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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПАЦИЕНТА С ОСТРЫМ ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ ТРИКУСПИДАЛЬНОГО КЛАПАНА И МУЛЬТИПЛЕКСНЫМ ПОДХОДОМ К ОЦЕНКЕ РИСКА ОСЛОЖНЕНИЙ

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Clinical Case of a Patient with Acute Tricuspid Valve Infective Endocarditis and A Multiplex Approach to Evaluation of The Complication Risk

Резюме

Инфекционный эндокардит (ИЭ) отличается трудностью диагностики, лечения и оценки риска неблагоприятного прогноза. На сегодняшний день отсутствуют одобренные для применения шкалы и калькуляторы риска осложнений и летального исхода, помогающие практикующему врачу принимать решения, особенно у пациентов с изолированным правосторонним ИЭ. Для правостороннего ИЭ сроки выполнения успешного хирургического лечения остаются неопределенными. Ранее разработанные калькуляторы риска (итальянский калькулятор Rizzi и французский Hubert) плохо валидированы на широкой популяции пациентов с ИЭ, в особенности для правостороннего ИЭ. Одним из обязательных параметров калькуляторов является определение этиологической принадлежности. Однако при отрицательных результатах микробиологических исследований, достигающих 56-83 %, данный параметр становится неинформативным. Более того существующие инструменты оценки риска не учитывают активность заболевания (в том числе лабораторную), которая интуитивно для каждого врача яв-

ляется важным ориентиром в принятии решений. На данный момент есть большая потребность во внедрении молекулярно-биологических методов для улучшения качества этиологической диагностики и в углубленном изучении возможных биомаркеров от простых (нейтрофильно/лимфоцитарный, тромбоцитарно/лимфоцитарный и системный иммуно-воспалительный индексы) до более сложных (нейтрофильные внеклеточные ловушки, цитокиновый профиль).

Представлено клиническое наблюдение молодого пациента с острым ИЭ трикуспидального клапана с гигантской вегетацией (28 мм), осложненным тяжелой клапанной недостаточностью без признаков сердечной недостаточности, с рецидивирующим эмболическим синдромом в систему легочной артерии с формированием легочной гипертензии, определяющих показания для кардиохирургического лечения. Этиологическая принадлежность ИЭ к *Staphylococcus aureus* установлена только при ПЦР-исследовании. Неотложные сроки вмешательства определены на основании повышения новых маркеров — нейтрофильно/лимфоцитальный индекс ≥20,0, системный иммуновоспалительный индекс ≥2314,0 и нейтрофильные внеклеточные ловушки ≥14,2, свидетельствующих о крайне высоком риске летального исхода. Фундаментальное патогистологическое исследование тканевого материала выявило малое содержание неповрежденных провоспалительных макрофагов CD86+, вероятно связанное с их избыточным разрушением и бесконтрольным выходом обильного количества провоспалительных цитокинов, приведших к быстрому и тяжелому поражению трикуспидального клапана. Таким образом современное ведение пациентов с ИЭ должно быть мультиплексным с применением актуальных методов этиологической и визуализирующей диагностики, и направленным на раннее выявление пациентов неблагоприятного риска для своевременного дифференцированного подхода к консервативной или кардиохирургической тактике лечения.

Ключевые слова: *инфекционный эндокардит, прогноз, трикуспидальный клапан, нейтрофильно-лимфоцитарный индекс, нейтрофильные внеклеточные ловушки, ПЦР*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

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Abstract

Infective endocarditis (IE) is characterized by the difficulty of diagnosis, treatment and risk assessment of an unfavorable prognosis. Currently there are no approved scales and calculators for the risk of complications and death that help the practitioner make decisions, especially in patients with isolated right-sided IE. For right-sided IE, the timing of successful surgical treatment remains uncertain. Previously developed risk calculators (Italian Rizzi calculator and French Hubert) are poorly validated in a wide population of patients with IE, especially for right-sided IE. One of the required parameters of calculators is the determination of etiological affiliation. However, with negative results of microbiological studies reaching 56-83 %, this parameter becomes uninformative. Moreover, existing risk assessment tools do not take into account the activity of the disease (including laboratory activity), which intuitively is an important guideline for every doctor in decision-making. At the moment, there is a great need for the introduction of molecular biological methods to improve the quality of etiological diagnosis and in-depth study of possible biomarkers from simple (neutrophil/lymphocytic, platelet/lymphocytic and systemic immuno-inflammatory index) to more complex (neutrophil extracellular traps, cytokine profile).

We present a clinical case of a young patient with acute tricuspid valve IE with giant vegetation (28 mm), complicated by severe valvular insufficiency without signs of heart failure, recurrent embolic syndrome in the pulmonary artery system with the formation of pulmonary hypertension, determining indications for cardiac surgical treatment. The etiological affiliation of IE to *Staphylococcus aureus* was established only by PCR. The urgent timing of intervention was determined based on an increase in new markers — neutrophil/lymphocytic index ≥20.0, systemic immuno-inflammatory index ≥2314.0 and neutrophil extracellular traps ≥14.2, indicating an extremely high risk of death. A fundamental pathohistological study of the tissue material revealed a low content of intact CD86+ proinflammatory macrophages, probably associated with their excessive destruction and uncontrolled release of copious amounts of proinflammatory cytokines, which led to rapid and severe damage to the tricuspid valve. Thus, modern management of patients with IE should be multiplex using current methods of etiological and imaging diagnostics, and aimed at early detection of patients at adverse risk for a timely differentiated approach to conservative or cardiac surgical treatment tactics.

Key words: *infective endocarditis, prognosis, tricuspid valve, neutrophil-lymphocyte index, neutrophil extracellular traps, PCR*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The study was carried out in accordance with the standards of Good Clinical Practice, the principles of the Declaration of Helsinki, and approved by the local ethics committee of the Medical Institute of the Patrice Lumumba Peoples' Friendship University of Russia (protocol No. 27 dated 03/18/2021). All patients signed informed consent for the collection of anonymized medical data.

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IE — infective endocarditis, CD — Cluster of Differentiation, PCR — polymerase chain reaction, TV — tricuspid valve, NLI — neutrophilic/lymphocytic index, TLI — thrombocytic/lymphocytic index, SIMI — system immune-mediated index, BMI — body mass index, RR — respiratory rate, BP — blood pressure, HR — heart rate, CT — computer tomography, AKI — acute kidney injury, CRP – C-reactive protein, CKD-EPI GFR — CKD-EPI glomerular filtration rate, EF — left ventricular ejection fraction, PASYS — pulmonary artery systolic pressure, DNA – deoxyribonucleic acid, *MRSA — methicillin resistant Staphylococcus aureus,* NET – neutrophil extracellular trap, COVID-19 — coronavirus infection 2019

Introduction

Infective endocarditis (IE) is known for its negative trends, associated with higher incidence rates, also due to primary IE, and number of hospitalisations with aggravated clinical forms, making diagnosis and therapy challenging and resulting in negative prognosis [1-5]. The versatile aetiological array of IE is characterised by dangerous trends in higher incidence rates of staphylococcal and enterococcal IE [1-5]. Isolated right-sided IE is rare in individuals, who do not take intravenous psychoactive substances and do not have intracardiac implants; and it obstructs identification of the entry of infection [1, 2, 6]. Microbiological IE pathogen identification is often challenging because of the method limitations and early antibacterial initiation, which affect the reduction in blood pathogen concentrations, especially in right-sided IE [1, 2, 7]. All the above affects timely initiation of etiotropic antibacterial therapy. Therefore, there is much discussion of modifications of the standard algorithm for aetiological diagnosis of IE and introduction of additional methods, such as immunochemistry and biomolecular methods; the latter offering ample opportunities.

Early evaluation of the prognosis and identification of the groups of the highest risk of unfavourable outcomes, primarily embolism and hospital mortality, are not optimal. Despite a series of studies to identify significant predictors of unfavourable outcomes and development of risk calculators, e.g. Rizzi (Italy) and Hubert (France), they are not widely used and are just mentioned in recommendations, without any mandatory use in routine activities [1, 2, 8, 9]. Moreover, a majority of studies included patients with left-sided IE, while right-sided IE is mentioned just in individual local studies [8, 10]. This issue is mentioned in national and European guidelines, where for left-sided IE, indications for surgery and optimal intervention window are specified, depending on the risk of unfavourable outcomes; whereas right-sided IE has only indications stated, without any clear timing for surgery [1, 2]. In general, it is worth mentioning that evaluation of the risk of complications takes into account demographics, presence of complications, aetiology, and echocardiography parameters. The high rates of negative microbiology results offset the significance of the aetiological parameter; besides, disease activity (also laboratory) is often disregarded, which is an important decision-making reference point. Therefore, besides imrpovement in the aetiological diagnosis quality, it is essential to study various biomarkers, both simple ones, which can be used at the point-of-care (neutrophilic/lymphocytic index, thrombocytic/lymphocytic index, and system immune-mediated index), and more sophisticated (neutrophil extracellular traps, cytokine profile), which will expand the capabilities for diagnosis evaluation and determination of the surgery window.

We present a clinical case study of a patient with no bad habits, who has damaged tricuspid valve (TV). The aetiological diagnosis in this patient was based on the use of additional biomolecular methods, while early evaluation of a high risk of unfavourable outcomes was possible due to identification of neutrophil extracellular traps and calculation of inflammation indices (neutrophilic/lymphocytic index (NLI), thrombocytic/lymphocytic index (TLI), system immune-mediated index (SIMI)). Also, unique histopathological changes, associated with the characteristics of tissue macrophages and contributing to the major involvement of the valve apparatus, were identified.

Clinical case study

Patient O, 36 years old, no bad habits and no history of cardiovascular diseases. The acute phase started rapidly with the body temperature of 40°C, dry dough, and chest pain. Outpatient therapy with cefixime 400 mg/day (6 days); no effect (Fig. 1). The patient was hospitalised with suspected pneumonia; TV IE was diagnosed, which was complicated by bilateral multisegmental pneumonia with destruction. With the therapy (vancomycin 2.0 g/day + gentamycine 240 mg/day, 6 days), the patient had persistent fever up to 39.0°C, large vegetations and recurring pulmonary artery embolism; the patient was moved to the cardiac surgery ward.

The patient was admitted to the cardiac surgery ward in moderately severe condition; body mass index (BMI): 24.7 kg/m^2; no oedema or rash; respiratory rate (RR): 22/min, harsh respiration, multiple sonorous wet small bubbling rales in projection of both lungs; blood pressure (BP): 110/70 mm Hg; heart rate (HR): 110 bpm, systolic murmur at the base of the ensisternum, hepatatosplenomegaly.

Initial blood count: WBC 21.8×10^9/L, NEU 20.2×10^9/L, LYM 0.59×10^9/L, RBC 4.33×10^{12}/L, Hb 126 g/L, platelets 157×10^9/L, **NLI 34.2,** TLI 266.1, **SIMI 5,361.9.** Repeated blood count: WBC 13.1×10^9/L, NEU 10.9×10^9/L, LYM 1.7×10^9/L, RBC 3.85×10^{12}/L, Hb 120 g/L, platelets 282×10^9/L, NLI 6.4, TLI 165.9, SIMI 1,808.1.

Blood biochemistry upon admission: creatinine 68.9 μmol/L, estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) 116 mL/min, urea 4.3 mmol/L, total bilirubin 57 g/L, C-reactive protein (CRP) 214.8 mg/mL. Seven days later: creatinine 307.4 μmol/L, $eGFR_{CKD-EPI}$ 21 mL/min (stage 3 acute kidney injury with over 3-fold increase in creatinine levels). Fourteen days later: creatinine 79.5 μmol/L, $eGFR_{CKD-EPI}$ 109 mL/min, CRP 4.8 mg/mL. Coagulation profile: unremarkable. Urinalysis: density 1015, microscopic haematuria (10–15 cells).

Chest CT (upon admission): bilateral polysegmental pneumonia, spreading; aggressive lesions and effusion in pleural cavities.

Transthoracic echocardiography (echoCG) (before surgery): left ventricular ejection fraction (EF) 65 %, vegetation on septal leaf of TV up to 2.8 cm with 3rd degree tricuspid regurgitation, pulmonary artery systolic pressure (PASYS) 33 mm Hg.

Transesophageal echocardiography (before surgery): EF 57 %; left heart is not dilated; right heart is dilated; vegetation on TV leaves up to 2.0 cm, 4th degree tricuspid regurgitation, PASYS 45 mm Hg.

On day 2 of hospitalisation to the cardiac surgery ward, the patient underwent TV replacement with biological prosthesis Biolab No. 33 (Fig. 1, 2).

The post-surgery period was uncomplicated; however, the antibacterial therapy needed replacement because of acute kidney injury (AKI) and allergic reaction: vancomycin 2.0 g/day (19 days, stage 3 AKI) → teicoplanin 400 mg/day (4 days, urticaria) → linezolid 1,200 mg/day (14 days).

Transthoracic echoCG (after surgery): EF 60 %, satisfactory bioprosthesis performance, PASYS 30 mm Hg.

Microbial examination of blood and valve tissue samples did not show any presence of the pathogen.

Blood and TV tissue PCR test showed DNA of *S. aureus MRSA* 5,4×106 copies/mL.

Pathohistological examination of resected TV tissues: purulent inflammation with a large blood clot (vegetation), focal fibrosis, macrophage accumulation (Fig. 2).

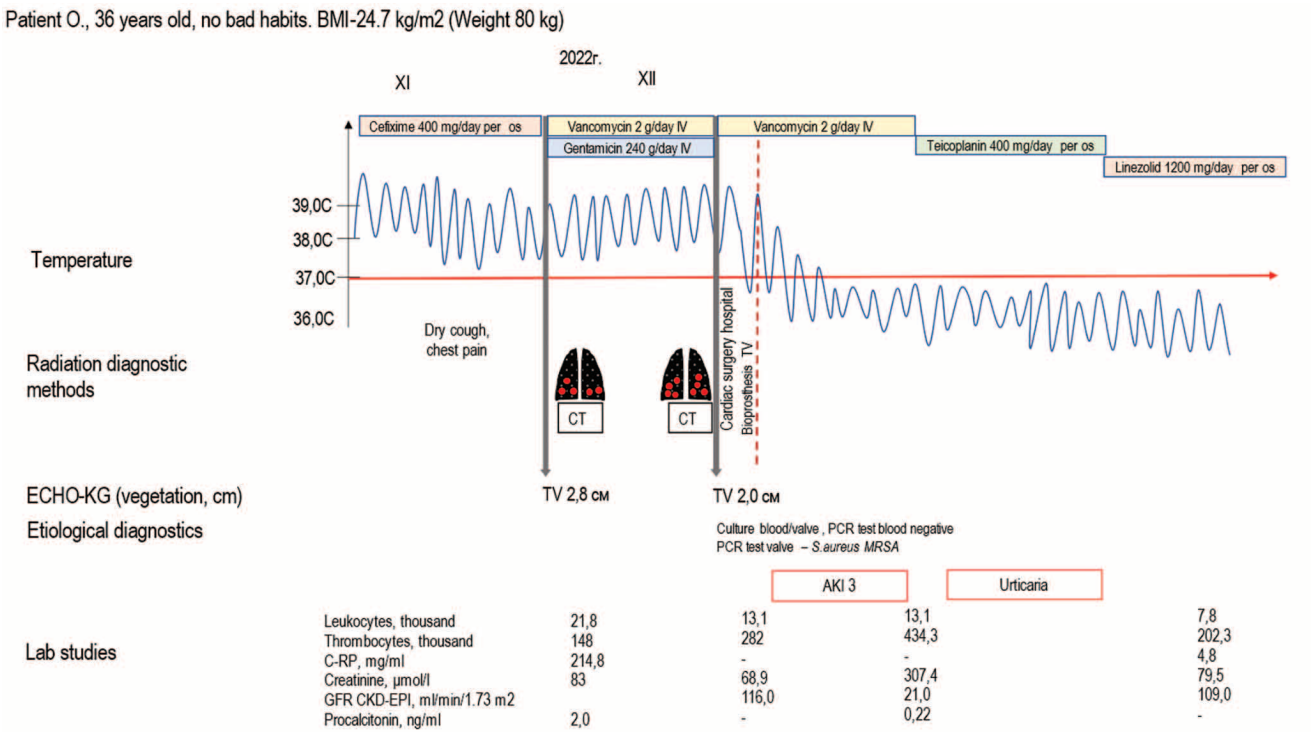

Figure 1. *Patient O. Case history diagram*

Notes: BMI — body mass index, CT — computed tomography, TV — tricuspid valve, PCR — polymerase chain reaction, AKI — acute kidney injury, C-RP — C-reactive protein, GFR CKD-EPI — glomerular filtration rate calculated using the CKD-EPI formula

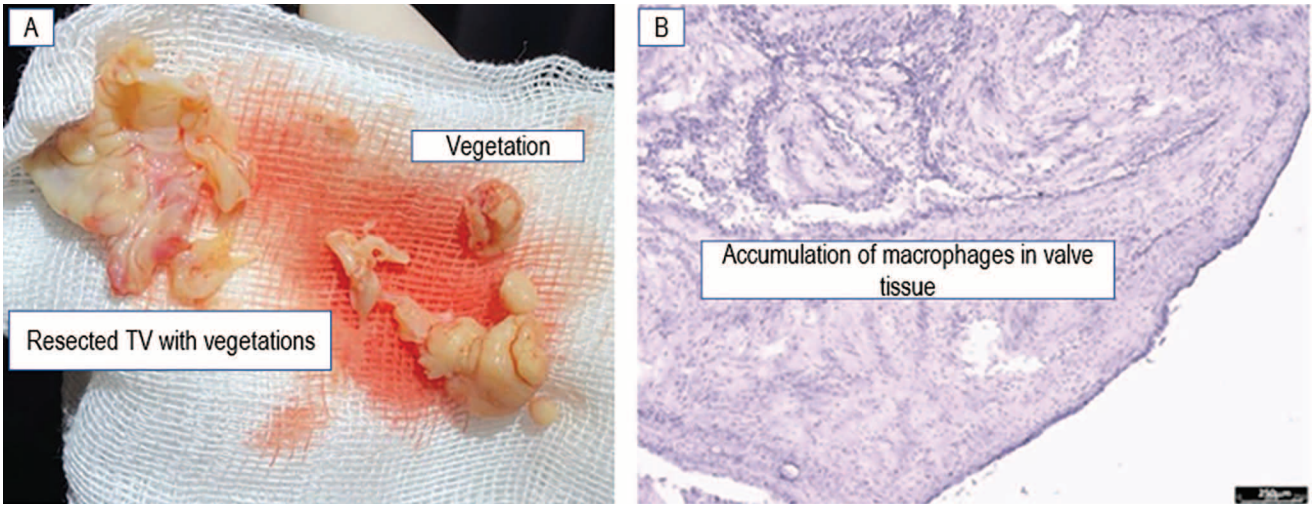

Figure 2. *Tricuspid valve (TV) tissue: A — Surgical material, B — Endocardial sections stained with hematoxylin. Scale bar 250 μm*

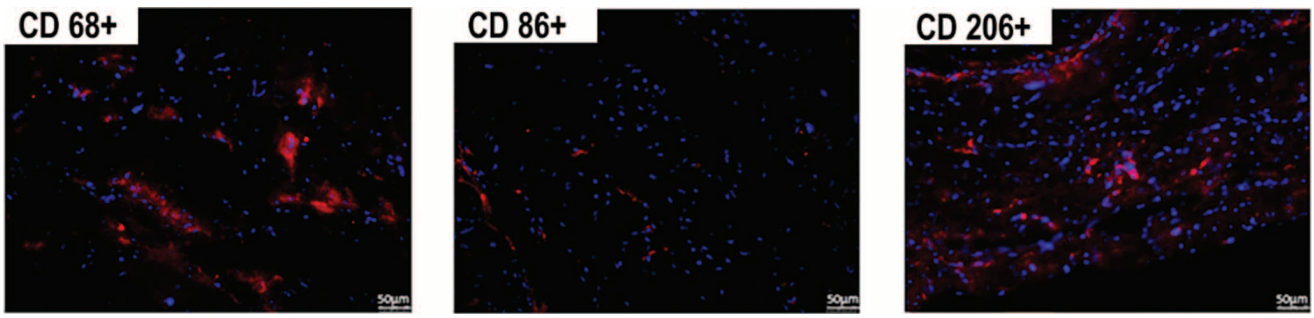

Figure 3. *Immunohistochemical staining of the endocardium of a patient with IE of the TV to detect CD 68+, CD 86+ and CD 206+ cells*

Note: Cluster of Differentiation (CD) 68+ (a common marker of macrophages), a small amount of CD 86+ (a marker of the pro-inflammatory phenotype of macrophages) and a large amount of CD 206+ (a marker of the anti-inflammatory phenotype of macrophages) cells are shown. Scale bar 50 μm. Red glow — expression of markers CD 68+, CD 86+, CD 206+. Blue glow — nuclei staining with DAPI (4',6-diamidino-2-phenylindole)

An immunohistochemical examination of resected valve tissue for the presence of whole macrophages showed CD 68+ (common macrophage marker), small amounts of CD 86+ (proinflammatory macrophage marker) and numerous CD 206+ cells (anti-inflammatory macrophage marker) (Fig. 3).

Also, upon patient admission we examined neutrophil extracellular trap (NET) levels using electron microscopy of monolayer blood smears, with eosin methylene blue and eosin azure blue staining [11]. NET levels (%) in smears (a share of transformed neutrophils in NET) were calculated as NET (%) = N_{NET} / ($N_{neutrophil}$ + $N_{eosinophil}$ + $N_{basophil}$ + N_{NET}), where N_{NET} is the number of neutrophil extracellular traps, $N_{neutrophil}$ is the number of native neutrophils, $N_{eosinophil}$ is the number of native eosinophils, $N_{basophil}$ is the number of native basophils [11]. Patient's NET upon admission was 14.7 %; seven days later, NET was 9.1 % (Fig. 4).

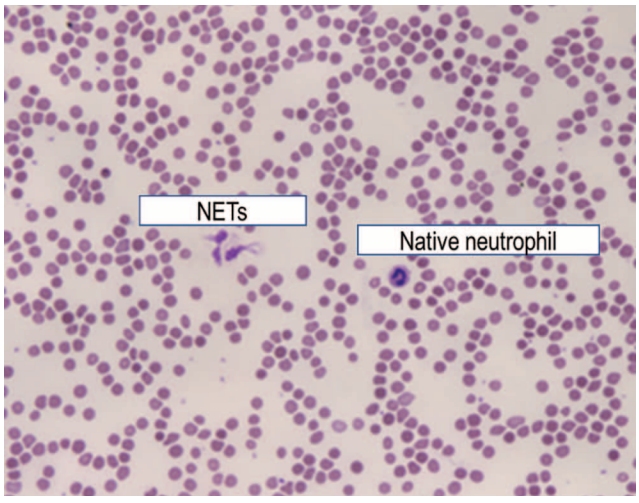

Figure 4. *A smear made as a monolayer to determine NETs in a patient with IE TV*

Note: NETs — neutrophil extracellular traps

Based on the medical record, clinical data, laboratory test and examination results, the following final clinical diagnosis was made for the patient on the first day of hospitalisation:

Diagnosis:

Primary: acute tricuspid valve IE, caused by *S. aureus MRSA*. Severe TV insufficiency. Pulmonary hypertension, degree 1. TV replacement with biological prosthesis Biolab No. 33.

Complications: bilateral polysegmental pneumonia. Bilateral dropsy of chest. Vancomycin-induced AKI, 3rd degree. Allergy reaction (urticaria fever) to teicoplanin.

The patient was discharged on day 35 in satisfactory condition Outpatient follow-up visits in 3 and 6 months: stable condition; normal body temperature; blood and urine test results: unremarkable; transthoracic echoCG: satisfactory prosthesis performance; no extra overlappings are seen.

Discussion

This clinical case study is interesting due to the development of complicated TV IE in a patient without predisposing factors, the key role in the aetiological diagnosis of which was played by PCR testing, allowing initiation of post-surgery etiotropic therapy. Despite obvious indications for heart surgery, the timing of the intervention was not clear, given the patient's haemodynamic stability. Assignment of the patient to the group of the high risk of short-term mortality was possible due to the measurement of blood neutrophil extracellular trap and inflammation indices (neutrophilic/lymphocytic index (NLI), thrombocytic/lymphocytic index (TLI), system immune-mediated index (SIMI)). Also, unique histopathological changes were found, which indicated elevated destruction of tissue macrophages and major damage to the valve apparatus.

IE remains a challenging condition for practitioners, both during diagnosis and selection of an adequate therapy, which is the cause of its unfavourable prognosis [1, 2, 12]. Very often this disease is confused with other pathologies, where false diagnoses are made, and IE diagnosis is delayed [1, 2, 13, 14]. In this clinical case study, first clinical manifestations were disguised as community-acquired pneumonia; however, its nature made it possible to assume an embolic site of infection and diagnose tricuspid valve IE at early stages. The period from first symptoms to IE verification is this patient did not exceed 14 days, meaning early diagnosis.

Native valve involvement in IE is very rare; it is recorded in 2 to 10 cases out of 100,000 person years [1, 2, 15]. Primary IE of the native tricuspid valve, not associated with intracardiac implants, congenital heart disorder or intravenous psychoactive substances, is very uncommon [1, 2]. We have presented a unique clinical case of a patient with IE of native unchanged TV without any predisposing factors. We were unable to identify the source of infection; however, given the disease aetiology, we suspect skin infections, which the patient is likely to have missed.

The aetiological nature of IE is traditionally a decisive factor in disease diagnosis, being both a major and manor Duke criterion, and also a factor for correct etiotropic therapy. Not only the fact of pathogen identification is of importance, but also its etiopathogenetic relation to active IE. The most challenging is high IE incidence with unknown aetiology, which accounts for 56–83 % and is associated not only with the features of bacteraemia, but also known for not only its low blood pathogen concentration (also as a result of early antibacterial therapy), but highly labour-intensive microbiological examination [1, 2, 7]. In this patient, microbiological examinations of blood and resected valve tissues yielded negative results at all stages of examination. We also conducted a PCR test of whole venous blood and resected valve tissue, which demonstrated DNA of methicillin-resistant *S. aureus*. We assume that this is the most probable pathogen, given the clinical manifestations and aggressive disease. Previous examinations and available own data also confirm the high diagnostic efficiency of molecular biological methods in aetiological diagnosis of IE, especially in making decisions whether to continue with antibacterials during the post-surgery period or not [16, 17].

Indications for surgery in right-sided IE are stricter than for the left heart and include the following requirements: right ventricular dysfunction caused by acute severe tricuspid regurgitation; diuretic resistance (class/level I/B); persistent vegetation with respiratory distress requiring artificial lung ventilation after recurrent embolism (I/B); **large residual vegetation on tricuspid valve (> 20 mm) after recurrent septic pulmonary embolism (I/C)**; patients with left heart involvement (I/C) [1, 2]. It is worth emphasising that the specific timing for heart surgery for right-sided IE is the same as for left-sided IE; it is not regulated and is at the doctor's discretion [1, 2]. In this case study, initial size of vegetations was 28 mm; vegetations were associated with embolism in the bed of the pulmonary artery. After the therapy, vegetations shrank to 20 mm, but recurrent embolism, fever and worsening tricuspid regurgitation persisted; they were correctly considered indications for heart surgery; however, the urgency remained unclear.

The pressing need for accurate and practically accessible markers of unfavourable prognosis is a result of high mortality rates in IE [1-6, 15, 18]. The most common

clinical and instrumental predictors of hospital mortality are: cardiac insufficiency, prosthetic cardiac valve, stroke, AKI, large vegetations, high Charlson Comorbidity Index, left heart involvement, *S. aureus*, therapy-induced embolism [1, 2, 19, 20]; and laboratory markers are: CRP, procalcitonin, total counts of WBC, neutrophils, NT pro-BNP, D-dimer [1, 2, 20, 21]. Overall, despite the seeming versatility of clinical, instrumental and laboratory markers, their predicative value is not optimal and is challenging for a medical practitioner. Moreover, the majority of these parameters were aimed at left-sided IE. It is generally worth concluding that to date there is no unique parameter. Of interest are user-friendly practical indices of inflammation — neutrophilic/lymphocytic index, thrombocytic/lymphocytic index and system immune-mediated index (platelets*neutrophilics/lymphocyts) [22, 23]. Bacterial infections, including sepsis and IE, are known to be associated with gradually increasing neutrophil and decreasing lymphocyte levels, and their ratio can be more accurate in indicating disease severity. Besides, clinically, there are often reduced platelet counts along with increased blood infection activity and the correlation between consumption thrombocytopenia and larger vegetations [24]. Therefore, the ratio of platelets and inflammation cells can also be informative (TLI, SIMI). A number of studies in patients with bacteraemia demonstrated that NLI is a more accurate marker of unfavourable outcome as compared to isolated WBC count [22, 23]. Hu W. et al. (2022) noted that with the threshold SIMI ≥ 1,960.9, there is 6.9-fold increase in the risk of embolic events [23], while Agus H.Z. et al. (2020) found out that with SIMI ≥ 2,314.0 (AUC 0.641, p=0.019) the risk of death increases [22]. According to our cohort study, the risk of death at hospital increases at NLI ≥ 20.0, SIMI ≥ 2,314.0, TLI ≤ 82.0 [25]. Upon admission, our patient had **NLI 34.2,** TLI 266.1, **SIMI 5,361.9,** which corresponds to a high risk of hospital death and is an indication for urgent heart surgery. Over time, the values decreased significantly: NLI — to 6.4, TLI — to 165.9, and SIMI — to 1,808.1, indicating stable satisfactory post-surgery period.

Neutrophils and platelets have a vital role to play in immune blood-clotting, including NET formation [26]. The key role of NET is to trap, neutralise and destroy pathogens [26]. NET dysregulation can contribute to pathological processes. Kumar S. et al. (2019) demonstrated the correlation between NET and sepsis severity [27]. A number of studies aimed at identification of a NET threshold value in order to evaluate unfavourable prognosis in various pathologies: NET ≥ 23 % — for sepsis, NET ≥ 16 % — for COVID-19, NET ≥ 12 % — for severe community-acquired pneumonia [28-30]. For IE patients, we had a NET threshold value of ≥ 14.2, i.e. a high risk of hospital death [31]. In this case study, NET upon admission was 14.7 %, indicating uncontrolled excessive inflammation and unfavourable prognosis, also confirming the need for urgent heart surgery.

Also, this clinical case study is unique for its additional analysis of the cellular composition of vegetations and resected valve tissue, in addition to a standard histological examination. The level of whole-cell pro-inflammatory macrophages in the surgical material was surprisingly low. We assume we have witnessed the "macrophage failure" phenomenon [32], resulting from increased macrophage destruction under the influence of NETs and uncontrolled release of pro-inflammatory cytokines, causing severe valve damage and the need for heart surgery.

Challenging management of almost every patient with IE in real-time clinical settings shaped the attitude of the national and international scientific communities of cardiologists in support of a multidisciplinary approach [1, 2]. The positive impact of such an approach for the patient in this case study was obvious; it affected the correct evaluation of indications for surgery and selection of the timing on the basis of comprehensive examination results. During hospitalisation, the patient had problems with antibacterial therapy caused by vancomycin-induced AKI, which required replacement of vancomycin with teicoplanin (complicated by urticaria), then with linezolid. During hospitalisation, the patient's kidney function restored completely, and the outcome of therapy was generally favourable.

Conclusion

The young patient had clinical acute suspected IE of tricuspid valve (one major and two minor Duke criteria — fever and vascular factor) with gigantic vegetation (28 mm), complicated by valve insufficiency, recurrent embolic syndrome in the pulmonary artery with pulmonary hypertension. Histopathological criteria confirmed the diagnosis of IE; however, aetiology was established only on the basis of PCR test results of blood and resected valve tissue. High NET, NLI and SIMI levels corresponded to a very high risk of death and necessitated an urgent surgery. Timely surgery resulted in patient recovery; all calculated inflammation indices and NET value decreased, indicating a low risk of complications. Low levels of undamaged pro-inflammatory CD 86+ macrophages in resected TV tissue is a sign of excessive macrophage destruction with release of numerous pro-inflammatory cytokine, which resulted in rapid and severe TV damage. A multiplex approach was a key to successful therapy and full recovery of the patient. Therefore, state-of-the-art management of IE patients should

be comprehensive, with the use of up-to-date methods of aetiological and imaging diagnostics, and should aim at early identification of patients with unfavourable risks in order to apply an individualised approach to the traditional or cardiac management strategy.

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