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Н.С. Чипигина*[1], Н.Ю. Карпова[1], А.С. Винокуров[1,2,3], Е.Е. Аринина[4], Ю.А. Иванова[1], А.А. Гаспарян[1], П.А. Кашковская[1], А.Г. Макаев[1], М.С. Сапко[1]

[1] — ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, Россия
[2] — ГБУЗ «Городская клиническая больница им. В.П. Демихова Департамента здравоохранения города Москвы», Москва, Россия
[3] — ГБУЗ «Московский многопрофильный клинический центр «Коммунарка» Департамента здравоохранения города Москвы», Москва, Россия
[4] — ФГБУ «Федеральный центр мозга и нейротехнологий» ФМБА России, Москва, Россия

СЕПТИЧЕСКАЯ ЭМБОЛОГЕННАЯ ПНЕВМОНИЯ — ОСОБЕННОСТИ КЛИНИКИ И ДИАГНОСТИКИ (ОБЗОР ЛИТЕРАТУРЫ И СОБСТВЕННЫЕ НАБЛЮДЕНИЯ)

N.S. Chipigina *[1], N.Yu. Karpova [1], A.S. Vinokurov [1,2,3], E.E. Arinina[4], Yu.A. Ivanova [1], A.A. Gasparyan[1], P.A. Kashkovskaya[1], A.G. Makaev[1], M.S. Sapko[1]

[1] — Pirogov National Research Medical University, Ministry of Health of Russia, Moscow, Russia
[2] — V.P. Demikhov City Hospital of Moscow City Health Department, Moscow, Russia
[3] — Moscow Multidisciplinary Clinical Center «Kommunarka», Moscow, Russia
[4] — «Federal Center for Brain and Neurotechnologies» of the Russian Federal Medical and Biological Agency, Moscow, Russia

Septic Embologenic Pneumonia — Clinical and Diagnostical Features (Review and Own Observations)

Резюме

В отличие от простой пневмонической инфильтрации, диагноз септической эмбологенной пневмонии ставит перед врачом принципиальную задачу поиска первичного септического эмбологенного очага, в том числе инфекционного эндокардита правых отделов сердца, и соответствующего изменения тактики ведения пациента. Сходство основных общих клинических и респираторных симптомов септической эмбологенной пневмонии с проявлениями других воспалительных процессов в легких делают их дифференциальную диагностику затруднительной без привлечения дополнительных лучевых методов исследования. В обзоре описаны особенности этиологии и патогенеза, а также клиника, осложнения и принципы диагностики септической эмбологенной пневмонии.

Ключевые слова: *септическая эмболия легких, пневмония, инфекционный эндокардит, наркомания, S. aureus*

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*Контакты: Наталия Семеновна Чипигина, e-mail: chipigina-natalia56@yandex.ru
*Contacts: Natalia S. Chipigina, e-mail: chipigina-natalia56@yandex.rufcv
ORCID ID: https://orcid.org/0000-0002-2083-0437

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Abstract

In contrast to trivial bacterial pneumonia, the diagnosis of septic pulmonary embolism poses a fundamental task for the doctor to search for primary sources of emboli, including right side infective endocarditis, and to change the tactics of managing the patient accordingly. The similarity of the main clinical common and respiratory symptoms of septic pulmonary embolism with symptoms of other inflammatory processes in the lung makes their differential diagnosis difficult without the involvement of additional radiologic investigation methods. The review describes the special features of etiology and pathogenesis, as well as the clinic, complications and principles of diagnosis of septic embolic pneumonia.

Key words: *septic pulmonary embolism, pneumonia, infectious endocarditis, drug use, S. aureus*

Conflict of interests

The authors declare no conflict of interests

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IE — infective endocarditis, CCT — chest computed tomography, SEP — septic embologenic pneumonia, EchoCG — echocardiography

Septic embologenic pneumonia (SEP) is a specific clinical syndrome developing as a result of infected emboli (usually septic thrombi) entering the pulmonary vasculature (predominantly small arteries), with their subsequent mechanical obstruction, invasion of microbial pathogens into the vascular wall and secondary infection, inflammation, impaired blood flow in the corresponding regions of the lung parenchyma with necrosis, suppuration, and destruction cavities [1–4]. The sources of such embolism (usually multiple one) include various primary extrapulmonary infectious pathological processes accompanied by the formation of septic thrombi — they can be classified into cardiogenic, peripheral endogenous, and exogenous embologenic foci [3, 5].

The sources used in the literature review were searched in PubMed and eLIBRARY.RU using the following key words: septic embologenic pneumonia, septic pulmonary embolism, right-sided infective endocarditis, Lemierre's syndrome, septic thrombophlebitis within the period of 1990–2023.

Extrapulmonary SEP sources

Typical SEP sources (traditional triad of active extrapulmonary SEP sources) include right-sided infective endocarditis (IE), acute thrombosis of the internal jugular vein with confirmed bacteremia (Lemierre's syndrome) in purulent inflammatory diseases of the head and neck, and septic thrombophlebitis of pelvic veins (including the postpartum one) [6–8]. SEP risk groups also include patients with a wide spectrum of acute or chronic purulent/septic processes — abscesses or cellulitis of soft tissues [7], abscesses of internal organs [9, 10], osteomyelitis [11], especially against the background of diabetes mellitus, hemodialysis, malignancies, and other diseases accompanied by immunodeficiency, increased risks of bacteremia and thromboses [1, 7, 12–14]. SEP morbidity has been increasing as a result of IE and septic thrombophlebitis in intravenous drug users [2, 7, 15], as well as in cases associated with the infection of central venous catheters, intracardiac devices, or medical interventions [2, 16–19].

The systematic literature review by Ye et al. (1978–2012) [2], which includes 76 articles with data about 168 patients with SEP, demonstrated that 26 % patients with SEP were intravenous drug users, 12.5 % had permanent intravascular catheters, and 3 % had permanent pacemakers. Most common diagnosis among patients with SEP included right-sided IE (12 %), hepatic abscess (9 %), skin and soft tissue infections, septic thrombophlebitis, Lemierre's syndrome, odontogenic infectious diseases (5–6 % each). In separate cases sources of infected emboli included pharyngeal abscess, purulent myositis, renal abscess and urinary tract infection, prostatic abscess, post-abortion purulent endometritis, osteomyelitis, septic arthritis. In 10 SEP cases (6 %) the primary infection focus was not verified [2]. Jing Jiang et al. [1] retrospectively analyzed 98 SEP cases hospitalized into the pulmonology department or the intensive care unit; the following SEP sources were the most significant: purulent skin and soft tissue infections (30.6 %), right-sided IE (20.4 %), hepatic abscess (14.3 %), catheter associated intravascular infections (9.2 %). In single cases SEP sources were represented by the urinary tract infection, perianal abscess, cholecystitis and cholangitis, infectious endophthalmitis, abdominal cavity abscess, periodontal abscess, meningitis; in 3 % of patients the SEP source

could not be diagnosed [1]. According to Goswami U et al. [18], 88 % of all SEP cases were associated with skin and soft tissue infections (44 %), right-sided IE (27 %), or septic deep vein thrombophlebitis (17 %).

SEP in right-sided IE

In right-sided IE the incidence of SEP diagnosis is 49.1–100 %; the lesions are usually bilateral and relapsing [20–26]. Based on our prior observations (data not published), SEP was diagnosed in 99 of 109 patients with right-sided IE (90.8 %); 85 % of those were referred to the inpatient department with the preliminary diagnosis of community-acquired pneumonia, 28.4 % were hospitalized into the intensive care unit as they required mechanical ventilation due to widespread pulmonary lesions, septic shock; the SEP diagnosis was morphologically confirmed in all 17 deceased patients with right-sided IE (15.6 %). Based on the Utsunomiya H et al. data, "new" embolic pulmonary lesions after the right-sided IE diagnosis and the onset of antibacterial treatment develop in 46.2 % of patients with the IE of the tricuspid valve [27]. IE affecting the tricuspid valve [9], especially with the maximum vegetation size of over 15 mm [27, 28] is an independent risk factor for "new" embologenic pulmonary lesions.

The modern right-sided IE in adults is most often associated with the drug abuse or intracardiac electronic devices, permanent vascular catheters in patients on hemodialysis; in rare cases it may be related to uncorrected congenital heart diseases [29, 30]. The increasing drug abuse trend observed in the latest decades in many countries has led to the enhanced significance of drug abuse IE as a SEP source [31–34]. IE in drug users is right-sided in 59–88.9 % cases [33, 35, 36] and complicates with SEP in 30.6–98.9 % [33, 35–37]. According to Moss R. and Munt B. data, echocardiographic signs of IE are detected in intravenous drug users with fever in 13 % cases; if bacteremia is also found in drug users with fever, the incidence of IE diagnosis reaches 41 % [38]. SEP is included into the minor IE signs of modified Duke diagnostic criteria; thus, when SEP is diagnosed in all cases (especially in drug users, patients with intracardiac devices, or congenital heart diseases), IE should always be considered, with echocardiography and blood cultures ordered within 24 hours [39, 40].

SEP: Causative agents

Causative agents of SEP correspond to the etiology of the primary embologenic infection focus [7]. Microorganisms isolated in the sputum culture correspond to the causative agents isolated from blood and the local septic focus.

The systematic literature review of Ye et al. [2] has shown that the blood cultures were positive in 90.7 % patients with SEP, and generally the most common causative agent was S. aureus (methicillin-sensitive (MSSA) in 28.6 % of patients with SEP and methicillin-resistant (MRSA) in 16 % of cases). Besides, this study underlines that bacteremia caused by Fusobacteria necrophorum (anaerobic flora of the oral cavity) was typically observed in Lemierre's syndrome or oropharyngeal infections, while Klebsiella pneumonia blood cultures were mostly positive in hepatic abscess cases. This coincides with other literature data regarding the SEP etiology in hepatic abscesses and descriptions of invasive Klebsiella pneumonia syndrome [10, 41, 42], while Candida growth was observed predominantly in SEP associated with infected permanent catheters [2]. At the same time, based on Doran HM et al. observations, 90 % of all SEP cases in patients with leukemias or lymphoproliferative diseases are caused by the fungal infection (Candida or Aspergillus) [43]. The majority of SEP cases in right-sided IE (60–90 %) are caused by S. aureus (MSSA or MRSA); more uncommon causative agents of right-sided IE with SEP include Staphylococcus lugdunensis, Streptococcus pneumonia, Pseudomonas aeruginosa and other Gram-negative bacteria, fungi (polymicrobial infection is possible) [44, 45]. Apart from impaired venous blood flow due to inflammatory edema, the pathogenesis of septic thrombophlebitis as a SEP source possibly presumes the capability of separate microorganisms (especially those, such as Fusobacterium necrophorum or S. aureus) to cause endothelial dysfunction and thrombosis due to inflammatory mechanisms and direct production of thrombogenic toxins [7, 46].

SEP: Clinical signs and diagnosis

SEP symptoms depend on the size of emboli, volume of pulmonary lesions, and presence of complications. At the disease onset they may vary from moderate respiratory symptoms — cough (dry or with purulent sputum; 14–100 % of patients), pleuritic pain (22–80 %), hemoptysis (4–80 %), dyspnea (19–91 %) combined with fever and chills (85–100 %) — to life-threatening conditions in the form of severe respiratory failure and septic shock (19 % of patients) [18, 20, 47, 48]. Crackles may be auscultated in lungs of 75 % patients [48]. These respiratory clinical SEP signs are non-specific and cannot be differentiated from the symptoms of other pneumonias. Chest X-rays are more significant for SEP diagnosis if the following signs are detected: bilateral lesions; multiple larger obscure round or irregular foci and shadows with a tendency to cavitate (in 50 % of patients), quick changes reflecting repeated embolic episodes, and slow

regression with preserved cystic thin-walled cavities (in 81 % of patients) [49, 50]. Such X-ray features in a patient with fever, bacteremia, and symptoms confirming the primary purulent-septic infectious focus or the SEP risk group (e.g., intravenous drug use) combined with hemoptysis episodes reflecting the formation of lung abscesses or infarctions can help to diagnose SEP. However, the sensitivity of X-rays in SEP diagnosis is currently insufficient [18, 47, 51], while signs of primary embologenic process at the onset of SEP are evident only in 24 % of patients [18]. In particular, 50–80 % of IE patients with tricuspid valve lesions develop the tricuspid regurgitation murmur later than signs of pulmonary lesions [52]. In any case, when SEP is suspected, chest computed tomography (CCT) is required for further evaluation and intepretation of pulmonary lesions. Its availability has significantly facilitated SEP diagnosis [18].

Chest CT: Modern standard of SEP diagnosis

CCT is the modern "golden standard" of SEP diagnosis which helps to detect typical diagnostic signs (Fig. 1) early: simultaneous presence of several (>2 in 93 % of patients) foci (80–100 %); dense infiltrates (75 %) without the air bronchogram symptom, including dense regions with the halo or inverse halo sign; cavities (57.9–71 %) of various sizes with chaotic peripheral locations (nearly 100 %); "nutrient vessel" sign (90 %), reflecting the hematogenous origin of lesions; quick (within several days) changes in abscesses, thin-walled cavities, and new foci in both lungs (80 %) [1, 4, 18, 42, 51, 53–55]. With that, the differential diagnosis should include other types of pulmonary lesions with focal cavitations — destructive metastases, lung abscesses of other origin, pulmonary tuberculosis, sterile lung infarction without infections,

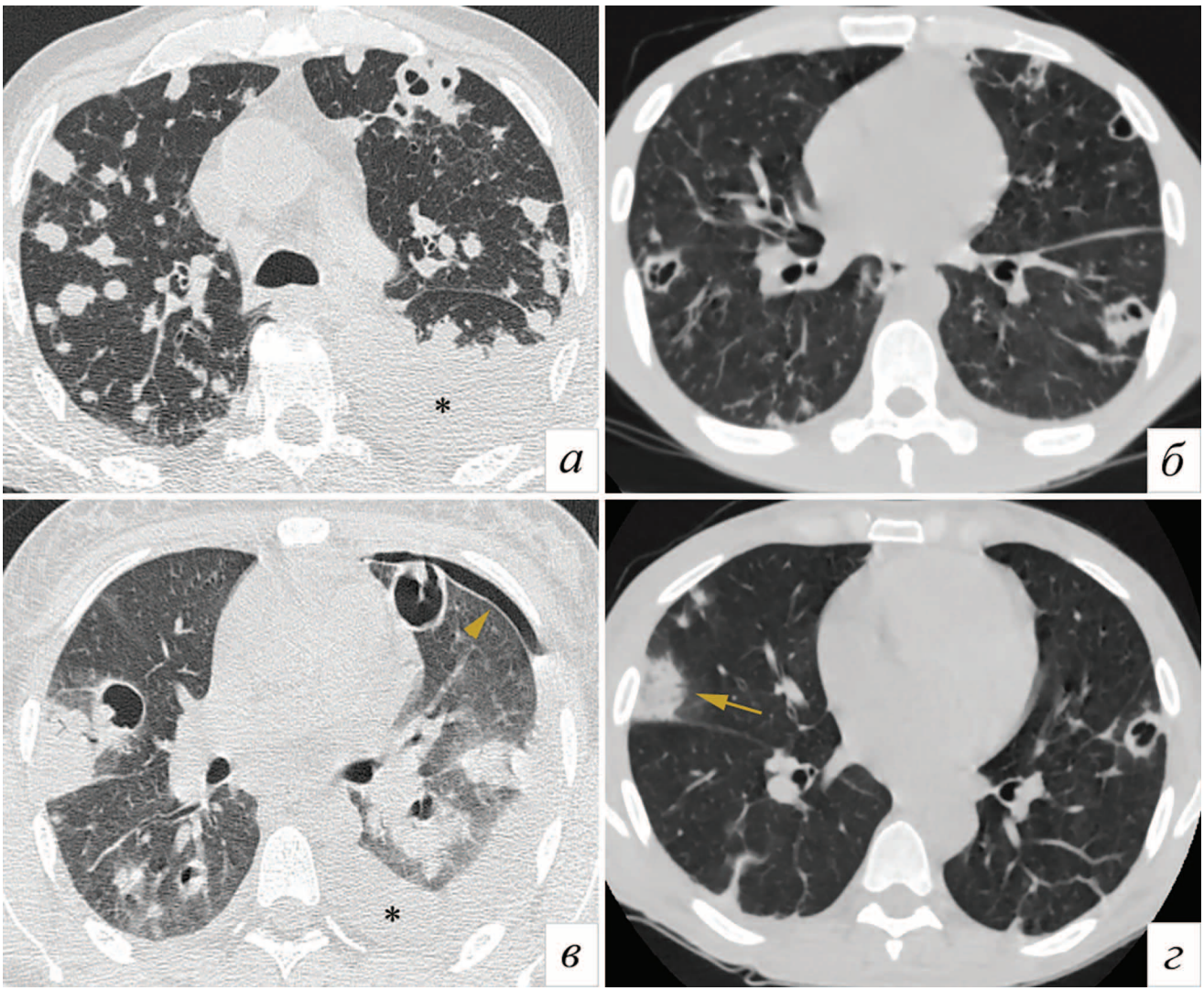

Figure 1. *Transversal chest CT images of different patients with septic pulmonary embolism (SPE). In cases of SPE in various combinations chaotic nodules (а), thin-walled cavities in subpleural location (б-г), as well as opacities- consolidations (в) and a "reverse halo" sign (arrow) are observed. SEP can be complicated by effusion into the pleural cavity (*) and even pneumothorax (arrow head)*

aspergillosis and other fungal infections, granulomatosis with polyangiitis [4, 56–58].

The diagnosis of SEP is still difficult; moreover, the term SEP is not included into the International Classification of Diseases 10 — this pneumonia is usually defined as "pneumonia in diseases classified in other sections". Without unified diagnostic criteria, the SEP syndrome may be diagnosed with the presence of all following four signs:

1) clinical symptoms of the inflammatory lung disease (fever, chills, cough, pleuritic pain, dyspnea, hemoptysis);

2) detection of multiple peripheral foci with cavitations, allowing to suspect the embologenic origin of the pulmonary disease, on imaging;

3) diagnosis of the extrapulmonary embologenic infectious focus;

4) exclusion of other causes of pulmonary changes [1, 7].

It is evident that SEP has specific etiological, pathogenetic, and diagnostic signs; in clinical practice the detection of SEP may become the "key" to the diagnosis of primary embologenic infectious focus, in particular right-sided IE [4, 50], which is demonstrated in the case below.

The male patient S., 46 years old, was hospitalized on April 21, 2020 to the inpatient department for COVID-19 patients with complaints of fever up to 38.0 °C, chills, dry cough, feeling of chest tightness, dyspnea at rest. The patient got sick a week before, when he developed fever up to 38.0 °C, myalgia, followed by the dry cough and worsening weakness. On April 20, 2020 he called an ambulance due to severe dyspnea; an outpatient lung CT was ordered — "multiple foci of pulmonary tissue consolidation of various sizes, with the most massive ones in the left lower lobe, together with ground glass opacities with preserved bronchial lumina; several consolidation areas with signs of cavitation (bronchiectasis?)" described in both lungs. The patient was urgently transferred to the inpatient department with suspected viral pneumonia. Within the prior 14 days the patient did not contact persons with laboratory-confirmed COVID-19 or under observation regarding the nSARS-CoV-2 infection. The patient was not occupied. Earlier he used intravenous drugs; he denied using the drugs in the months prior, though multiple traces of intravenous injections were detected on the skin. On admission to the emergency department, the patient's condition was severe. The patient's consciousness was clear. He was oriented in place and time. Body temperature 38.8 °C. Peripheral lymph nodes were not palpated. The nasal breathing was free. RR 26–28/min. Oxygen saturation on room air 88 %. BP 105/70 mm Hg. The pulse was regular. HR 124/min. The abdomen was soft and nontender on palpation. The liver was not enlarged. The spleen was not palpable. The heart and lungs were not auscultated. The following lab results were derived on admission: white blood cells 15×10^9/L, band neutrophils 18 %, hemoglobin 119 g/L, platelets 80×10^9/L; creatinine 198 μmol/L, AST 144 U/L, ALT 78 U/L, albumin 28 g/L, CRP 488 mg/L, sharply increased procalcitonin level. The patient was hospitalized into the intensive care unit with the preliminary diagnosis "Unspecified coronavirus infection, community-acquired bilateral polysegmental severe pneumonia, CT stage 2, Grade 2 respiratory failure". Treatment for coronavirus pneumonia was started, with oxygen insufflation via nasal cannula with the rate of 10 L/min. Repeated chest MSCT (April 21, 2020; 2.40 a.m.) revealed the following: bilateral asymmetric decrease of pulmonary tissue pneumatization due to the presence of more than 3 "ground glass" opacity areas, predominantly in peripheral and subpleural regions, with irregular shape, unclear contours, dense rims and the "inverse halo" pattern, sized approximately up to 30 mm. Multiple foci with irregular contours and uneven cavitation in the largest structures are detected in all segments of both lungs (predominantly in peripheral and subpleural regions in a peribronchovascular pattern). The following conclusion was made: "The probability of viral etiology is average; detected changes may correspond to the polysegmental bilateral inflammatory process related to septic embolism. Differential diagnosis is primarily required with granulomatosis with polyangiitis" (Fig. 2). Based on the history (drug abuse) and CT signs of SEP, right-sided IE was suspected. The negative PCR coronavirus test returned on April 21, 2020; blood cultures were collected, and transthoracic EchoCG was ordered, which revealed signs of tricuspid IE lesions (marginal coarse small vegetations, Grade 2–3 tricuspid regurgitation).

The following diagnosis was established: "Primary acute infectious endocarditis with tricuspid valve lesions. Grade 2–3 tricuspid regurgitation. Septic embologenic bilateral pneumonia with abscesses. Secondary thrombocytopenia. Secondary anemia. Background condition: Intravenous drug abuse. Complications: Septic shock. Grade 2 respiratory failure. Acute kidney injury syndrome". Based on the highest probability of staphylococcal IE etiology, vancomycin treatment (10 mg/kg of body weight) was started. The patient's condition was unstable against the background of therapy administered; O_2 saturation up to 85 % at the oxygen flow of 15 L/min. The patient underwent orotracheal intubation, and mechanical ventilation was started in the SIMV-PC-PS mode. The fever persisted. The repeated EchoCG (April 23, 2020) revealed the following: "Tricuspid valve leaflets had increased echogenicity,

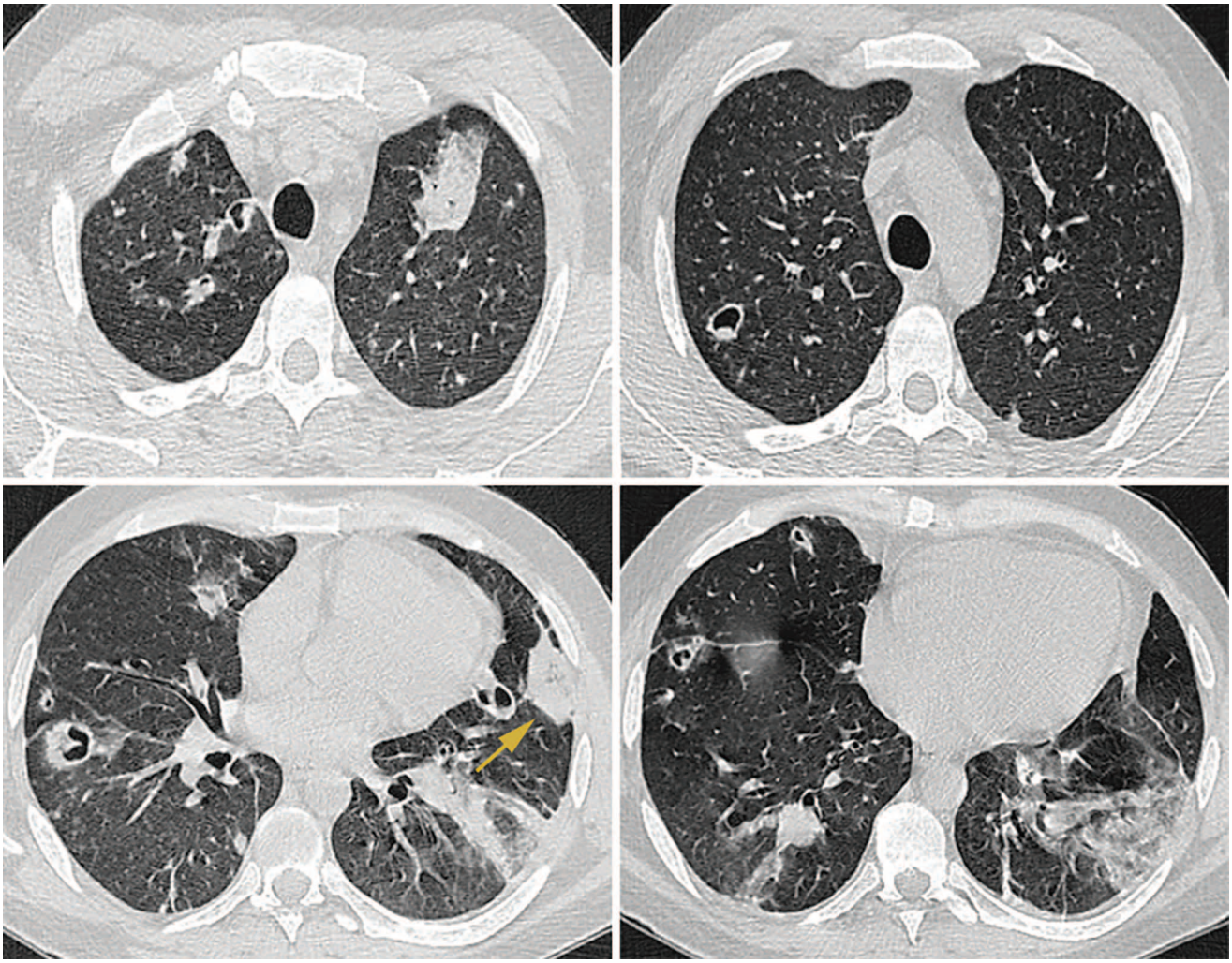

Figure 2. *Transversal chest CT images of patient C. from 21.04.2020 г. In both lungs there are chaotic nodules and opacities of the lung tissue, multiple thin–walled cavities*

with marginal indurations, but were not thickened. The round-ovoid pedunculated lesion with moderately increased echogenicity sized 12×6 mm was detected on the valvular leaflet, partially entering the right ventricle. Moderate to significant valvular regurgitation. Estimated systolic pressure in the pulmonary artery was approximately 55 mm Hg" (Fig. 3).

The patient's condition progressively worsened; on April 23, 2020 (Day 3 of treatment) the patient dies after worsening respiratory failure. The autopsy confirmed the diagnosis of acute IE with the tricuspid valve lesion, complicated with bilateral septic polysegmental embologenic pneumonia with abscesses, acute focal tubulo-interstitial nephritis with the acute kidney injury syndrome. No signs of diffuse pulmonary lesions were detected. The antemortem blood cultures confirmed that the most probable IE causative agent was S. aureus sensitive to oxacillin, vancomycin, linezolid, cefoxitin, ciprofloxacin (the growth was obtained in three blood cultures dated April 21, 2020).

During the first months of COVID-19 epidemics, due to maximum awareness of physicians regarding the viral pneumonia combined with insufficient diagnostic experience with the pathology described, patients with respiratory symptoms and fever of various etiology often were hospitalized erroneously to COVID-19 inpatient departments. The decision on hospitalization was often made based just on CT changes in lungs, which could be interpreted incorrectly. Unlike SEP, typical CT signs of viral pneumonia include "ground glass" opacities, while focal lesions and cavities are quite rare, which should be accounted for in the differential diagnosis of these conditions [4, 59, 60]. In the case presented, the diagnosis of tricuspid valve IE was timely established due to the correct evaluation of SEP signs detected in the repeated CCT. Unfortunately, the condition severity (mechanical ventilation required) and intensive care in the patient with the right-sided IE was initially associated with the unfavorable outcome [61].

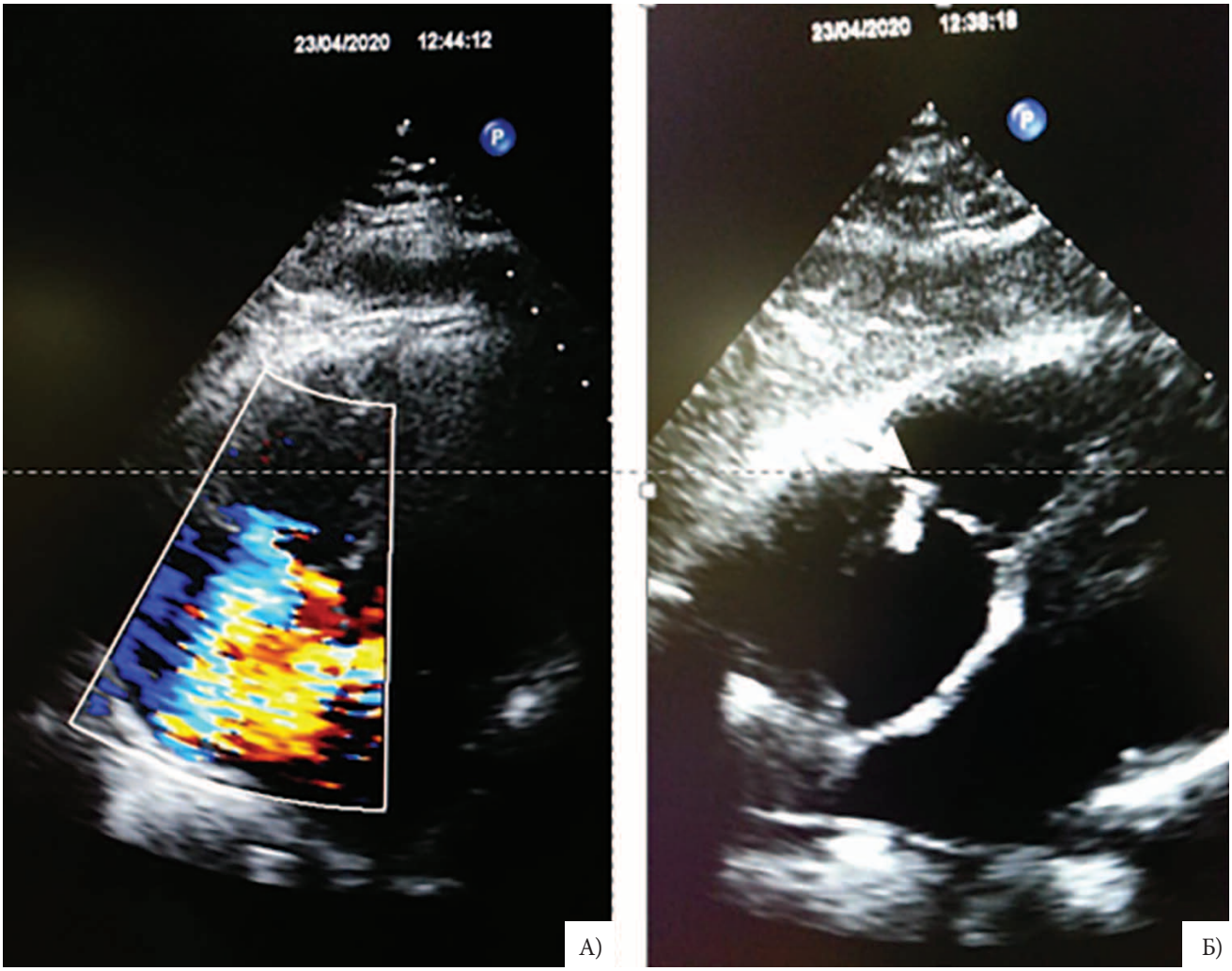

Figure 3. *Echocardiographic images of patient C.*
A) tricuspid valve regurgitation of 2-3 degrees
Б) large vegetation on the tricuspid valve

SEP: Complications and outcomes

In 23.8–65 % cases SEP is complicated with pleural effusion, pleural empyema (8.3 %) [2, 18, 19, 42], pneumothorax (3.5 %) [14, 62–65], pulmonary hemorrhage in single cases, including due to the rupture of infectious pulmonary artery aneurysm; bronchopleural fistulae have been described as well [7, 66]. SEP often leads to quick worsening of the patient's condition with the development of respiratory failure, respiratory distress syndrome, septic shock, disseminated intravascular coagulation syndrome, impaired consciousness — thus, 25.5–63 % of patients require treatment in the intensive care unit [1, 18, 19, 42].

SEP treatment with antibiotics is administered based on the sensitivity of the causative agent which is isolated or most probable in the clinical situation; primary antibacterial treatment should usually be broad-spectrum [7, 42, 67, 68]. Managing the patient with SEP may require mechanical ventilation, surgical interventions in empyema, pneumothorax, pulmonary hemorrhage. If necessary, purulent-septic primary processes, including right-sided IE, are treated surgically, intracardiac or intravenous devices are removed. Thus, persistence of a large vegetation on a tricuspid valve or the pulmonic valve, especially its enlargement, despite recurrent embologenic episodes in lungs against the background of antibacterial treatment, is a sign of ineffective infection control, being one of the indications to surgical IE treatment [39, 40]. In cases of septic thrombi complicated with SEP, anticoagulant therapy is often added; however, due to the high risk of pulmonary hemorrhages, the issue of anticoagulant therapy safety and duration in SEP is still debatable [2, 7]; in right-sided IE such therapy is not indicated due to high bleeding risk and lack of safety evaluation in controlled trials [39, 40, 48].

Mortality in SEP reaches 10–30 %, it depends both on efficient control of primary embologenic infectious focus

and severity of SEP signs [1, 2, 10, 18, 19, 42]. Mortality risk factors include low oxygen saturation and impaired consciousness in patients with SEP [19], fungal infections or causative agents multiresistant to antibiotics, inefficacy or late onset of empiric antibacterial treatment, refractory septic shock with multiorgan failure, severe coagulation disorders, pulmonary hemorrhage [1, 2, 18, 42]. The multidisciplinary approach is required in the majority of cases for successful SEP treatment, including the participation of intensive care specialists, general practitioners, pulmonologists, cardiologists, surgeons, ENT physicians, neurologists, and other medical specialists.

Conclusion

SEP is a special life-threatening pulmonary pathology which is difficult to diagnose, develops secondarily as a complication of several purulent-septic processes, including right-sided IE and septic thromboses associated with purulent inflammatory diseases of soft tissues, internal organs, osteomyelitis. Accurate SEP diagnosis presumes the way to understanding the risk of corresponding complications and often the key to the diagnosis of primary sources of septic embolism in the pulmonary artery system. The detection of typical CCT signs is currently the most important step in the SEP diagnosis. Timely diagnosis and adequate treatment of SEP requires awareness and knowledge about this rare pathology among general practitioners, pulmonologists, intensive care specialists, cardiologists, ENT physicians, dentists, surgeons, and other specialists.

Вклад авторов:

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Чипигина Н.С. (ORCID ID: https://orcid.org/0000-0002-2083-0437): концепция работы, сбор и обработка материала, написание текста, редактирование

Карпова Н.Ю. (ORCID ID: https://orcid.org/0000-0002-7546-4841): концепция работы, редактирование и утверждение окончательного варианта статьи

Винокуров А.С. (ORCID ID: https://orcid.org/0000-0002-0745-3438): концепция работы, написание текста статьи, редактирование, подготовка лучевых изображений

Аринина Е.Е. (ORCID ID: https://orcid.org/0000-0002-6431-037X): наблюдение и описание случая, представленного в статье

Иванова Ю.А. (ORCID ID: https://orcid.org/0009-0005-1446-7722): подбор и анализ литературы

Гаспарян А.А. (ORCID ID: https://orcid.org/0000-0003-1699-7717): подбор и анализ литературы

Кашковская П.А. (ORCID ID: https://orcid.org/0009-0001-0856-9503): подбор и анализ литературы

Макаев А.Г. (ORCID ID: https://orcid.org/0000-0003-2628-2440): подбор и анализ литературы

Сапко М.С. (ORCID ID: https://orcid.org/0009-0009-8151-8023): подбор и анализ литературы

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Chipigina N.S. (ORCID ID: https://orcid.org/0000-0002-2083-0437): the concept of work; data mining, analysis and interpretation; preparation of a draft of the manuscript, editing

Karpova N.Yu. (ORCID ID: https://orcid.org/0000-0002-7546-4841): the concept of work; final editing

Vinokurov A.S. (ORCID ID: https://orcid.org/0000-0002-0745-3438): the concept of work; preparation of a draft of the manuscript, editing; ray images preparation

Arinina E.E. (ORCID ID: https://orcid.org/0000-0002-6431-037X): observation and description of the case presented in the article

Ivanova Yu.A. (ORCID ID: https://orcid.org/0009-0005-1446-7722): selection and analysis of literature

Gasparyan A.A. (ORCID ID: https://orcid.org/0000-0003-1699-7717): selection and analysis of literature

Kashkovskaya P.A. (ORCID ID: https://orcid.org/0009-0001-0856-9503): selection and analysis of literature

Makaev A.G. (ORCID ID: https://orcid.org/0000-0003-2628-2440): selection and analysis of literature

Sapko M.S. (ORCID ID: https://orcid.org/0009-0009-8151-8023): selection and analysis of literature

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