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LAMBL'S EXCRESCENCES: ASSOCIATION WITH CEREBROVASCULAR DISEASE AND PATHOGENESIS

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Abstract

Background—Lambl's excrescences (LEx) are detected by transesophageal echocardiography (TEE) and are characterized as thin, elongated, and hypermobile structures located at the leaflets' coaptation point of the heart valves. The association of LEx with cerebrovascular disease (CVD) is still undefined and yet patients with LEx and suspected CVD receive unproven effective antiplatelet or anticoagulant therapy or even undergo valve surgery. Also, the association of LEx with aging and atherogenic, inflammatory, or thrombogenic parameters has not been reported.

Methods—77 patients with systemic lupus erythematosus (SLE) (71 women, age 37±12 years) and 26 age-and-sex matched healthy controls (22 women, age 34±11 years) prospectively underwent routine history and physical exam, transcranial Doppler, brain MRI, transesophageal echocardiography (TEE), carotid duplex, and clinical and laboratory evaluations of atherogenesis, inflammation, platelet activity, coagulation, and fibrinolysis. Subjects without stroke/TIA on enrollment (with and without LEx) had a median follow-up of 57 months.

Results—On enrollment, 33 (43%) of 77 patients had CVD manifested as acute stroke/TIA (23 patients), cerebromicroembolism by transcranial Doppler (17 patients), or cerebral infarcts by MRI (14 patients). Mitral or aortic valve LEx were equally frequent in healthy controls (46%) as in patients with and without any CVD (39% and 43%), stroke/TIA (35% and 43%), cerebromicroembolism (41% and 42%), or cerebral infarcts (36% and 43%) (all $p \geq 0.72$). Also, other mechanisms for CVD other than LEx such as Libman-Sacks vegetations, patent foramen ovale or interatrial septal aneurysm, aortic or carotid atherosclerosis, or thrombogenesis were found in ≥94% of patients with CVD. In addition, 36 subjects with and 44 without LEx had similar low incidence of stroke/TIA [1(1.3%) and 2(2.5%), respectively, p=1.0] during follow-up. Finally, LEx were not associated with aging, atherogenic risk factors, atherosclerosis, inflammation, or thrombogenesis.

Conclusions—In this study, LEx are similarly prevalent in healthy controls and SLE patients, are not associated with CVD, and are not associated with pathogenic risk factors. Therefore, the

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CONFLICTS OF INTEREST

None of the authors has conflicts of interest to disclose.

study findings suggest that LEx may not be cardioembolic substrates, may not represent pathologic valve structures, and may not require therapy.

Keywords

Lambl's excrescences; cerebrovascular disease; magnetic resonance imaging; transcranial Doppler; transesophageal echocardiography

INTRODUCTION

Lambl's excrescences (LEx) were first described in 1856, are currently detected by transesophageal echocardiography (TEE), and are characterized as thin, elongated, and hypermobile structures located at the coaptation point of valves' leaflets [1–5]. An association of LEx with stroke/transient ischemic attacks (TIA) has been reported in retrospective or case-control studies, small case series, and isolated case reports [2, 3, 6–11]. However, patients >60 years old with risk factors for atherothrombosis or atheroembolism were included in those reports and other mechanisms of stroke/TIA and indicators of cerebroembolism such as cerebromicroembolism detected by transcranial Doppler or cerebral infarcts by magnetic resonance imaging (MRI) were not investigated. Therefore, the association of LEx with CVD is still undefined. Also, the association of LEx with aging and atherogenic, inflammatory, or thrombogenic markers has not been reported [2–11]. Patients with systemic lupus erythematosus (SLE) have a high prevalence and incidence of stroke/TIA, ischemic brain lesions on MRI, atherogenic risk factors, premature atherosclerosis, inflammation, and hypercoagulability [12–15]. Thus, patients with SLE are an ideal subset for studying the association of LEx with CVD and their potential pathogenic factors.

This 6-year, prospective, controlled, cross-sectional, and longitudinal study in SLE was designed with 2 objectives: 1) to determine if there is an association of LEx with CVD manifested as acute stroke/TIA, cerebromicroembolism by transcranial Doppler, or cerebral infarcts on MRI; and 2) to determine if there is an association of LEx with clinical and laboratory parameters of aging, atherogenesis, atherosclerosis, inflammation, platelet activity, coagulation, or fibrinolysis.

METHODS

Study Populations

This study is part of a protocol approved by the National Institutes of Health and Institutional Review Board for the study of cardiovascular and CVD in SLE [14]. All participants provided informed consent.

From December 2006 to December 2012, 77 (29%) of 266 patients with SLE [age 37±12 years (range, 18–60), 71 women)] actively followed at the rheumatology clinics of the University of New Mexico Health Sciences Center met inclusion criteria and agreed to participated in the study.

Exclusion criteria included: age <18 or >60 years, pregnancy, atrial fibrillation/flutter, cardiomyopathy (ejection fraction <50%), intracardiac thrombi, drug abuse, renal dysfunction, and heart or brain disease unrelated to SLE.

To provide a control reference and to validate blinded interpretation of studies, 26 age-and-sex matched volunteers [age 34±11 years (range, 18–57), 22 women] with a negative medical history and physical examination were studied.

All 103 participants prospectively underwent clinical and laboratory evaluations, brain MRI, transcranial Doppler, TEE, and carotid duplex within 1 week of enrollment. All studies were de-identified, coded, and interpreted by independent experienced observers unaware of subjects' clinical and imaging data.

Clinical and laboratory evaluations

On enrollment, all participants were assessed for: 1) acute stroke/TIA (preceding 1–2 weeks); 2) general demographics; 3) parameters of atherogenesis; and 4) parameters of inflammation, platelet activity, coagulation, and fibrinolysis (Table 3). Also, SLE patients were characterized with regard to SLE duration, activity, and damage; standard inflammatory markers and autoantibodies; antiphospholipid antibodies (aPL); and corticosteroid, antimetabolite immunosuppressive, antimalarial, and antithrombotic therapy (Table 4).

Brain MRI

Standard volume-acquired T1-weighted, T2-weighted fluid attenuated inversion recovery (T2-FLAIR), and diffusion-weighted images were obtained using a 1.5-T Siemens Sonata scanner with an 8-channel head coil. Brain lesions were classified as recent or old cerebral infarcts using standard criteria [15]. Inter-observer agreement for detection of cerebral infarcts in 72 studies was 93% (Kappa 0.72).

Transcranial Doppler

Both middle cerebral arteries were interrogated for 90 minutes for detection of microembolism defined as audible, high intensity, and short lasting unidirectional signals within the Doppler blood flow velocity and vessel lumen [16]. Intraobserver agreement for detection of microembolism was 96% (Kappa 0.83).

Transesophageal echocardiography

Participants underwent TEE with IE-33 Philips systems (Andover, Massachusetts, USA) and images were digitally acquired for off-line interpretation. Heart valves were carefully imaged in multiple planes at depths of 4–8 cm with a narrow sector scan to improve image resolution.

Criteria for interpretation

LEx were defined as thin (≤2 mm) and elongated (≥6 mm) structures with independent and undulating hypermobility seen at the leaflet's coaptation point, on the atrial side of the mitral leaflets and ventricular side of the aortic cusps [2–5]. In 53 randomly selected TEE studies

(27 patients, 26 controls), inter-observer agreement for the detection of mitral and aortic valve LEx were 96% (Kappa 0.92) and 91% (Kappa 0.81), respectively. To further validate the presence and characteristics of LEx, a third observer measured and averaged the length and width of LEx during 3 cardiac cycles. Finally, the length and width of LEx were measured by a fourth observer in 20 randomly selected studies (13 patients, 7 controls) with 25 LEx. The length and width of LEx were similar between the third and fourth observers (all $p \geq 0.20$) (Supplemental Table 1).

Other cardiogenic mechanisms for CVD were carefully assessed: 1) Libman-Sacks vegetations defined as abnormal localized, sessile, oval shape, and protruding echodensities of ≥3 mm in diameter with well-defined borders either as part of or adjacent to valve leaflets, subvalvular apparatus, or great vessels [14]. Inter-observer agreement for detection of vegetations in 30 randomly selected TEE studies (22 patients, 8 controls) was 93% (kappa 0.87). 2) Intracardiac thrombus and spontaneous echocardiographic contrast on the left atrium and ventricle. 3) Patent foramen ovale or interatrial septal aneurysms by two-dimensional, color-Doppler, and saline contrast imaging. And 4) atherosclerosis of the ascending aorta, arch, and descending thoracic aorta by two-dimensional and M-mode imaging and defined as intima-media thickening (≥2SD above the mean of healthy controls) or plaques (focal thickening of the intima-media exceeding 50% of the surrounding vessel wall) [14, 17]. Inter-observer variability for measurement of aortic intima-media thickness in 10 randomly selected studies (7 patients, 3 controls) demonstrated a mean percent error of 4.9%.

Carotid duplex

From longitudinal B-mode images of both common carotid arteries, 6 measurements of intima-media thickness of the far and near walls were performed [18]. Inter-observer variability for measurement of carotid intima-media thickness in 10 randomly selected studies (6 patients, 4 controls) revealed a mean percent error of 3.8%. Carotid atherosclerosis was defined with the same criteria described for the aorta.

Cerebrovascular disease

After completion of evaluations, the presence of CVD was defined as acute stroke/TIA, cerebromicroembolism, or cerebral infarcts.

Follow-up

Subjects without stroke/TIA on enrollment had a median follow-up of 57 months (IQR 25–64 months) to assess an association of LEx with incident stroke/TIA.

Statistical analysis

Descriptive statistics were mean±SD, median (IQR) for asymmetrically distributed data, or frequencies (%). Comparisons between 3 study groups were performed by analysis of variance (ANOVA) for continuous measures and verified by Kruskal-Wallis tests. Fisher's exact tests were used for comparisons of binary measures among 3 groups. Student's t-tests (Wilcoxon's rank sum test for asymmetrically distributed data) and Fisher's exact tests were

used to compare continuous and binary measures between 2 groups, respectively. A two-tailed p value <0.05 was considered significant. Analyses were performed using SAS 9.3.

RESULTS

On enrollment, 33 (43%) of 77 SLE patients had CVD manifested as acute stroke/TIA in 23 patients (stroke in 7, TIA in 16), cerebromicroembolism in 17 patients with 28 microembolic events, or cerebral infarcts in 14 patients with 47 infarcts (11 recent, 36 old). No CVD was detected in healthy controls.

The frequency of LEx on the mitral, aortic, or either valve were similar in patients and controls [21 (27%), 20 (26%), or 32 (42%) versus 7 (27%), 9 (35%), or 12 (46%), respectively, all p≥0.45]. Of most importance, the frequency of LEx was similar in patients with and without CVD as well as in healthy controls (all p≥0.55) (Table 1, Figure 1 with video clips).

Also, the length and width of LEx were similar in patients with (11.9 ± 4.9 mm and 0.77 ± 0.25 mm) and without CVD (11.7 ± 3.5 mm and 0.90 ± 0.20 mm) and in controls (9.1 ± 3.4 mm and 0.85 ± 0.18 mm, respectively) (all p≥0.13 for length and p≥0.24 for width) (Supplemental Table 2).

In addition, sources of cardioembolism other than LEx, aortic or carotid atherosclerosis, or thrombogenesis were found in ≥94% of patients with CVD (Table 2).

Furthermore, the incidence of stroke/TIA during follow-up was similarly low in 36 subjects with LEx and 44 without LEx [1(1.3%) versus 2(2.5%), respectively, p=1.0]. The patient with LEx and stroke/TIA also had Libman-Sacks vegetations and aPL.

Finally, in SLE patients and controls, LEx were not associated with aging [age <30 (43%), 30–39 (45%), 40–49 (35%), and 50–60 (47%); Jonckheere-Terpstra trend test p=0.93], atherogenic risk factors, atherosclerosis, inflammation, or thrombogenesis (Table 3). Also in SLE patients, LEx were not associated with disease duration, activity, and damage; standard parameters of inflammation; serology and autoantibodies including aPL antibodies; and anti-inflammatory or antithrombotic therapy (Table 4).

DISCUSSION

Major findings

This study demonstrated 4 major findings: 1) LEx had similar frequency, distribution, and characteristics in healthy controls as in SLE patients with and without CVD; 2) most patients with CVD had other proven sources of cardioembolism, atherosclerosis, or increased thrombogenesis; 3) LEx were not associated with incident stroke/TIA; and 4) LEx were not associated with aging, atherogenic risk factors, atherosclerosis, inflammation, or thrombogenesis. To our knowledge, this is the first highly integrated, multidisciplinary, controlled, cross-sectional and longitudinal study to support that LEx may not be pathologic valve structures, may not be cardioembolic substrates, and therefore may not warrant therapy. LEx may be normal variants with a protective blunting effect on the leaflets from

the impact of valve closure or from shear forces of blood flow jets or are normal variants resulting from constant bending and buckling of leaflets leading to transient tearing of endothelial cells and subendothelial collagen and elastic fibers with subsequent normal reparative endothelialization [5, 19, 20]. The predominance of LEx on the left heart valves where high ventricular and aortic pressure gradients impact valve closure may support such pathogeneses. In fact, pathology studies of normal valves report similar frequency of LEx during different decades of age with equal sex distribution, and with similar frequency, distribution, and characteristics to those described by TEE in healthy subjects [4, 5, 19–22]. Finally, the histology of LEx consisting of a core of connective tissue with collagen and elastic fibrils or of an acellular hyaline material covered by normal endothelium does not indicate an aging, atherogenic, inflammatory, or thrombogenic process [1, 19–22] (Figure 2).

Comparison with previous studies

Four previous studies support our findings. Cohen et al [23] in a case-control study of 284 patients with stroke (all >60 years old) and 276 controls reported mitral valve LEx in 22.5% of cases and 12.1% in controls (p=0.005). However, during 2–4 years of follow-up, incident stroke was similarly low in patients with and without LEx (6.0 and 4.2 per 100 person-years, respectively), LEx were not independent predictors of recurrent stroke (relative risk 1.3, 95% CI 0.5–3.1, p=0.54), and incident stroke in patients with LEx was unrelated to antiplatelet, anticoagulant, or no therapy (7.1, 6.9, and 0 per 100 person-year, respectively). Our group [5] in 1997 in a different population and in part retrospective study reported similar frequency of LEx in 38% of 90 healthy volunteers, in 47% of 88 patients undergoing TEE for reasons other than cardioembolism, and in 41% of 49 patients undergoing TEE for suspected cardioembolism, of whom 85% had other cardiovascular mechanisms for CVD. Also, incident stroke/TIA in subjects with and without LEx was similarly low (≤2%) during 5-years of follow-up. Nighoghossian et al [24] reported LEx in 30 of 160 (18.8%) patients with stroke. In that study, all 30 patients had atherogenic risk factors, atrial septal aneurysms and patent foramen ovale were the predominant abnormalities in patients with presumed cardioembolic stroke, 40% had large or small vessel disease as cause of stroke, one patient with recurrent stroke had pathologic confirmation of thrombotic vegetations, and 85% of LEx persisted on follow-up TEE despite antithrombotic therapy. Of most importance, Homma et al [4], in a large, prospective, cross-sectional and longitudinal study of 619 patients with carefully categorized stroke types, meticulously assessed TEE studies for LEx, and randomly and double blindly assigned patients with and without LEx to warfarin or aspirin therapy reported LEx in 244 (39%) of 619 patients with stroke (in 38.6% with cryptogenic stroke and in 40.1% with known cause of stroke). During 2-year follow-up and independent of stroke type or of warfarin or aspirin therapy, the incidence of stroke or death was similar in those with and without LEx (16.4% versus15.5%, respectively).

Other studies suggesting LEx as cardioembolic substrates have design and methodologic characteristics that preclude establishing a causal association. Recently, Leitman, et al (6) in a 5-year retrospective case-controlled echocardiographic database study reported valve strands in 150 of 21,000 studies (0.7%, the lowest ever reported prevalence of LEx). They report a 27% frequency of stroke/TIA or peripheral ischemia in 40 (27%) of those 150

patients with as compared with 20 (13%) of 150 case-controls without strands. However, an association of valve strands with cerebral or peripheral ischemia cannot be established for several reasons: 1) study design, 2) ascertainment bias given that records of patients in whom LEx were reported upon were retrospectively reviewed aware that echocardiographic studies were frequently performed for suspected cardioembolism, 3) 43% of patients had transthoracic echocardiography with an expected low sensitivity and low specificity for valve strands, and 4) study population with high risk for atherothrombosis, atheroembolism, or proven sources of cardioembolism as follows: a) elderly population [mean age, 61±17 years (range 18 to >80)], b) 76% hospitalized patients, c) 63% with atherogenic risk factors, d) 37% with coronary artery disease; e) ≥68% with thickened or calcified heart valves; f) 23% with atrial fibrillation, and g) an undefined proportion with prosthetic valves. Lee et al [2] in a non-controlled study reported mitral valve LEx in 11 (22%) of 50 patients undergoing TEE for suspected cardioembolism. However, patients' mean age was 63 years, 9 had valve thickening or calcification, and 7 had history of arrhythmias, myocardial infarction, cardiomyopathy, or hypertension. Freedberg et al [3], in a retrospective analysis of 1,559 patients with a mean age of 66 years identified LEx by TEE in 63 (10.6%) of 597 patients with suspected cardioembolism as compared to 23 (2.3%) of 962 without. However, their study population was old and also had a 10% prevalence of prosthetic or native valve disease. Roberts et al [7] in a retrospective case-control study reported LEx in 34 (47%) of 73 patients with stroke as compared to 12 (16%) of 73 stroke-free age-matched controls (OR=4.4; 95% CI=2.0–9.6). However, the cases mean age was 63 with a high prevalence (≥55%) of atherogenic risk factors and paradoxically lower frequency (27%) of LEx in patients with presumed cardioembolic stroke than in those with atherothrombotic (42%) or lacunar (62%) strokes. Isolated case reports of LEx and stroke have either alternative mechanisms of stroke or incomplete stroke work-up [8–10, 25–27]. Finally, 4 cases of stroke associated with "giant LEx" described as long (>20 mm) and multiple strands forming a complex are suggestive of papillary fibroelastomas on echocardiography and histology [9, 11, 28–30]. In this study, one subject had a LEx of >20 mm.

Study limitations

The discrete control group may have led to overestimation of the frequency of LEx as compared to that of a general healthy population. However, similar high frequency of LEx were reported in a study with larger number of healthy controls [5] and this limitation does not affect the main finding of the lack of an association of LEx with prevalent and incident CVD in SLE patients. Although lack of histologic confirmation limits conclusions about the nature of LEx seen on TEE, autopsy studies report similar frequency, distribution, and characteristics of LEx as those described by TEE [21, 22]. Concomitant Libman-Sacks vegetations may decrease the specificity of TEE for LEx, yet such vegetations are structurally distinct from LEx [14] (Figure 1B). Although the study included predominantly females as is typical of SLE, similar frequency of LEx has been reported in males [2–5, 21, 22].

Clinical implications

The detection of LEx in patients with CVD poses a diagnostic and therapeutic challenge. The detection of LEx is of particular importance in a relatively large proportion (~25%) of

young patients with presumed cryptogenic stroke/TIA [31] in whom TEE is recommended. The detection of LEx in these patients, which will increase further with the use of three-dimensional TEE [32], may lead to misclassification of a stroke/TIA as cardioembolic, underdiagnosis of the true etiology of stroke/TIA, and potentially to unnecessary antiplatelet or anticoagulant therapy or even valve surgery. Thus, detection of LEx in a patient with suspected cardioembolism should not be considered a de facto cause of cerebroembolism. In such a patient other known cardiovascular sources of embolism and mechanisms of CVD should be thoroughly investigated before initiating a specific therapy or considering valve surgery [4, 5, 14, 23,24, 31]. Patients with suspected cardioembolism and a normal transthoracic echocardiogram may not need to undergo TEE for detection of LEx. In these patients, clinical, laboratory, and transthoracic echocardiography predict absence on TEE of established cardioembolic substrates in ≥95% of patients [34]. The incidental finding of LEx in patients undergoing TEE for reasons other than suspected cardioembolism may not warrant prophylactic antiplatelet therapy. Finally, awareness of the high frequency, distinctive echocardiographic characteristics, lack of association with pathogenic factors, and lack of response to anti-inflammatory and antithrombotic therapy of LEx should improve the diagnostic accuracy of TEE for detection of echocardiographically distinctive non-infective and infective vegetations and papillary fibroelastomas [5, 14, 35, 36].

Conclusions

In this study, LEx are similarly prevalent in healthy controls and SLE patients, are not associated with CVD, and are not associated with pathogenic risk factors. Therefore, the study findings suggest that LEx may not be cardioembolic substrates, may not represent pathologic valve structures, and may not require therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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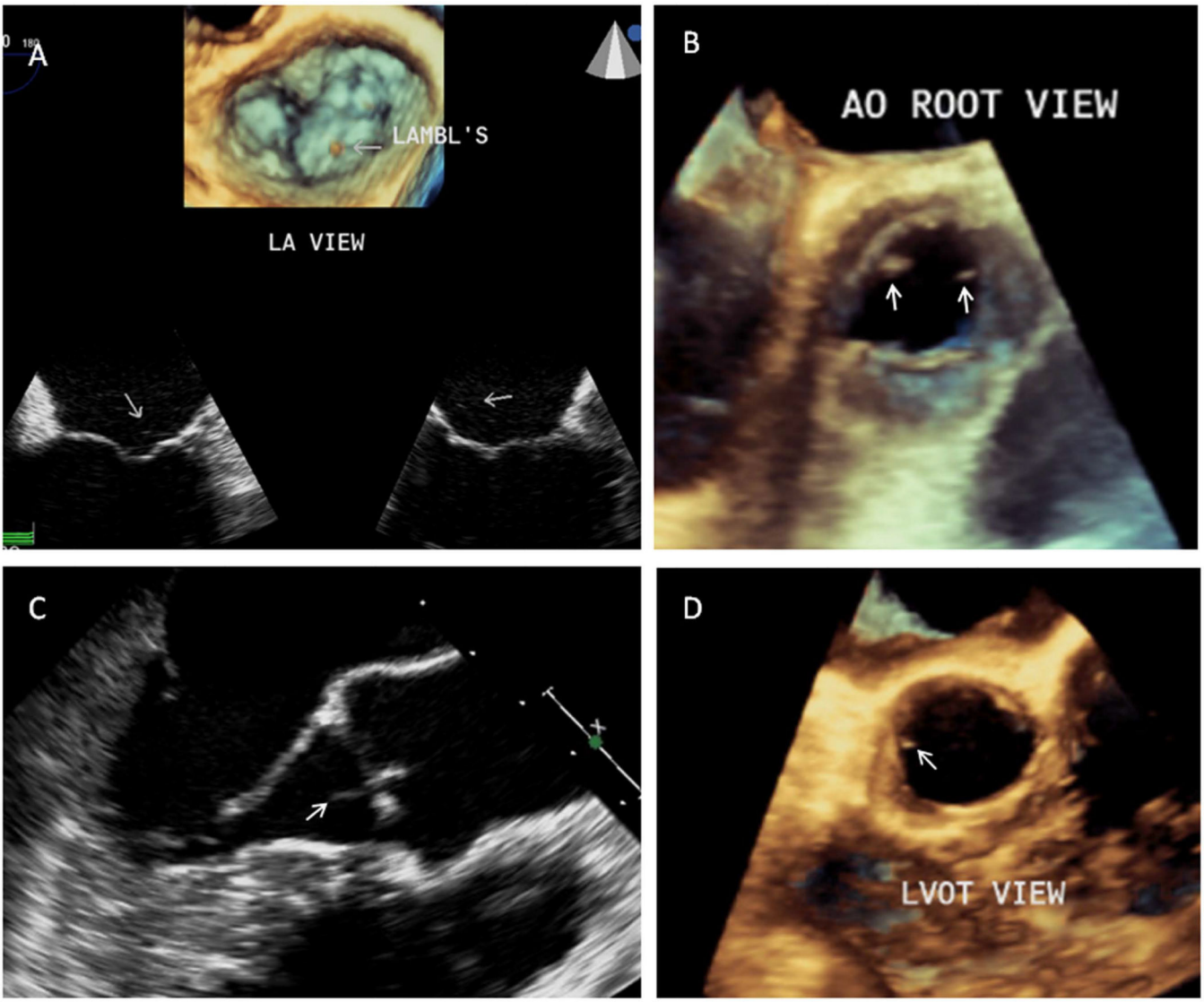

Figure 1. Lambl's excrescences of the mitral and aortic valves

A. Two-dimensional (2D) TEE 4 and 2-chamber views of the mitral valve (*bottom images*) in a 21 year-old healthy female demonstrate a long, thin, and hypermobile Lambl's excrescence located at the coaptation point and atrial side of normal mitral leaflets (Figure 1A video clip). Corresponding three-dimensional (3D) TEE atrial view of the mitral valve (*top image*) shows a Lambl's excrescence at the coaptation point of the middle anterior and posterior mitral scallops (Figure 1A video clip). **B**. This aortic root 3D-TEE view of the aortic valve in a 44 year-old female with SLE demonstrates a Lambl's excrescence (*right arrow*) on the tip and ventricular side of the left coronary cusp and a Libman-Sacks vegetation (*left arrow*) located on the tip and ventricular side of a thickened non-coronary cusp (Figure 1B video clip). **C,D**. This longitudinal 2-D TEE view (**C**) of the aortic valve in a 34 year-old female with SLE demonstrates a thin, elongated, and mobile Lambl's excrescence at the coaptation point of the left and right coronary cusps prolapsing into the ventricular outflow tract during diastole (*arrow*) (Figure 1C video clip). Corresponding left

ventricular outflow tract (LVOT) 3D-TEE systolic view (**D**) demonstrates a Lambl's excrescence located on the ventricular side and tip of the left coronary cusp (Figure 1D video clip).

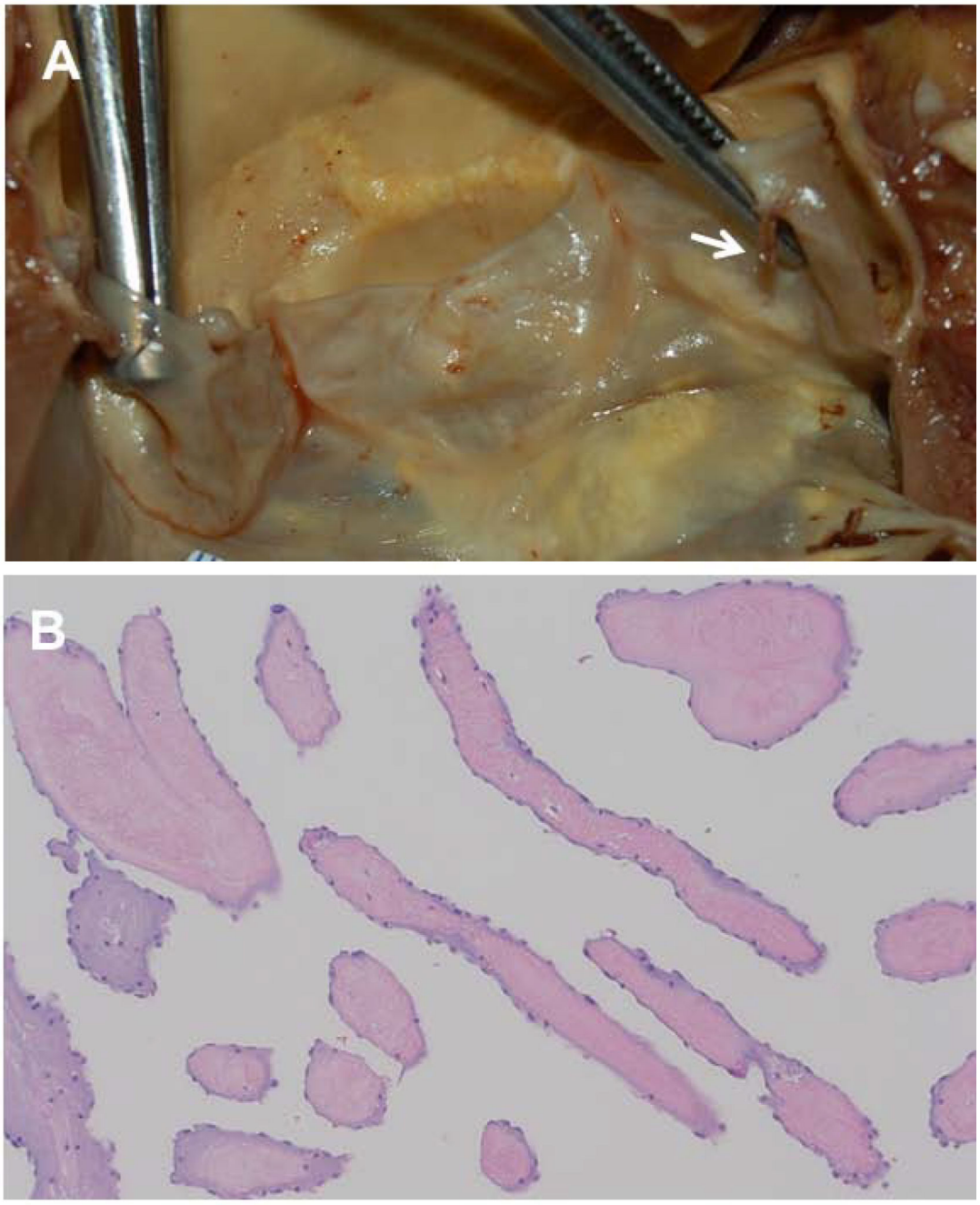

Figure 2. Histology of Lambl's Excrescences

A. Gross anatomic view of a mildly sclerotic aortic valve with a thin (1 mm) and elongated (6 mm) Lambl's excrescence (arrow) at the coaptation point and ventricular side of the left coronary cusp. **B**. Histology of longitudinal, cross-sectional, and oblique cuts of the Lambl's excrescence demonstrate a core of fibroelastic, hypocellular, and avascular connective tissue covered by a single layer of endothelial cells.

Table 1

Frequency and Distribution of Lambl's Excrescences in 77 SLE Patients with and without Cerebrovascular Disease and in 26 Healthy Controls

	Stroke/TIA (N = 23)	No Stroke/TIA (N = 54)	Controls (N = 26)	P value
MV LEx	4 (17%)	16 (30%)	7 (27%)	0.58
AoV LEx	7 (30%)	13 (24%)	9 (35%)	0.59
Either	8 (35%)	23 (43%)	12 (46%)	0.72
	Cerebromicroembolism (N = 17)	**No Cerebromicroembolism (N = 60)**	**Controls**	
MV LEx	4 (24%)	17 (28%)	7 (27%)	0.95
AoV LEx	5 (29%)	15 (25%)	9 (35%)	0.65
Either	7 (41%)	25 (42%)	12 (46%)	0.96
	Cerebral Infarcts (N = 14)	**No Cerebral Infarcts* (N =61)**	**Controls**	
MV LEx	3 (21%)	17 (28%)	7 (27%)	0.95
AoV LEx	5 (36%)	15 (25%)	9 (35%)	0.57
Either	5 (36%)	26 (43%)	12 (46%)	0.81
	†Overall CVD (N = 33)	**No CVD (N = 44)**	**Controls**	
MV LEx	8 (24%)	13 (30%)	7 (27%)	0.96
AoV LEx	10 (30%)	10 (23%)	9 (35%	0.55
Either	13 (39%)	19 (43%)	12 (46%)	0.91

*One patient refused MRI and a second patient had poor quality MRI.

†Overall CVD = stroke/TIA, cerebromicroembolism, or cerebral infarcts.

Abbreviations: LEx=Lambl's excrescences, MV=mitral valve, AoV=aortic valve, TIA=transient ischemic attack.

Table 2

Mechanisms of Cerebrovascular Disease in SLE Patients

Abnormality	Stroke/TIA (N = 23)	Cerebro-Microembolism (N = 17)	Cerebral Infarcts (N = 14)	Overall Cerebrovascular Disease (N = 33)
Libman-Sacks vegetations	22 (96%)	12 (71%)	14 (100%)	27 (82%)
PFO/IASA	1 (4%)	3 (18%)	0	4 (12%)
Aortic atherosclerosis	9 (39%)	6 (35%)	7 (50%)	13 (39%)
Carotid atherosclerosis	6 (26%)	2 (12%)	5 (36%)	8 (24%)
Positive aPL	16 (70%)	10 (59%)	9 (64%)	19 (58%)
Any abnormality	23 (100%)	16 (94%)	14 (100%)	32 (97%)

Abbreviations: PFO=patent foramen ovale, IASA=interatrial septal aneurysm, Positive aPL= abnormal levels of IgG, IgM, or IgA anticardiolipin antibodies or positive lupus-like antibody or β2-glycoprotein antibody.

Table 3

Clinical and Laboratory Parameters in SLE Patients and Healthy Controls with and without Lambl's Excrescences.

	SLE Patients (N = 77)			Healthy Controls (N = 26)		
Parameter	**LEx (N = 32)**	**No LEx (N = 45)**	**P value**	**LEx (N = 12)**	**No LEx (N = 14)**	**P value**
Demographic Parameters						
Age (years)	36 ± 13	37 ± 12	0.88	36 ± 11	32 ± 10	0.38
Women	31 (97%)	40 (89%)	0.39	8 (67%)	14 (100%)	0.03‡
Body mass index	28 ± 5	27 ± 6	0.79	27 ± 5	27 ± 6	0.91
Parameters of Atherogenesis and Atherosclerosis						
HTN (>140/90 mmHg)	3/27 (11%)	5 (11%)	1.0	0	0	
Cholesterol (mg/dl)	188 ± 48	174 ± 44	0.21	194 ± 48	192 ± 39	0.88
HDL (mg/dL)	52 ± 17	49 ± 15	0.38	43 ± 14	58 ± 20	0.10
LDL (mg/dL)	111 ± 43	107 ± 38	0.69	111 ± 41	112 ± 23	0.98
Triglicerides (mg/dL)	160 ± 89	149 ± 74	0.59	170 ± 99	150 ± 97	0.61
Dyslipidemia	13/28 (46%)	21 (47%)	1.00	6 (50%)	3/13 (23%)	0.23
Diabetes mellitus	0/29 (0%)	3 (7%)	0.28	0	0	
Smoking (currently)	7/31 (23%)	17 (38%)	0.21	2 (17%)	4 (29%)	0.65
Any risk factor	16/31 (52%)	26 (58%)	0.64	6 (50%)	3 (21%)	0.22
Aortic or carotid atherosclerosis	13 (41%)	19 (42%)	1.00	4 (33%)	1 (7%)	0.15
Parameters of Inflammation, Platelet Activity, Coagulation, and Fibrinolysis						
White blood cell count (×10^3/mm3)	6.5 ± 3.1	5.9 ± 2.2	0.41	6.4 ± 1.8	6.6 ± 1.5	0.75
C3a (pg/mL)	1443 (967–1999)	1350 (1084–2034)	0.71*	1440 (1197–1839)	1335 (1206–1601)	0.78*
C5a (pg/mL)	26 ± 10	29 ± 11	0.28	26 ± 11	28 ± 9	0.55
Total microparticles (U/mL)	3206 (2321–5265)	2750 (1857–3820)	0.11*	2150 (1512–2799)	2987 (2777–4158)	0.06*
Monocyte-derived microparticles (U/uL)	182 (82 – 719)	256 (55 – 676)	0.90*	195 (81–280)	664 (228–1080)	0.03*‡
Platelets (×10^3/mm3)	252 ± 91	234 ± 83	0.37	269 ± 36	279 ± 46	0.52
P-selectin (ng/dL)	35 ± 17	42 ± 25	0.16	40 ± 20	36 ± 12	0.48
Platelet-derived microparticles (U/uL)	268 (67–579)	453 (111–820)	0.11*	298 (179 – 404)	405 (225–936)	0.27*

	SLE Patients (N = 77)			Healthy Controls (N = 26)		
Parameter	**LEx (N = 32)**	**No LEx (N = 45)**	**P value**	**LEx (N = 12)**	**No LEx (N = 14)**	**P value**
Endothelium-derived microparticles (U/uL)	43 (20–63)	86 (20–162)	0.15*	61 (31–93)	152 (55–319)	0.09*
Peak thrombin generation (nmol/L)	336 ± 165	306 ± 165	0.47	382 ± 132	481 ± 107	0.05*‡
Thrombin-antithrombin complexes (ng/mL)	4.6 (3.1–8.8)	2.7 (1.6–5.1)	0.02*†	3.0 (2.5–4.0)	2.8 (2.6–6.2)	0.51*
D-dimer (mg/dL)	0.4 (0.5–0.9)	0.40 (0.1–0.6)	0.41*	0.11 (0.1–0.3)	0.35 (0.1–0.5)	0.04*‡
Tissue plasminogen antigen (ng/mL)	10.1 ± 4.2	9.8 ± 6.3	0.79	9.6 ± 4.2	6.4 ± 3.6	0.06
Plasminogen activator inhibitor-1 (U/mL)	4.3 (2.2–8.9)	5.4 (2.0–10.3)	0.56*	8.5 (3.9–14.9)	3.5 (1.7–11.3)	0.24*

Values are n (%), mean ± SD, or median (interquartile range).

*By Wilcoxon Rank Sum test.

†p value non-significant after Bonferoni's correction.

‡p value non-significant after Bonferoni's correction and association occurred in the opposite direction.

Abbreviations: HTN = hypertension, HDL = high density lipoproteins, LDL = low density lipoproteins Other abbreviations as in previous Tables.

Table 4

Clinical, Laboratory, and Therapy Data in SLE Patients with and without Lambl's Excrescences

Variable	Excrescences (N = 32)	No Excrescences (N = 45)	P Value
Disease Duration, Activity, and Damage			
Duration of SLE (years)	7.3 ± 6.9	8.3 ± 6.6	0.55
Age of onset of SLE	28 ± 12	29 ± 13	0.80
Total SLE-Disease Activity Index (SLEDAI) (U)	14 ± 13	11 ± 8	0.33
Non-Neurologic SLEDAI (U)	9.2 ± 7.2	7.0 ± 4.8	0.15
Neurologic SLEDAI (U)	0 (0 – 8)	0 (0 – 8)	0.99*
Total SLE Damage Index (U)	2.9 ± 1.6	3.2 ± 2.6	0.51
Non-Neurologic SLE Damage Index (U)	2.4 ± 1.5	2.4 ± 1.8	0.95
Neurologic SLE Damage index (U)	0 (0 – 1)	0 (0 – 1)	0.66
Parameters of Inflammation			
C-reactive protein (mg/dl)	0.6 (0.4 – 1.3)	0.6 (0.5 – 0.9)	0.90*
Erythrocyte sedimentation rate (mm/hr)	33 ± 23	26 ± 25	0.23
C3 (mg/dl)	91 ± 40	99 ± 32	0.35
C4 (mg/dl)	14 (7 – 21)	16 (11 – 23)	0.15
CH50 (mg/dl)	71 ± 44	82 ± 38	0.23
Standard Autoantibodies			
dsDNA positive	17/31 (55%)	21/43 (49%)	0.64
dsDNA titer	15 (0 – 122)	10 (0 – 45)	0.35
Ribonucleoprotein titer	0 (0 – 1)	0 (0 – 1)	0.06*
Smith antibody positive	18/31 (58%)	12 (27%)	0.01†
SSA antibody positive	14/31 (45%)	17 (38%)	0.64
SSB antibody positive	9/31 (29%)	6 (15%)	0.14
Antiphospholipid Antibodies			
Any antiphospholipid antibody positive	14/31 (45%)	31 (69%)	0.06
Beta-2 glycoprotein I antibody positive	2/29 (7%)	16/43 (37%)	0.005‡
Lupus-like inhibitor positive	7/31 (23%)	18 (40%)	0.14
IgG, IgM, or IgA anticardiolipin positive	10/31 (32%)	23 (51%)	0.16
IgM anticardiolipin antibody (IU)	4.6 (1.8 – 12)	8.8 (2 – 21)	0.19*
IgG anticardiolipin antibody (IU)	6.1 (2.2 – 12)	8 (3 – 25)	0.19*
IgA anticardiolipin antibody (IU)	2.9 (0.8 – 5.5)	2.9 (1 – 9)	0.49*
Anti-inflammatory and Anti-thrombotic Therapy			
Prednisone therapy	17/31 (55%)	14 (31%)	0.06
Average prednisone (mg/day)	8.0 ± 7.7	6.0 ± 5.3	0.21
Prednisone current dose (mg/d)	5 (0 – 10)	0 (0 – 10)	0.07*

Variable	Excrescences (N = 32)	No Excrescences (N = 45)	P Value
Years of prednisone	4 (1 – 9)	6 (1 – 10)	0.46*
Cyclophosphamide therapy	11/31 (35%)	16 (36%)	1.00
Years of cyclophosphamide	0 (0 – 1)	0 (0 – 1)	0.55*
Mycophenalate, methotrexate, or rituximab	6/31 (19%)	15 (33%)	0.20
Hydroxycloroquine or cloroquine therapy	24/31 (77%)	27 (60%)	0.14
Aspirin, warfarin, or either	12/31 (39%)	20 (44%)	0.64

Values are n (%), mean ± SD, or median (interquartile range).

*By Wilcoxon Rank Sum test.

†p value non-significant after Bonferoni's correction.

‡Association occurred in the opposite direction.

Abbreviations: SLE = systemic lupus erythematosus, DNA = double stranded nuclear antibody, ANA = antinuclear antibody, SSA = Ro antibody, SSB = La antibody, U = units, IU = international units.