggests that up to 58% of patients without obstructive CAD have MCD[7]. Adenosine cardiac magnetic resonance imaging (CMRI) is a noninvasive method that can detect stress-induced hypoperfusion in a diffuse, circumferential pattern indicating MCD. Studies have shown that an impaired endothelial-dependent vasomotor response to acetylcholine in this setting results in adverse cardiac events; further, an abnormal coronary flow reserve to intracoronary reactivity testing with adenosine is also associated with adverse cardiac outcomes in women with no obstructive CAD[10,11]. However, only recently has the occurrence of MCD been investigated in patients with SLE.

MCD that occurs in CSX may account for a significant proportion of the chest pain reported by patients with SLE. We investigated the presence of myocardial ischemia in 18 women with SLE who displayed anginal chest pain in the absence of obstructive CAD on coronary angiography[1]. Eighteen patients and 10 asymptomatic controls underwent adenosine stress CMRI and 64-slice coronary computed tomography (CT) angiography. We observed a 44% prevalence of abnormal stress myocardial perfusion in patients with SLE. Compared with controls, patients with SLE had reduced myocardial perfusion reserve index (MPRI), with SLE being a significant predictor of abnormal MPRI. Our finding is consistent with circumferential subendocardial hypoperfusion attributed to MCD in CSX, leading us to hypothesize that chest pain in patients with SLE and non-obstructive CAD may be attributable to MCD. A Japanese study of 16 consecutive SLE patients by CMRI detected perfusion defects indicating MCD in 7 patients (43.8%), although these patients were not selected on the basis of having angina[3].

Our group also reported the case of a 47-year-old woman with SLE who was referred for persistent chest pain[2]. As often seen in these patients, she did not have obstructive CAD, as evidenced by normal CT angiography and echocardiogram. However, an adenosine stress CMRI perfusion study demonstrated nearly circumferential subendocardial hypoperfusion consistent with MCD. Again we noted that chest pain in patients with SLE, when not related to obstructive CAD, myocarditis, or pericarditis, can alternatively be caused by MCD.

As a result of this accumulation of evidence we believe that the possibility of MCD should be considered as etiologic in patients with SLE who present with anginal chest pain. This evaluation should accompany patient assessments for traditional risk factors, given the increased risk for CAD in general in these diseases. Further investigation into microvascular angina in patients with SLE is warranted. We await mechanistic investigations that could pinpoint the anatomic pathologic correlates of this potentially treatable condition; the well-recognized premature mortality and morbidity assigned to cardiac ischemia in patients with SLE[12,13,14,15,16] should spur us to find the answers that are relevant to our care of these patients.

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REFERENCES

1. Ishimori ML, Martin R, Berman DS, Goykhman P, Shaw LJ, Shufelt C, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. J Am Coll Cardiol Img 2011;4:27-33.
2. Goykhman P, Mehta PK, Minissian M, Thomson LE, Berman DS, Ishimori ML, et al. Subendocardial ischemia and myocarditis in systemic lupus erythematosus detected by cardiac magnetic resonance imaging. J Rheumatol 2012;39:448-50.
3. Kobayashi H, Giles JT, Arinuma Y, Yokoe I, Hirano M, Kobayashi Y. Cardiac magnetic resonance imaging abnormalities in patients with systemic lupus erythematosus: A preliminary report. Mod Rheumatol 2010;20:319-23.
4. Ngian GS, Sahhar J, Wicks IP, Van Doornum S. Cardiovascular disease in systemic sclerosis — An emerging association? Arthritis Res Ther 2011;13:237.
5. Ishimori M, Gal NJ, Rogatko A, Berman DS, Wilson A, Wallace DJ, et al. Prevalence of angina in patients with systemic lupus erythematosus. Arthritis Res Ther 2012;14:A62.
6. Hurst T, Olson TH, Olson LE, Appleton CP. Cardiac syndrome X and endothelial dysfunction: New concepts in prognosis and treatment. Am J Med 2006;119:560-6.
7. Arthur HM, Campbell P, Harvey PJ, McGillion M, Oh P, Woodburn E, et al. Women, cardiac syndrome X, and microvascular heart disease. Can J Cardiol 2012;28:S42-9.
8. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: A changing philosophy. JAMA 2005;293:477-84.
9. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ,

Handberg EM, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: A report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med 2009;169:843-50.
10. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825-32.
11. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: Results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722-5.
12. Aranow C, Ginzler EM. Epidemiology of cardiovascular disease in systemic lupus erythematosus. Lupus 2000;9:166-9.
13. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2407-15.
14. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
15. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham Study. Am J Epidemiol 1997;145:408-15.
16. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221-5.

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