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LAMBL'S EXCRESCENCES AS RISK FACTOR OF CARDIOVASCULAR DISORDERS PARTICULARLY ISCHEMIA WITH NON-OBSTRUCTIVE CORONARY ARTERIES

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The purpose of the study was to observe the patients with Lambl's excrescences and to reveal the principal complaints and primary cardiovascular diagnosis in this cohort. We paid special attention to possible pathogenetic links of ischemia with non-obstructive coronary arteries which were provoked by Lambl's excrescences with intracardial thrombi and phenomena of hyperechogenicity in the current group. All patients with registered echocardiography Lambl's excrescences underwent anamnesis taking, physical examination, and 24-hours Holter monitoring. As substantiation of our survey one case of Lambl's excrescences with intracardial microthrombi in a young female patient with ischemia with non-obstructive coronary arteries was elucidated in current manuscript. It was highlighted the importance of microrheological changes as a paramount link in patients with cardiovascular disorders. Mindful pathogenetic-oriented treatment was discussed for optimization of the patients' management. The article arises the awareness of the scientific community regarding Lambl's excrescences as risk factor of quite common cardiovascular disorders.

Key words: Lambl's excrescences, cardiovascular disorders, cardiac microthrombosis, ischemia with non-obstructive coronary arteries, spontaneous echocardiographic contrast, blood viscosity.

В.Г. Лизогуб, О.В. Савченко, Ю.В. Тиравська, Т. Надім, В.О. Соболев, В.Н. Крамарова НИТКИ ЛАМБЛА ЯК ФАКТОР РИЗИКУ СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАНЬ, ЗОКРЕМА ІШЕМІЇ, БЕЗ ОБСТРУКЦІЇ КОРОНАРНИХ АРТЕРІЙ

Метою роботи було обстежити пацієнтів з нитками Ламбла та виявити основні скарги та серцево-судинні захворювання, що реєструвалися у даній групі. Особливу увагу звернено на можливі патогенетичні механізми при ішемії без обструкції коронарних артерій, що була спровокована нитками Ламбла з внутрішньокардіальними мікротромбами та феноменом локальних гіперехогенних змін у даній групі. Всім пацієнтам окрім ехокардіографії проводився збір анамнезу, фізикальне обстеження, 24-годинне Холтеровське моніторування. Як приклад, наведений випадок ниток Ламбла з внутрішньокардіальним мікротромбозом у пацієнтки молодого віку з ішемією без обструкції коронарних артерій. Підкреслено необхідність вивчення мікрореологічних змін, як важливої патогенетичної ланки серцево-судинних захворювань. Запропоновано патогенетично обґрунтоване лікування пацієнтів з даною патологією. Стаття націлена звернути увагу наукової спільноти на нитки Ламбла, як фактор ризику кардіоваскулярних захворювань.

Ключові слова: нитки Ламбла, серцево-судинні захворювання, ішемія без обструкції коронарних артерій, кардіальний мікротромбоз, ефект спонтанного контрастування, в'язкість крові

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Lambl's excrescences (LE) on the cardiac valves during echocardiography have been reported to be registered by scientists for the last 15 years. The mechanism of their occurrence is still unknown. Presumably, these may be filaments of collagen and fibrin [3]. These structures may result from damage to the valvular endothelium and lead to local disorders of blood rheology [1, 5, 9]. Consequently, in individual cases observed structures are associated even with acute myocardial infarction or stroke due to its embolization [3]. However, there is no profound list of cardiovascular disorders LE are connected with.

Approximately 70 % of patients with angina pectoris (AP), particularly 30 % of elderly patients have either hemodynamically insignificant atherosclerotic plaque in the coronary artery (CA) or absolutely no plaques are registered. This type of AP is defined as INOCA – ischemia and no obstructed CA. The number of patients with intact CA at a young age is significantly higher in comparison with older ones and is characterized by a female preponderance [6]. Cardiac microvascular dysfunction (CMD) plays a crucial role in INOCA occurrence [11]. Management of patients with INOCA due to various mechanisms is still questionable.

Local disorders of blood rheology cause intracardiac thrombosis with micro-embolization of the coronary microvasculature and the clinic of microvascular AP [11, 13]. Notably, in scientific literature, few cases of CA microembolization in patients with LE have been elucidated [3].

The purpose of the study was to assess the cohort of patients with Lambl's excrescences regarding cardiovascular disorders, particularly ischemia and no obstructed coronary artery.

Materials and methods. For the period of 2018–2023, we have registered LE in 42 outpatients, and we have further analyzed medical histories. The points under question were baseline characteristics of the patients (age, sex, body mass index), anamnesis (smoking history, SARS-CoV-2 history (from 2021), family history of LE), chief complaints while clinic visit, hemodynamic characteristics (systolic and diastolic blood pressure (BP), heart rate (HR)), features on electrocardiograms (ECGs) with rhythmogram, 24-hours Holter monitoring (HM), echocardiography (EchoCG), test with hyperventilation, established diagnosis. The hand-written informed consent of the patient was obtained after a detailed explanation of the purpose of the investigations.

Questioning and physical examination of the patients were provided according to established routinely used algorithms. The BP of the patients was measured three times using a standardized electronic measuring instrument during patient visits.

Two-dimensional transthoracic EchoCG (2D-TTE) was conducted by one expert sonologist using the ultrasound unit of the expert class (Toshiba Artida, SSH-880CV). The frequency range of the transducer was 1–5 MHz. 2D-TTE scanning guidelines by Mitchell C. et al. were used. The apical four chamber and two chamber views, parasternal short and long axis, thoracic aorta, upper abdominal aorta, and inferior vena cava were visualized. Also, wall motions were assessed. Valves were evaluated with color Doppler imaging.

12-lead surface ECG at rest were recorded. In addition, 24-hours HM was performed. For this purpose, the HM system “Diacard” 2.1 manufactured by “SOLVAIG” (Kyiv, Ukraine) was used. According to HM ECG data, the following indicators were determined: the average HR, the average and total duration of episodes of ST-segment depression or elevation, pathological T-wave inversion, arrhythmias (supraventricular extrasystoles single, paired, group, ventricular extrasystoles single, paired, group), episodes of atrial fibrillation, supraventricular tachycardia, pauses. ST-segment elevation was defined as a J-point elevation of ≥ 2 mm in precordial leads and ≥ 1 mm in limb leads. ST-segment depression was defined as a J-point decline of ≥ 1.5 mm in precordial leads and ≥ 1 mm in limb leads.

Data were analyzed using SPSS (version 22.0, IBM Corp, USA). The distribution was checked using the Shapiro-Wilk test. Data were expressed as absolute numbers (percentage) for nominal variables and median (IQR) for continuous variables based on distribution type. We used Chi²-test to compare categorical variables. The difference at $p < 0.05$ was considered statistically significant.

Results of the study and their discussion. The characteristics of the patients with LE are aggregated in Table 1.

Table 1

Characteristics of the observed patients with LE

Parameter	Observed group, n=42
Age, years	26.4 (19.8–34.5)
Females, n./total (%)	25/42 (59)
Body mass index, kg/m ²	24.3 (18.2–26.2)
Smoking history, n./total (%)	11/42 (26)
Family history of LE, n./total (%)	0
SARS-CoV-2 history, n./total	17/24 (71)
Systolic BP, mmHg	129.4 (99.7–140.3)
Diastolic BP, mmHg	74.2 (59.1–92.8)
HR, beats/min.	79.5 (68.1–95.2)
Purpose of the patient's visit / chief complaint	
Check-up, n./total (%)	4 (10)
Syncope, n./total (%)	6 (14)
Dizziness, n./total (%)	24 (57)
Stabbing chest pain, n./total (%)	27 (64)
Dull chest pain, n./total (%)	11 (26)
Headache, n./total (%)	29 (69)
Palpitation, n./total (%)	19 (45)
Easy fatigability, n./total (%)	31 (74)
Shortness of breath, n./total (%)	35 (83)

In the observed population we did not notice statistically significant predominance of LE in certain gender ($p>0.05$). Regarding SARS-CoV-2, before the SARS-CoV-2 pandemic onset we observed 18 patients (42 %). Thus, a statistically significant difference in cases of LE in the period before and after pandemic onset was registered ($\chi^2<0.05$).

Analysis of the results of HM ECG showed that it was registered episodes of displacement of the ST segment of the ischemic type in 2 patients out of 42 (5 %), and T-wave inversion was noticed in 19 out of 42 patients (45 %). Regarding arrhythmias, no group supraventricular extrasystole, pathologic quantity of single ventricular extrasystoles, no paired as well as group ventricular extrasystoles, no episodes of atrial fibrillation, supraventricular tachycardia, pauses were registered. Positive test with hyperventilation was registered in 38 out of 42 patients (91 %).

The established diagnoses in observed group were neurocirculatory dystonia with hypertensive syndrome (6 out of 42 patients (14 %), hypotensive syndrome (5 out of 42 patients (12 %), cardiac syndrome (10 out of 42 patients (24 %), mixed type (19 out of 42 patients (45 %), INOCA (2 out of 42 patients (5 %).

Below-described case of young female patient demonstrates possible cardiovascular comorbidity in patients with LE, particularly INOCA with microthrombosis intracardially.

Patient information. Female patient I., 28 years old, visited a cardiologist on an outpatient basis with complaints of recurrent episodes of stabbing pain in the heart region without a clear connection with physical activity without irradiation.

History of present illness. For the first-time paroxysmal pain with pressure in the heart region and behind the sternum, accompanied by shortness of breath, occurred 1 month before visiting the doctor. The attack was coped on its own, but since that time periodic stabbing pain has begun to disturb the patient. The first attack was associated with stress – death of the patient's father.

Personal history. The patient had no history of any therapeutical disorders (including autoimmune diseases), surgeries, traumas, no harmful habits. Nothing remarkable in obstetric history was: no pregnancies, no history of miscarriage or spontaneous abortion. No allergic reactions were registered. The patient did not take any medications, including oral contraceptives. She was vaccinated against coronavirus twice (mRNA vaccine) 2 months prior to current episode of disorder manifestation.



Fig. 1. ECG of the patient.

Family history. The father's cause of death was pulmonary embolism. It has been known that for many years he was observed by a surgeon for chronic thrombophlebitis of the lower extremities. 6 months before his death, the diagnosis of permanent form of atrial fibrillation was established. One month later, he had a stroke for which he was hospitalized and was discharged in a relatively satisfactory condition. 3 weeks before the date of death, he was vaccinated with 1 dose of the vaccine against coronavirus (mRNA vaccine).

Clinical findings. General condition of the patient was normal. She was normostenik, body mass index – 23.2 kg/m². The skin and visible mucous membranes were clean. BP – 120/80 mm Hg, pulse 80 bpm, rhythmic. While physical examination no pathological changes were noticed in the internal organs.

Diagnostic assessment.

On the ECG (Fig. 1), sinus regular rhythm, negative T wave in lead III, and no other peculiarities were registered.

The patient underwent 2D-TTE (Toshiba Artida, SSH-880CV). The heart volumes, wall thickness and ejection fraction (EF=65 %) were normal. However, an additional floating thread-like structure in aorta was noticed. We suspected it was LE which were attached to the non-coronarogenic aortic cusp. In the lumen of the aorta in the region of the right coronary cusp and the outflow tract of the left ventricle, we noticed the local areas of spontaneous echocardiographic contrast (local

hemorheological changes). At the same time, larger areas of spontaneous echocardiographic contrast were registered in the region of the left atrium. Besides, a more echogenic and formed microthrombus on a thread (presumably fibrin) was attached to the anterior leaflet of the mitral valve. Though this microthrombus was localized in the left atrium, it passed through the mitral valve into the left ventricle and then returned to the left atrium (Fig.2).

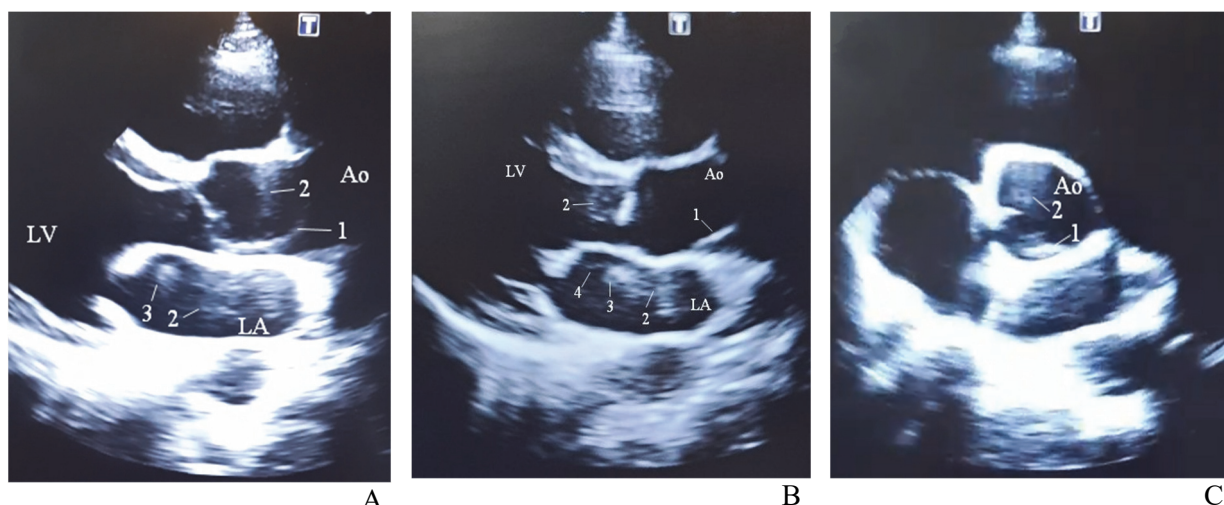


Fig. 2. EchoCG of the patient: A, B – Parasternal long axis view; C – Apical short axis view; 1 – Lambl's excrescences; 2 – phenomena of spontaneous echocardiographic contrast; 3 – microthrombus; 4 – thread of thrombus; LV – left ventricle, LA – left atrium, Ao – aorta.

Results of laboratory assessments have been aggregated in Table 2.

Table 2

Laboratory tests of the patient

Parameter	Result	Reference range
Leukocytes, $\times 10^9/L$	4.86	3.5–10.6
Erythrocytes, $\times 10^{12}/L$	4.52	4.0–5.2
Hemoglobin, g/L	135	110–160
Hematocrit, %	42.8	35.0–47.0
Mean corpuscular volume, fL	94.7	75–98
Mean corpuscular hemoglobin, pg	29.9	27–34
Platelets, $\times 10^9/L$	216	150–390
Mean platelets volume, fL	11.1*	6.5–11
Thrombocrit, %	0.24	0.1–0.4
Erythrocyte sedimentation rate, mm/h	6	<15
Prothrombin time, s	11.6	9.8–12.5
Prothrombin index, %	88.4	70–130
International normalization ratio	1.10	
Activated partially thromboplastin time, s	30.2	22–32
D-fibrinogen, g/L	3.09	2–4
Thrombin time, s	19.6	14–21
Closure time		
Epinephrine/ Collagen, s	152	84–160
Adenosine diphosphate / Collagen, s	88	68–121
Cholesterol, mmol/l	4.86	<5.2
Triglycerides, mmol/l	0.48	<2.26
High-density lipoproteins, mmol/l	2.4	>1.68 – no risk
Low-density lipoproteins, mmol/l	2.67*	<2.59 – optimal level
Very low-density lipoproteins, mmol/l	0.22*	0.26–1.00
Serum glucose, mmol/l	4.81	4.11–5.89

Notes: * – out of reference ranges.

Diagnostic challenges. The patient had to go abroad a few days after the visit. Consequently, access to further profound investigational procedures was limited.

Diagnosis. We suspected AP was caused by INOCA.

Therapeutic intervention. It was prescribed clopidogrel bisulfate 75 mg orally once a day and trimetazidine hydrochloride 35 mg MR twice a day.

Follow-up and outcomes. In 6 months, though the patient had no possibility to visit the clinic to pass over the investigations, via cell phone call, she mentioned improvement in her condition (no pain in the heart area, dyspnea or other unpleasant feelings) and well-tolerated physical activity as well as emotional stresses.

From our point of view, regarding pathogenetic mechanisms in the presented case of atypical chest pain in a young female with LE, we should pay attention to the possible reasons for microthrombosis according to the Virchow triad, namely slow blood flow and its turbulence, violation of the vessel wall's integrity (damage to the endothelium) and violation of the rheological properties [1].

The endothelium also lines the endocardium and the heart valves. The coronavirus has a tropism for endothelial damage and microthrombosis. Thus, according to autopsies of patients who died from coronavirus infection, the basement membrane remained bare for a long distance, only individual cells retained their normal appearance [8].

As microthrombus is attached to the anterior leaflet of the mitral valve we suspect the damage of the valvular endothelium which can be among mechanisms of LE formation in current patient. Anyway, these findings highlight the increased risk of major adverse cardiovascular events in the patient [3]. Further investigations are warranted to elucidate the association of these accessory structures on cardiac valves with immune-inflammatory processes in COVID-19.

In terms of erythrocytes sludge, that was manifested as local areas of phenomenon of spontaneous echo contrast [5] in the aorta (the right and left CAs anatomically branch out from the aorta), as well as in the left atrium, it led to the formation of a mobile microthrombus. The phenomenon of local disorders in the blood rheological properties may be suspected. Erythrocyte's aggregation coincides with an increase in blood viscosity leading to stasis [1]. The tissue or organ that is supplied with blood by these microvessels remains ischemic with all the ensuing consequences (hypoxia, acidosis, accumulation of metabolites, low-grade inflammation) [4, 9, 10, 11]. In the presented clinical episode, this is the microvasculature in the pool of the right CA.

The slowdown in regional blood flow as a result of blood circulation centralization during stress is another factor causes widespread erythrocytes aggregation and sludge [1]. In the discussed particular clinical case, the patient had pain in the region of the heart after stress.

In complete blood count it was registered slightly increased mean platelets volume which is another marker of higher risk of cardiovascular events in patients as a sign of platelets activation triggered by endothelium dysfunction [12].

In the latest guides about INOCA management evidence-based data regarding treatment peculiarities for women are still absent [6]. However, according to small sample-sized, short-term pilot studies of symptomatic women with INOCA, it is considered that statins in combination with angiotensin-converting enzyme inhibitor or receptor blockers improve angina, stress testing, myocardial perfusion, coronary endothelial function, and microvascular function [2].

The management of patients with enhanced blood viscosity is even less understandable. The principles for normalization of blood rheological properties should be based on [7]:

1. Normalization of hemodynamics (restoration of blood flow velocity);
2. Controlled hemodilution (blood thinning and viscosity reduction);
3. Antiplatelet agents and anticoagulants (prevention of thrombosis);
4. The usage of drugs that reduce the rigidity of erythrocyte membranes;
5. Normalization of the acid-base state of the blood;
6. Normalization of the protein composition of the blood (albumin solutions).

For the purpose of hemodilution and disaggregation of cells, hemodez and low molecular weight dextrans are used, which increase the electrostatic forces between blood cells due to an increase in the negative charge on their surface, lower blood viscosity by attracting water into the vessels, cover the endothelium and vessels with a separating membrane, form complex compounds with fibrinogen, reduce the lipids concentration [7].

Conclusions

1. LE is an underinvestigated pathology in the heart, which may be either an accidental finding in patients or even be associated with thromboembolism in cerebral arteries and CAs.
2. In young patients, cardialgia may be caused by either microvascular ischemia due to local disturbance of blood rheology with the formation of intracardiac thrombi or vasospasm caused by mental stress.
3. Physicians should take into account INOCA as one of the possible differential diagnoses in young females with chest pain and cardiovascular risk factors including LE.

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