Coronary Artery Disease in Systemic Lupus Erythematosus: A Review of the Literature

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Context: Coronary artery occlusive disease is a common though underappreciated complication of systemic lupus erythematosus (SLE), typically a disease of young women. A case of a premenopausal patient with SLE and an acute myocardial infarction is presented, and the etiology and management of coronary artery disease in SLE reviewed.

Objectives: To review the incidence, risk factors, pathology and treatment of coronary artery disease in systemic lupus erythematosus.

Data Sources: MEDLINE search of articles in English-language journals from 1980 to 2000. The index words “systemic lupus erythematosus” and the following co-indexing terms were used: “coronary artery disease,” “atherosclerosis,” “vasculitis,” “anticardiolipin antibodies,” “antiphospholipid syndrome.”

Selection Synthesis and Abstraction: Papers identified were reviewed and abstracted by the authors with a presentation of a summary.

Results: The prevalence of coronary artery disease among women with SLE between the ages of 35 and 44 years is at least 50-fold greater than among age-matched control subjects. Of these, coronary atherosclerosis accounts for the vast majority of cases; vasculitis of the coronary arteries and other causes generally believed to be more typical of SLE are comparatively rare.

Conclusions: The evidence suggests that SLE is a significant risk factor for coronary atherosclerosis independent of the classic risk factors of hypertension, tobacco use, and hyperlipidemia.


INDEX WORDS: Coronary artery disease; systemic lupus erythematosus; atherosclerosis; premenopausal women; antiphospholipid syndrome; anticardiolipin antibodies.

Coronary Artery Disease (CAD) is common among patients with systemic lupus erythematosus (SLE) and is responsible for a great deal of morbidity and mortality associated with SLE. The incidence of myocardial infarction among women with SLE in the 35- to 44-years-old age cohort has been estimated to be 50-fold greater than that of age matched controls (1), and these patients appear to have an overall prevalence of coronary disease of approximately 7% (1). Because the pathophysiology of coronary involvement in SLE is multifactorial, the diagnosis and appropriate therapy may be complex. A case of acute myocardial infarction in the setting of a young patient with SLE is presented, and a review of the literature and of the therapeutic dilemmas confronted by the treating physicians is described.

CASE

A 36-year-old African American woman with a 10-year history of SLE was transferred to Rush-
Presbyterian-St. Luke’s Medical Center (Chicago, IL) with a diagnosis of myocardial infarction. She had presented with typical retrosternal chest pain, electrocardiographic abnormalities characterized by ST segment elevations in leads II and V3 through V5, and elevated cardiac enzymes. The pain was refractory to medical therapy and to streptokinase infusion before transfer. Emergency coronary angiography revealed a thrombus in the left anterior descending coronary artery. Angioplasty and stent placement were performed, and her chest pain resolved. A discoid lupus rash, polyarthritis, nephritis, hypertension, and hypercholesterolemia had complicated the patient’s 10-year course of SLE; she had no known history of antiphospholipid antibodies or coagulopathy. Before admission, her SLE had been controlled with prednisone, 10 mg/d, and she was taking no other medications. She did not use alcohol, tobacco, or illicit drugs, and the rest of her medical history was remarkable only for having had 2 miscarriages and 4 normal pregnancies.

Her physical examination on admission was remarkable only for a discoid rash on the face, patchy alopecia, and synovitis of the knees. The pulmonary and cardiac examination results were normal. Laboratory analysis was significant for mild anemia (hemoglobin 11.4g/dL) and azotemia (serum creatinine 1.5 mg/dL). Her serum total protein concentration was 3.7g/dL (normal, 6.0 to 8.2), and albumin level was 1.4g/dL (normal, 3.5 to 5.0). Serum total cholesterol was 274 mg/dL, with high-density lipoprotein (HDL) of 65.6 mg/dL, low-density lipoprotein (LDL) of 194 mg/dL, and triglycerides of 70 mg/dL (normal, 30 to 135 mg/dL). Creatine kinase was 6,002 U/L (normal, 5 to 200 U/L), muscle brain fraction was 388.4 U/L, and the creatinine kinase–muscle brain fraction index was 6.5. Serum troponin I was greater than 750 ng/mL (normal, 0.157 ng/mL). Urinalysis revealed a white blood cell count of 10 cells/µL, a red blood cell count of 32 cells/µL, and numerous white cell and granular casts per high power field, and there were 6.6 g of protein in a 24-hour urine collection. Tests for anti–double-stranded DNA and antcardiolipin antibodies were negative, and complement levels were low: C3, 60 mg/dL and C4, 10 mg/dL. Chest radiography was normal, and echocardiography showed left ventricular systolic dysfunction with an ejection fraction of 40% and no pericardial effusion.

COMMENT

Thus, this premenopausal woman had clinically and serologically active lupus, was hyperlipidemic, and had a history of multiple miscarriages. She was therefore at risk for each of the most important underlying causes of coronary artery involvement in SLE. The thrombus occluding her coronary artery may have been related to atherosclerosis, a hypercoagulable state, or vasculitis; the therapy and prognosis depended on correctly assigning the underlying cause.

DISCUSSION

Clinically significant CAD is prevalent among patients with SLE; however, because SLE commonly affects premenopausal women, an otherwise low-risk demographic group, the diagnosis is often not considered even in the presence of clear anginal symptoms (1). Although ischemic pain may be confused with pericarditis, a universally appreciated complication of SLE, the enhanced prevalence of myocardial infarction among young patients with SLE suggests that a high index of suspicion for coronary ischemic disease is important to the care of SLE patients. Moreover, despite concerns of vasculitis among patients with SLE, the overwhelming majority of coronary occlusive disease in SLE results from atherosclerosis and/or thrombosis.

The mean age of first myocardial infarction among SLE patients has been reported to be 49 years, which is 20 years younger than that of the general population (2). Among young SLE patients—those less than 35 years—acute myocardial infarction is the most common initial clinical manifestation of CAD, followed by congestive heart failure, sudden death, and angina (3). Thus, laboratory findings that may have low positive predictive value among healthy young women, such as electrocardiographic abnormalities, may indeed carry greater clinical significance in the setting of a patient with a diagnosis of SLE (2). The coronary arteries may be affected in SLE via several mechanisms, the most prominent of which include premature atherosclerosis, with or without hyperlipidemia or hyperhomocysteinemia; coagulopathy, especially related to antiphospholipid antibodies; and coronary aneurysms and vasculitis.
Atherosclerosis and Hyperlipidemias

Significant atherosclerosis is common among SLE patients. The majority of SLE patients dying of noncardiac causes have pathologically moderate to severe multifocal atherosclerosis in autopsy studies (4). Moreover, an autopsy series of women aged 16 to 37 years showed that over 90% had more severe atherosclerosis than an age-matched control population and that almost half had evidence for a greater than 75% occlusion in at least one coronary artery (5). Thus, whereas coronary vasculitis must be included in the differential diagnosis of coronary artery occlusion in the setting of systemic autoimmune disease, the majority of such patients with symptoms and signs of coronary disease will have early-onset atherosclerosis rather than vasculitis (5).

Many of the risk factors for the development of coronary artery atherosclerosis among SLE patients are similar to those of the general population: hypertension, diabetes mellitus, and hyperlipidemia. Although there does not appear to be a direct correlation between glomerulonephritis and CAD (6), nephrosis is associated with hypercholesterolemia. The hyperlipidemias may be particularly significant in SLE because of the high prevalence of chronic renal failure, hypertension, and glucocorticoid use. In fact, some authors believe that the high rate of coronary atherosclerosis in SLE may be a direct result of glucocorticoids (7). Bulkley and Roberts (8) noted that before the use of glucocorticoids there was no clear association of SLE with atherosclerosis. Retrospective analyses have concluded that SLE patients treated with glucocorticoids (>10 mg of prednisone or equivalent per day) had higher levels of serum triglycerides, cholesterol, and LDL than matched controls (9,10), whereas SLE patients not exposed to glucocorticoids had lipid levels similar to normal patients (9). Similarly, serum cholesterol levels appear to increase with increasing dose and duration of steroid use (11): For every increment of 10 mg/d of prednisone, systolic blood pressure has been noted to increase by 1.1 mm Hg, cholesterol by 9 mg/dL, and weight by 5.5 pounds (11). Finally, a retrospective analysis among SLE patients who suffered myocardial infarctions showed that the patients had almost a 2-fold increased exposure to glucocorticoids than SLE patients without infarctions (6).

It is important to note, though, that each of these studies represents a retrospective analysis and suffers from acquisition bias. It is likely that patients with the most severe disease would also independently be the group at highest risk for coronary disease and the most likely group to be treated with aggressive steroid therapy. Thus, none of these studies definitively implicates glucocorticoids in the pathogenesis of SLE-related atherosclerosis. Furthermore, it can be argued that disease duration may play a greater role in CAD. Patients with ischemic heart disease had lupus for 19.5 years, versus 6.5 years in the rest of the cohort (6).

The association between hyperlipidemias and atherosclerotic CAD has long been appreciated, and lipid abnormalities have been described in patients with SLE. A so-called lupus pattern of hyperlipidemia, consisting of elevated very-low-density lipoprotein and triglycerides and low HDL, has been described (12). This has been observed even among patients with relatively quiescent disease, as defined by low SLE disease activity index (SLEDAI) scores (13), though there may be worsening of the hyperlipidemia with increased disease activity (13). Other lipid alterations that have been described in SLE include elevation of serum lipoprotein (a) (12), alterations in the metabolism of chylomicrons, and modification of lipoprotein lipase activity resulting in a so-called immune lipidemia (13). Reductions in serum HDL levels may be particularly important in the development of atherosclerosis among SLE patients.

In the murine model of F2 mice, which carry the lpr mutation of the fas gene, the primary determinant of autoimmune disease, HDL is reduced (14). Atherosclerotic lesions analogous to human disease can be induced by combining a high-cholesterol diet with injections of heterologous proteins to initiate immunologic injury (15). Comparable immune deposits reported in the vessels of human SLE-involved myocardium (16) suggest that a similar process may be involved in the premature atherosclerosis of SLE (15). In addition, peroxidation of LDL and its accumulation in the cell wall result in an inflammatory response that leads to atherosclerosis (17). Recently identified autoantibodies that recognize malondialdehyde-modified lipoprotein (a) react with LDL, thus supporting the role for oxidative phenomena in the pathogenesis of atherosclerosis and of the antiphospholipid syndrome (18).
Homocystinemia

Recent epidemiology studies have shown that moderate elevations in serum homocysteine levels are associated with increased risks for fatal and nonfatal CAD (19). Approximately 15% of patients with SLE have elevated serum homocysteine (20), an abnormality that is especially pronounced among men and in patients with diminished creatinine clearance (20), possibly as a reflection of the decreased renal clearance of homocysteine. Every log-order increase of serum homocysteine is associated with a 2.4-fold–increased risk of stroke and a 3.5-fold–increased risk of arterial thrombosis (20), although there are no data specific for CAD.

There is evidence among the rheumatoid arthritis population that methotrexate use may represent another risk factor for elevated serum homocysteine levels and that this is unrelated to other disease-modifying agents (21). In one study, patients with rheumatoid arthritis who had cardiovascular disease at the start of the study had a crude risk-ratio of death 4.1-fold greater than the cohort treated with disease-modifying agents other than methotrexate (21). These findings have special relevance in light of the increasingly common use of methotrexate in the chronic therapy of SLE. Treatment with folate and vitamins B6 and B12 are effective in reducing serum homocysteine levels, but there are no data to confirm a concomitant decrease in thrombotic or atherosclerotic CAD (19).

Antiphospholipid Antibodies and Coagulopathy

The risk of thrombotic events in the presence of isolated antiphospholipid antibodies among the normal population remains unclear, although it is quite low. Similarly, even among a cohort of patients with unstable angina or myocardial infarction, there is no obvious association with antiphospholipid antibodies (22).

In contradistinction to the normal population, antiphospholipid antibodies in patients with SLE pose a significant risk for the development of clinically significant coagulopathy. An early study documented a 17% prevalence of cerebrovascular accidents and 4% prevalence of myocardial infarction among SLE patients with detectable antiphospholipid antibodies (23). CAD among SLE patients with antiphospholipid antibodies is presumably mediated via the associated coagulopathy. There is good evidence that such patients may present with myocardial infarctions with angiographically normal coronary arteries (24–26). At times, thrombi are not evident in the large coronary arteries at the time of angiography; this may be due to spontaneous breakup of a significant clot in the epicardial vessel or to spasm (27) or thrombosis of the small cardiac vessels (24,25). Small-vessel thrombosis has been documented at postmortem evaluation (26), though it may be difficult to document antemortem. There is some evidence that endomyocardial biopsies may be used successfully for diagnosis (24,25), though the sensitivity of the procedure has not been evaluated.

Because myocardial infarction may occur with antiphospholipid antibodies in the absence of significant structural disease in the coronary arteries and even in the absence of angiographically detectable thrombi, the diagnosis is frequently made based on clinical criteria. The presence of elevated anticardiolipin antibodies, lupus anticoagulant, or a biologically false-positive test result for syphilis or for β2 glycoprotein-1 antibodies would support the diagnosis. Similarly, a history of previous deep-vein thrombosis or other evidence of arterial or venous thrombosis would provide additional support. In addition, high-titer antibodies are thought to have greater significance than those with lower titers; anticardiolipin antibodies have been associated with such noncoronary complications as venous thrombosis and pulmonary embolism only when the antibody titer was greater than the 95th percentile (28). In general, high antibody titers have greater significance than low titers. Comparable data are not available for CAD, though it is likely that coronary thrombosis occurs via a similar mechanism.

A definite diagnosis of antiphospholipid syndrome is further complicated by the fact that transient anticardiolipin antibodies may be associated with a variety of infections, medications, and malignant and nonmalignant conditions (29). For example, antibodies to the chlamydia envelope lipopolysaccharide cross-react with phospholipids and may be detected as antiphospholipid antibodies (17). Thus, a single positive test result for antiphospholipid antibody in the presence of CAD does not provide valuable prognostic or diagnostic information (30). Rather, the detection of persistently elevated titers may be more closely associ-
ated with the thrombotic syndrome than single abnormal values (29).

A further complication posed by the antiphospholipid antibody syndrome in patients with CAD is that these patients are at high risk for reocclusion of the coronary arteries after coronary artery bypass grafting, and this trend appears to be related to the titers of circulating antiphospholipid antibodies (31). Among patients with very high titer—greater than 4 standard deviations above normal—the risk of reocclusion is greater than 50% (31).

Coronary Aneurysms and Vasculitis

Vasculitis of the coronary arteries has been well described in SLE (5,24,32,33), though it accounts for only a small number of deaths from myocardial infarction (13,33-35). Although coronary vasculitis is far less common than premature atherosclerotic disease among patients with SLE, the clinical diagnosis is often difficult and is frequently made only at postmortem examination (36). Pathologically, affected vessels are typically narrowed by cellular intimal fibrosis (8) with areas of aneurysmal dilatation; when present, aneurysms are most commonly detected in the proximal right circumflex artery, occasionally occluded by a thrombus, although the reason for this apparent tropism remains unclear (37). Like other arteritides of muscular arteries, the radiographic diagnosis depends on the identification of aneurysms by angiography. However, in the case of CAD, the detection of a single aneurysm on an angiogram may be compatible with atherosclerosis as well as with vasculitis (37). The Coronary Artery Surgery Study (CASS) reported that 4.9% of 978 patients with atherosclerosis had evidence of coronary aneurysms at angiography (38). More convincing evidence for vasculitis may be provided by the demonstration of aneurysm formation followed by rapid stenosis (39).

A further level of complexity in the diagnosis of coronary artery vasculitis in SLE is that there does not appear to be a relationship between clinical or serologic disease activity and the development of symptomatic vasculitis. Thus, there are reports of pathologically shown coronary vasculitis in patients dying of myocardial infarction who were clinically and serologically inactive (33), as well as in patients with coronary artery aneurysms in the absence of detectable disease activity (39). Conversely, it is common to observe severe coronary atherosclerosis without vasculitis in patients who die with severe chronically active SLE (39).

DIAGNOSIS

Chest pain is common among patients with SLE. Its source may be varied, but ischemic heart disease should not be discounted, even in premenopausal women and children (33).

The use and interpretation of various noninvasive screens for CAD in SLE should be geared to the altered pretest probability of disease. For example, electrocardiographic abnormalities in SLE are common, with ST-T wave changes observed 4 times more frequently than in patients with rheumatoid arthritis (2). The presence of Raynaud’s phenomenon may serve as a surrogate marker of SLE patients with underlying vascular disease (2). Segmental perfusion defects have been described in 46% of SLE patients undergoing thallium–201 scanning, with nearly half of these being fixed defects (40) and with no correlation with steroid dose, organ involvement, or duration of disease (40). Interestingly, a significant association with a previous history of pericarditis was identified (40).

Carotid ultrasonography may provide a noninvasive screening procedure to identify those at risk for CAD. There appears to be a high concordance between carotid and coronary atherosclerosis in SLE (41,42). However, there have been no cost-effectiveness analyses that suggest that this would be appropriate in large-scale clinical practice. Coronary angiography remains the gold standard to confirm the diagnosis of atherosclerotic CAD. Angiitis of the coronary vessels, thrombosis due to hypercoagulable states, and coronary spasm are additional important considerations in SLE, which also may be evaluated via angiography. As with other forms of vasculitis, it may be difficult to differentiate coronary arteritis from atherosclerosis exclusively on the basis of the classical angiographic criteria of arteritis such as of beading of the vessels. Evidence of peripheral vasculitis or atherosclerosis may be suggestive, but often the diagnosis rests on the overall clinical presentation.

TREATMENT

Ischemic heart disease is a leading cause of death in SLE; its recognition and management by rheumatologists, who often assume primary care for these patients, is critical to minimize morbidity and mortality. Appropriate management should in-
clude preventive care. Thus, as with atherosclerosis in the general population, risk factor reduction, when possible, should be sought. This includes control of hypertension, smoking cessation, and dietary counseling. In addition, minimizing glucocorticoid therapy may result in decreases of serum cholesterol but may be impractical for patients with active or smoldering SLE. There is abundant recent evidence that there is a large inflammatory component to atherosclerotic disease; however, the practical aspects of limiting systemic inflammation as prevention therapy for coronary disease in SLE remain to be defined (43).

Despite efforts at risk-factor reduction, patients with SLE and CAD have fewer traditional risk factors when compared with non-SLE patients (44). After adjusting for known risk factors for atherosclerosis, the relative risks for myocardial infarction and stroke in SLE are 10-fold and 6.3-fold higher, respectively (44). Thus, SLE itself should be considered a major risk factor for coronary disease, and the need to further stratify the risks in these patients is imperative.

The routine use of hormone replacement in postmenopausal women is being re-evaluated in light of recent conflicting evidence concerning its efficacy for the reduction of coronary heart disease rates (45), as well as the associated risks of thromboembolic and gall bladder diseases (44,45). Hydroxychloroquine may be considered both for its activity against SLE and because it has been associated with lowering serum cholesterol levels (30).

The various coronary revascularization strategies have not been systematically evaluated in SLE. In general, lupus surgical candidates are at a higher risk than the general population, because they often have multisystem disease and have been treated with various immunosuppressive and glucocorticoid regimens. Complication rates have been reported to be high (46). Both angioplasty and coronary artery bypass grafting are routinely performed in SLE (47,48). Not infrequently, coronary artery bypass is combined with valvular surgery. The combined postoperative mortality ranges from 12.5% (47) to 25% (3), but the series are small.

SUMMARY

Patients with SLE, even premenopausal women, are at increased risk for CAD and myocardial infarction over and above that which is observed with the well-recognized risk factors in the general population. Raynaud’s phenomenon, a history of pericarditis, and duration of SLE also may be risk factors. Cost-effective screening methods need to be identified and evaluated for this high-risk group, but recognition of the significance of CAD in this population will assist in the early identification of SLE patients with coronary disease and may assist in reducing the accompanying morbidity and mortality. Currently, conventional screening approaches for CAD are recommended, albeit with an added index of suspicion and pretest probability of disease, especially among young women. Low-dose aspirin coupled with optimization of blood pressure and lipid control and smoking cessation must be accompanied by awareness that chest pain, even in a premenopausal woman, may represent CAD. Percutaneous transluminal coronary angioplasty and or surgical bypass graft using the internal thoracic artery provide symptomatic relief and probably prolong life, although the data are limited.

REFERENCES


