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Е.В. Резник[1,2], М.А. Батов*[3], Т.В. Апарина[1], О.В. Ким[1], М.Х. Шурдумова[1,2], Л.М. Михалева[2,4], А.П. Смирнов[1,5], Г.Н. Голухов[2]

[1]— Федеральное государственное автономное образовательное учреждение высшего образования «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Министерства здравоохранения Российской Федерации, Москва, Россия
[2]— Государственное бюджетное учреждение здравоохранения города Москвы «Городская клиническая больница № 31 имени академика Г.М. Савельевой Департамента здравоохранения города Москвы», Москва, Россия
[3] — Московский научный исследовательский онкологический институт имени П.А. Герцена, Москва, Россия
[4]— Научно-исследовательский институт морфологии человека имени академика А.П. Авцына» Федерального государственного бюджетного научного учреждения «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия
[5]— Государственное бюджетное учреждение здравоохранения города Москвы «Городская поликлиника № 212 Департамента здравоохранения города Москвы», Москва, Россия

ЛЕЙКЕМОИДНАЯ РЕАКЦИЯ У ПАЦИЕНТА СТАРЧЕСКОГО ВОЗРАСТА С ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ АОРТАЛЬНОГО КЛАПАНА И АДЕНОКАРЦИНОМОЙ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

E.V. Reznik[1,2], M.A. Batov*[3], T.V. Aparina[1], O.V. Kim[1], M.Kh. Shurdumova[1,2], L.M. Mikhaleva[2,4], A.P. Smirnov[1,5], G.N. Golukhov[2]

[1]— Pirogov Russian National Research Medical University, Moscow, Russia
[2]— Academician G.M. Savelyeva City Clinical Hospital № 31, Moscow, Russia
[3]— P.A. Hertsen Moscow Oncology Research Institute — National Medical Research Radiological Center of Ministry of Healthcare of the Russian Federation, Moscow, Russia
[4]— Avtsyn Research Institute of Human Morphology of Federal state budgetary scientific institution «Petrovsky National Research Centre of Surgery», Moscow, Russia
[5]— City Polyclinic № 212, Moscow, Russia

Leukemoid Reaction in an Elderly Patient with Aortic Valve Infective Endocarditis and Pancreatic Adenocarcinoma

Резюме

Лейкемоидная реакция (ЛР), связанная с солидными опухолями, документируется на протяжении многих десятилетий, и часто ассоциирована с неблагоприятным прогнозом и агрессивным течением заболевания. Вместе с тем, дифференциальная диагностика ЛР представляет значительные трудности при наличии у пациента нескольких потенциальных этиологических факторов, каждый из которых по отдельности может быть причиной ЛР, или, напротив, приводить к системной реакции организма в рамках общего патогенетического сценария.

*Контакты: Максим Александрович Батов, e-mail: md.batov@gmail.com
*Contacts: Maxim A. Batov, e-mail: md.batov@gmail.com
ORCID ID: https://orcid.org/0000-0002-3780-4358

Нами представлено клиническое наблюдение пациентки старческого возраста, госпитализированной в отделение реанимации и интенсивной терапии в связи с впервые развившейся слабостью в правых конечностях. При клинико-лабораторно-инструментальном обследовании подтверждено острое нарушение мозгового кровообращения по ишемическому типу на фоне нарастания в течение 5 суток лейкоцитоза до 60 тыс. клеток/мкл со сдвигом лейкоцитарной формулы влево и декомпенсацией состояния пациентки с последующим летальным исходом, несмотря на проводимую терапию.

При аутопсии выявлена низкодифференцированная аденокарцинома хвоста поджелудочной железы с множественным метастатическим поражением региональных лимфатических узлов и печени, а также конкурирующее заболевание — острый инфекционный эндокардит аортального клапана, явившийся причиной развития сепсиса по типу септикопиемии и тромбоэмболии как по большому кругу кровообращения с наличием ишемического инфаркта головного мозга, инфарктов селезенки, так и по малому кругу с развитием тромбоэмболов в правых сегментарных ветвях легочной артерии. Учитывая распространенный характер рака поджелудочной железы и отсутствие прямых данных за активный инфекционный процесс на этапе первичной диагностики, более вероятен паранеопластический характер ЛР, однако инфекционный эндокардит и сопутствующая патология могли также внести свой вклад в развитие ЛР.

Ключевые слова: *лейкемоидная реакция, острый инфекционный эндокардит, аортальный клапан, аденокарцинома поджелудочной железы, паранеопластический синдром*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Leukemoid reaction (LR) associated with solid tumors has been documented for many decades. LR is often associated with an unfavorable prognosis and aggressive course of the disease. However, the differential diagnosis of LR is of significant difficulty when a patient has several potential etiological factors, each of them individually may cause LR or, on the contrary, lead to a systemic reaction of the body within a single pathogenetic chain.

We present a clinical observation of an elderly patient admitted to the intensive care unit due to the first-time encountered weakness in the right extremities. Clinical and instrumental examination revealed an acute cerebral ischemia with leukocytosis increase up to 60.000 cells/μL with leukocyte formula left shift and subsequent patient decompensation with lethal outcome, despite the intensive treatment.

Autopsy revealed a low-differentiated adenocarcinoma of the pancreatic tail with multiple metastatic lesions in regional lymph nodes and liver, as well as a competing disease — acute infective endocarditis of the aortic valve, which was the cause of sepsis development with septicemia type and thromboembolism both in the great circulation circle with the presence of ischemic cerebral infarction, spleen infarcts, and in the small circle with the development of thromboembolism in the right segmental branches of the pulmonary artery. Given the advanced stage of pancreatic cancer and lack of direct evidence of sepsis at primary diagnosis, paraneoplastic nature of LR is more likely, but infective endocarditis and concomitant pathology also may have contributed to the development of LR.

Key words: *leukemoid reaction, acute infective endocarditis, aortic valve, pancreatic adenocarcinoma, paraneoplastic syndrome*

Conflict of interests

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G-CSF — granulocyte colony-stimulating factor, US examination — ultrasound examination, CT — computer tomography, LR — leukemoid response, echoCG — echocardiography

Introduction

Leukemoid response (LR) is characterised by persistent leukocytosis of over 50 k cell/μL in the absence of bone marrow involvement, where acute or chronic myelogenous leukaemia has been ruled out. The relative count of immature forms in LR is negligible or moderate, myelocytes rarely exceed 5–15 %, blasts are practically absent, whereas in leucosis these values are high. LR does not manifest with signs of neoplastic proliferation usually seen in leucosis, therefore, LR is not associated with metaplastic anaemia and thrombocytopenia [1].

There are 4 types of LR. Type 1 — myeloid reactions; most common are neutrophilic reactions with neutrocytosis of over 9×10^9/L and left shift to metamyelocytes and myelocytes; promyelocytic reactions with high promyelocyte counts; eosinophilic reactions, if the absolute

blood eosinophilic leukocyte count is over 0.45×10^9/L, and reactions of two and three myelogenesis lineages, which manifest as neutrocytosis (or leukopenia), hyperthrombocytosis (or thrombocytopenia) and normoblastosis (normocytosis) in peripheral blood. Type 2 — a lymphocytic reaction, which is secondary reactive lymphocytosis with an increase in the absolute lymphocyte count of over 4×10^9/L. Type 3 is represented by monocytic-macrophagal blood reaction, associated with an increase in peripheral blood monocytes over 0.8×10^9/L as a result of infectious, fungal, rickettsial, and protozoan diseases. Type 4 is pseudoblast LR, which is characterised by the presence of numerous cells with a homogeneous nucleus, individual nucleoli, blue thin cytoplasm without granularity, which are mistaken for blast cells, in blood and bone marrow [1, 2].

LR is not an independent pathology; usually, it is secondary to an underlying disease. LR can be caused mostly by severe infections, various intoxications, heavy bleeding or blood clots, more rarely — by solid tumours as part of paraneoplastic syndrome [3, 4]. Despite being quite rare, paraneoplastic LR is a well-described event associated with solid tumours, particularly lung cancer, clear-cell carcinoma and pancreatic cancer [4].

The definitive pathogenesis of paraneoplastic LR is still unclear due to insufficient materials for a detailed investigation; however, data from some publications describe secretion of granulocyte colony-stimulating factor (G-CSF) in the presence of cytokine-producing tumour. G-CSF is a natural glycoprotein which stimulates proliferation and maturation of progenitor cells of bone marrow to become fully differentiated neutrophils. Normally, G-CSF is produced by endotheliocytes, fibroblasts, monocytes, and macrophages. In patients with paraneoplastic LR, G-CSF is secreted directly by tumour cells and results in cytokine-mediated leukocytosis [5].

Outcomes in patients with paraneoplastic LR and solid tumours in various locations show that LR is a predictor of poor outcome. In a retrospective study by Granger et al. (2009), 76 % of patients with paraneoplastic LR died within 12 weeks, which correlates with individual published clinical observations, describing mostly adverse outcomes in these patients [6, 7].

We present a case study of an elderly female patient with metastatic pancreatic cancer, acute infective endocarditis of aortic valve with sepsis in the form of septicopyaemia and thromboembolism, which caused cardioembolic stroke, spleen infarction and marked LR.

Case Study

Female patient E., 83 years old, was admitted to the ICU for patients with acute cerebrovascular accidents; she was complaining of marked weakness in her right-side limbs. Her medical record states that the patient has had high blood pressure and type 2 diabetes mellitus for a long time.

Upon examination, patient's condition is serious; contact with the patient is challenging due to cognitive disorders; skin is pale pink, warm, without swelling. Body temperature — 37.6 °C, body mass index — 24 kg/m^2.

Breathing is regular, rhythmic; chest excursion is symmetric; respiratory rate is 19 per minute. Saturation is 93 % atm. Chest auscultation revealed harsh breathing, bilaterally weakened in lower sections, without secondary respiratory murmurs.

Cardiac tones are muffled, rhythm is regular; heart rate is 87 bpm, blood pressure: 170/85 mm Hg. Main and peripheral artery pulse is adequate. Tongue is dry, with brown plaque. Abdomen is symmetric, soft, painless. Kidney punch is negative on both sides.

Neurological status evaluation: state of consciousness — obtundation, sensorimotor aphasia, meningeal signs are absent. Pupils are symmetric, sensitive to light. Eye bulbs are deflected to the left, right gaze deviation. The right nasolabial fold is smoothened. No nystagmus; swallowing is preserved; the tongue is on the midline. Moderate dysarthria. Quadriparesis: right side — strength reduced to 2 points in the leg, plegia — in the arm; left side: to 3 points in the leg, 1 point in the arm. Overactive tendon and periosteal reflexes on the left side. Babinski's sign is positive on both sides. Sensory and coordination impairment cannot be verified due to the serious condition of the patient. NIHSS (National Institutes of Health Stroke Scale) score is 20 points.

During hospitalisation, leukocytosis got worse with thrombocytopenia up to 70×10^9/L and hypochromatic normocytic anaemia with Hb values as low as 93 g/L (Figure 1). The highest recorded neutrocytosis level was 60.86×10^9/L, with an increase in the relative banded neutrophil value to 94.5 % and left shift to metamyelocytes and appearance of up to 1 % of myeloblasts in peripheral blood (Table 1). Blood procalcitonin was 1.48 ng/mL.

Blood biochemistry results showed hyperglycemia up to 14.9 mmol/L, bilirubinemia up to 24.6 μmol/L, elevated alkaline phosphatase and minor elevation of aspartate aminotransferase (Table 2). Troponin upon admission — 50.7 ng/mL.

Coagulation profile was unremarkable.

Clinical urinalysis: significant proteinuria (protein 6.0 g/L), glucosuria (28.0 mmol/L), erythrocyturia (25–30 per HPF), bacteriuria.

Cerebrospinal fluid examination: light yellow, liquor xanthochromia 1+, completely clear, cytosis 81/3, liquor protein 0.645 g/L, lymphocytes 3, neutrophils 78, liquor glucose 9.6 mmol/L.

ECG upon admission: sinus rhythm, heart rate: 72 bpm, left-sided axis deviation, signs of macrofocal cicatrical changes in the myocardium of the lower left ventricle wall (Figure 2).

Echocardiography (echoCG) showed induration of aorta and cusps of aortic and mitral valves, calcifications on cusps of aortic and mitral valves, minor enlargement of the left atrium to 4.2 cm, left ventricular hypertrophy

(posterior wall thickness of left ventricle: 1.2 cm, interventricular septum thickness: 1.3 cm). Absence of adequate systolic induration of anterior, septal walls at the level of apical segment, apex of left ventricle. Global contractility is slightly lower than normal, Simpson left ventricular ejection fraction: 50 %. Doppler imaging: grade I mitral regurgitation, grade I aortic regurgitation, grade II tricuspid regurgitation. Pericardium is unremarkable. Minor pulmonary hypertension: elevated systolic pressure in pulmonary artery to 40 mm Hg. It is interesting to note that, echoCG upon admission did not reveal any signs of valve vegetation.

Ultrasound examination (US examination) of neck vessels showed signs of atherosclerotic changes in brachiocephalic arteries, signs of haemodynamically insignificant left- and right-side stenosis of carotid bifurcation to 30 %, as well as abnormal tortuosity of internal carotid artery and left subclavian artery without haemodynamic disorders.

Brain computer tomography (CT) upon admission (day 1): intracranial artery atherosclerosis, post-stroke transformation in right hemisphere and right cerebellum. Brain CT two days later demonstrated signs of an ischemic cerebrovascular event in the bed of the left medial cerebral artery and left posterior cerebral artery related to previous changes.

Chest CT upon admission: moderate hypoplastic changes in the posterior basal surface of the lungs. Repeated chest CT showed bilateral multisegmental pneumonia. Microbial examination of blood revealed growth of Enterococcus faecalis, Klebsiella pneumoniae, Acinetobacter baumannii.

Table 1. *Dynamics of complete blood count with differential during the period of hospitalization*

Parameter	07.01	08.01	09.01	10.01	11.01	Reference	Units
Erythrocytes, RBC	**4,65**	**4,51**	**3,31**	**3,34**	**3,34**	4,2-5,6	10^{12}/L
Hemoglobin, HGB	**130**	**131**	**92**	**94**	**93**	131-172	g/L
Hematocrit, HCT	41,2	41,3	29,1	29,4	29,3	39-50	%
Mean corpuscular volume, MCV	88	91,5	88	88	92,2	80-100	μm^3
Mean corpuscular hemoglobin, MCH	28	29	27,7	28,2	29,2	27-35	pg
Mean corpuscular hemoglobin concentration, MCHC	316	317	315	320	317	320-360	g/L
Red cell distribution, RDW	13	-	15	17	-	11-14,8	%
Platelets, PLT	**151**	**131**	**89**	**78**	**70**	150-400	10^9/L
Mean platelet volume, MPV	10	10,1	11	11	14,2	6-11	μm^3
Plateletcrit, PCT	0,151	-	0,093	0,088	-	0,1-1	%
Platelet distribution width, PDW	13	-	15	17	-	12-18	%
Leucocytes	**18,4**	**15,18**	**22,1**	**53,4**	**60,86**	4-9	10^9/L
Myelocytes	-	-	-	-	17	0	%
Metamyelocytes	-	-	-	-	2	0	%
Myeloblasts	-	-	-	-	1	0	%
Promyelocytes	-	-	-	-	1	0	%
Segmented Neutrophils	-	88	-	-	80 43	47-72	%
Band Neutrophils	-	88,7	-	-	94,5	1-6	%
Lymphocytes	-	6,6	-	-	5	19-37	%
Monocytes	-	4,7	-	-	2	3-11	%
Eosinophils	-	0,1	-	-	0	0,5-5	%
Basophils	-	0,1	-	-	0,6	0-1	%
Neutrophils, ANC	-	**14**	-	-	**57**	2,04-5,8	10^9/L
Lymphocytes, ANC	-	6	-	-	5	1,2-3,0	10^9/L
Monocytes, ANC	-	4	-	-	2	0,09-0,6	10^9/L
Eosinophils, ANC	-	0,02	-	-	0,02	0,02-0,3	10^9/L
Basophils, ANC	-	0,01	-	-	0,38	0,0-0,065	10^9/L

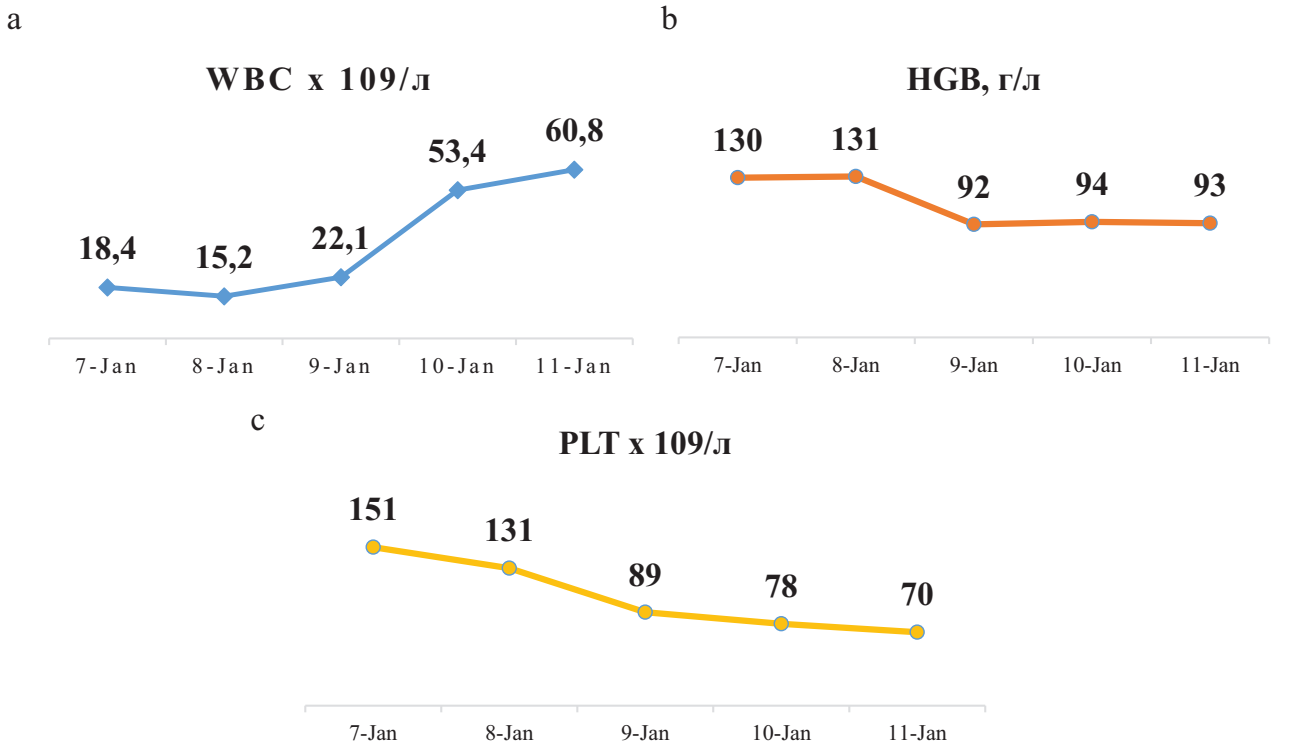

Figure 1. *Complete blood count dynamics: a — leukocytes; b — hemoglobin; c — platelets; WBC — white blood count, HGD — hemoglobin, PLT — platelets.*

Table 2. *Dynamics of the biochemical blood test during the period of hospitalization*

Parameter	07.01	08.01	Reference	Units
Total protein	68	65,5	66-83	g/L
Albumin	-	31,1	35-52	g/L
Total bilirubin	**23,6**	**24,6**	5-21	μmol/L
Direct bilirubin	8,3	8	0-4,4	μmol/L
Bilirubin indirect	15,3	16,6	0-16,6	μmol/L
Cholesterol	6,2	6,46	0-5,20	μmol/L
Urea	**9,7**	**10,8**	2,8-7,2	μmol/L
Creatinine	82,5	77,5	74-110	μmol/L
Blood glucose	**14,9**	**14,1**	4,1-5,9	mmol/L
Potassium	3,82	4,2	3,5-5,1	mmol/L
Sodium	137,6	139	135-145	mmol/L
Chlorine	97,5	98	98-107	mmol/L
Aspartate aminotransferase	**46,8**	**48,8**	11-36	U/L
Alanine aminotransferase	23,9	21,7	10-37	U/L
Creatine phosphokinase	116,5	115,5	26-145	U/L
Alkaline phosphatase	**515**	**453**	30-120	U/L

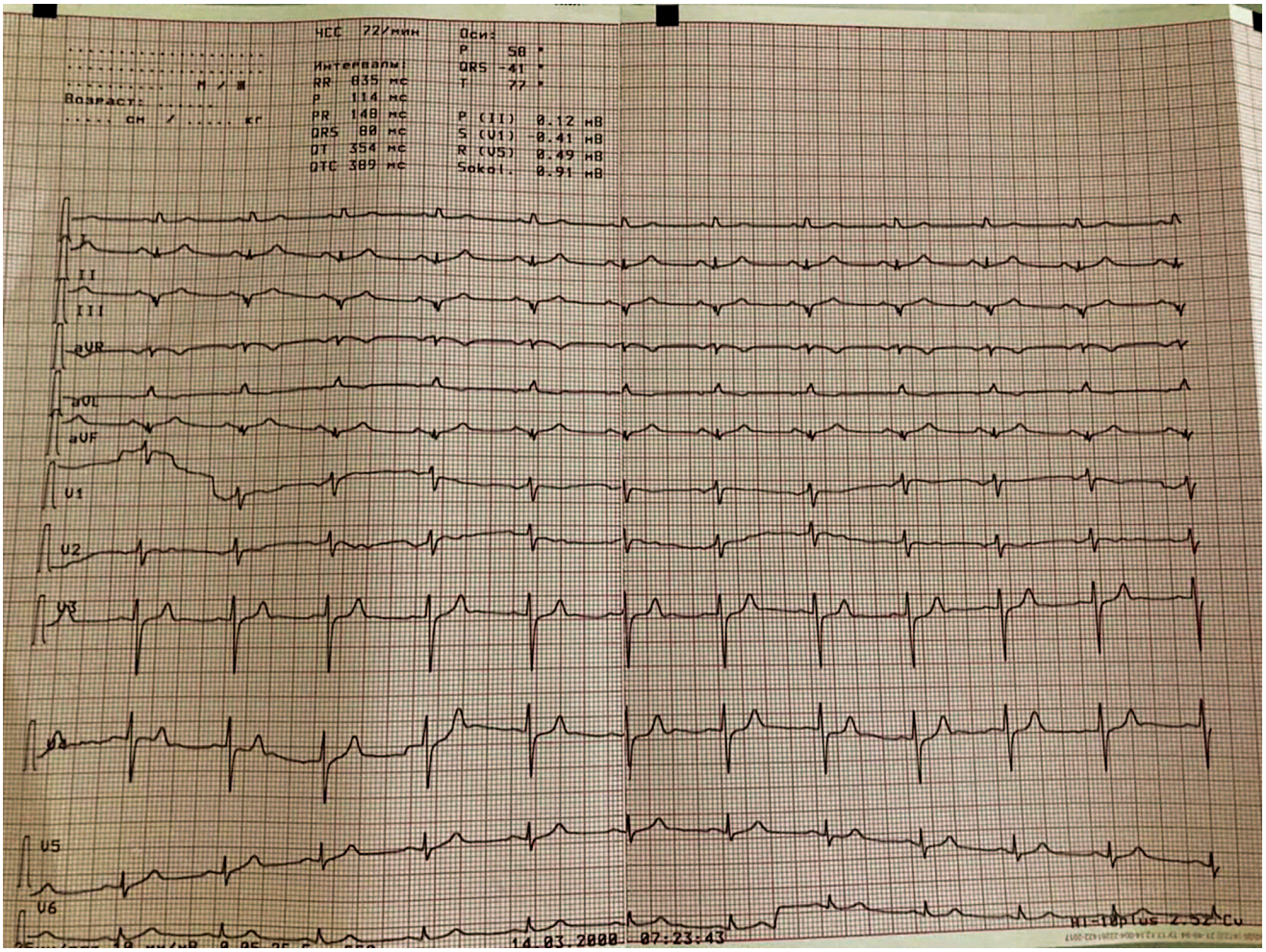

Figure 2. *Electrocardiogram of patient E., 83 years old at admission*

Abdominal ultrasound examination: due to hepatomegaly, both hepatic lobes have numerous mass lesions up to 26 mm with uneven contour, likely to be lot metastatic spread or abscess formation, diffuse changes in pancreas, gall bladder congestion.

US examination of lower extremity veins: signs of vena saphena magna obstruction in the right lower extremity, varicose transformation in branches of the vena saphena magna of lower extremities.

Clinical and instrumental examination results were used to make the *final clinical diagnosis*: *Primary disease*. Ischemic stroke in the bed of the left medial cerebral artery and left posterior cerebral artery, unspecified pathogenetic variant.

Comorbidities: Stage III hypertension, uncontrolled AH. Dyslipidemia. Type 2 diabetes mellitus, target HbA1c level < 7.0 %, very high risk (risk 4).

Primary disease complications: Brain swelling. Dislocation syndrome. Vena saphena magna obstruction in the right lower extremity. Pulmonary embolism. Severe bilateral community-acquired multisegmental pneumonia. Stage III respiratory distress. Sepsis. Hepatic abscesses, cytolytic syndrome, cholestatic syndrome, liver cell failure syndrome. Type 2 myocardial infarction. Killip III pulmonary edema. Multiple organ injury syndrome. Hypochromic anaemia. Thrombocytopenia.

In in-patient settings, the patient was undergoing antibacterial (Cefoperazone + Sulbactam), anticoagulation (nadroparin calcium) and detoxication therapy, corrections of fluid and electrolyte disorders and other symptomatic therapy (Sterofundin, meglumine sodium succinate). The patient was consulted by a haematologist because of a marked increase in leukocytosis and blasts in peripheral blood; it was recommended to consider sternal puncture in order to clarify the nature of LR. However, despite the therapy before the examination, on day 5 of hospitalisation, cardiac arrest was observed; resuscitation was inefficient; and natural death was recorded.

Postmortem examination of the brain showed an area of softening in parietal-temporal-occipital region of the left brain. Near basal ganglia, there were cysts with dark reddish walls 0.1–0.2 cm in diameter; near the right cerebellar hemisphere cortex, there is a cyst with yellowish-brown walls 1.5 cm in diameter. The tissue specimen contains cerebellum tissue with marked perivascular and pericellular swelling, an area of cortex necrosis with a significant plasmocytic macrophagal reaction.

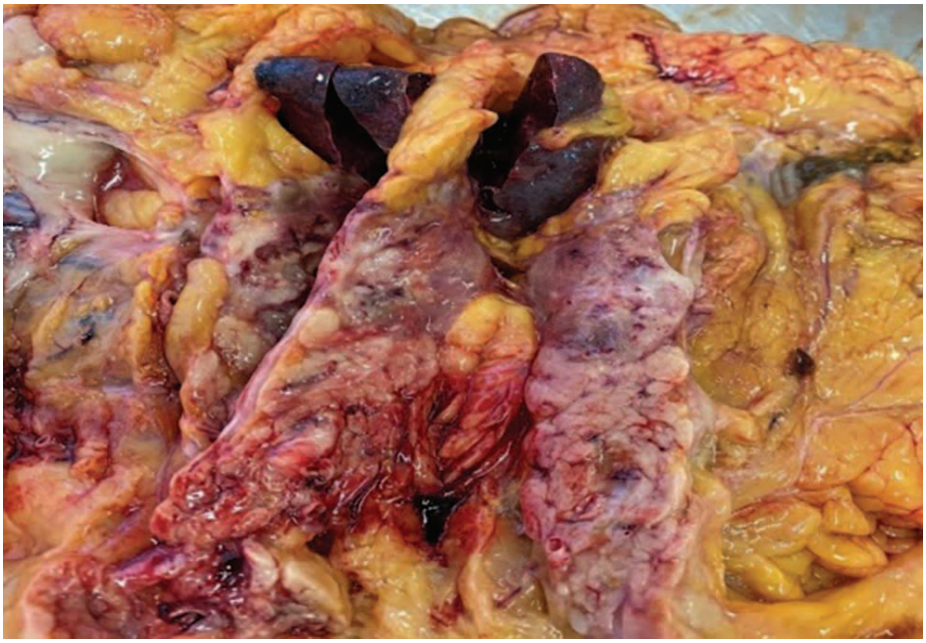

Figure 3. *Pancreatic tumor of the tail with parapancreatic soft tissue and spleen involvement*

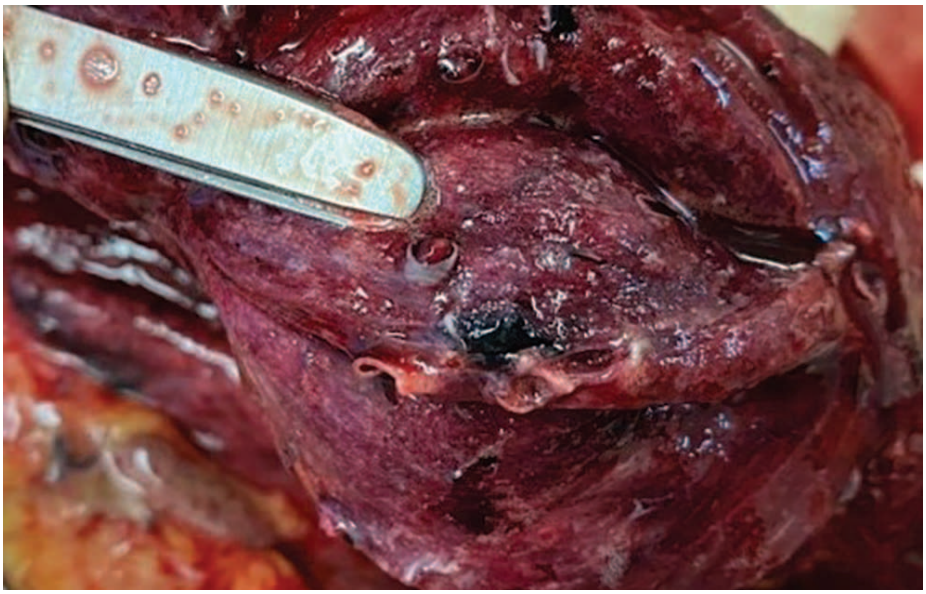

Figure 4. *Thrombus of segmental branches of the right pulmonary artery*

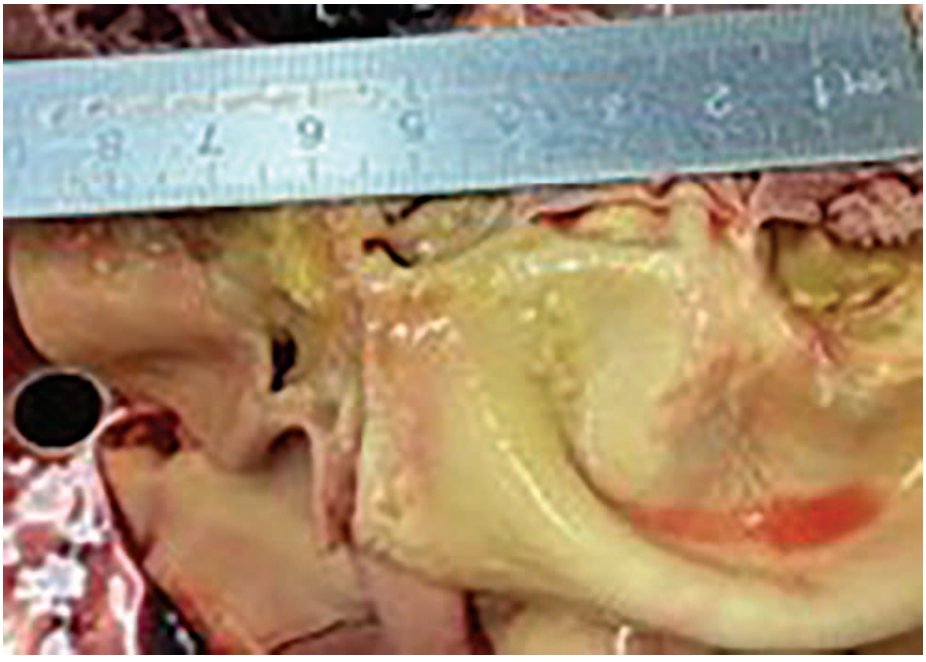

Figure 5. *Vegetations on the aortic valve leaflet*

Pancreas examination: the tissue is dense and elastic, 14.0 × 3.0 × 2.0 cm. Near the pancreatic head, there is grey-pink lobular proliferation with haemorrhaging; near the pancreatic tail, there is an area of dense whitish-grey tissue, 4 × 3 × 4.5 cm, invading adjacent parapancreatic cellular tissue and splenic hilum area, with haemorrhaging; and also whitish areas of 3.0 × 4.0 × 0.7 cm with clear contours and haemorrhaging in 200.0 g splenic pulp. The splenic valve has a dark-cherry blood clot (Figure 3).

Spleen segment histology: marked hyaline degeneration of artery and vein walls, extensive haemorrhaging and necrosis — infarction.

The liver is brown-yellowish with nutmeg pattern and roundish whitish-pink masses in its parenchyma up to 0.5–5 cm in diameter with haemorrhaging and degradation. Para-aortic lymph nodes are dense, enlarged up to 1.0 × 1.0 × 0.5 cm.

The histological examination confirmed high-grade ductal pancreatic adenocarcinoma with metastases to para-pancreatic and para-aortic lymph nodes, lymph nodes in hepatic hilum and parenchyma: adenocarcinoma metastasis with degradation and inflammatory infiltration. Adjacent hepatic tissue has preserved frame and lobular pattern, marked oedema; necrobiosis of hepatic cells; between hepatic cells, there is focal inflammatory infiltration with neutrophils and lymphocytes; portal ducts have marked lymphatic histiocytic infiltration with some segmented neutrophils, sinusoidal repletion and uneven repletion around central veins.

Dark-red and dark-cherry blood clot parts can be seen in the lumen of segmental branches of the right pulmonary artery (Figure 4).

Heart examination: the endocardium of the aortic valve has a greyish wrinkled polypoid mass, tightly fused with the valve cusp, 1.2 × 0.7 × 0.6 cm.

The histological examination shows that the flap of the aortic valve is swollen and has extensive areas of necrosis, parietal blood clots with segmented infiltration (Figure 5).

A microbiological examination of the aortic valve tissue shows Enterococcus faecalis, Klebsiella pneumoniae, Acinetobacter baumannii. A microbiological examination of sputum revealed Acinetobacter baumannii.

Morphological examination: a sample of red bone marrow is represented by three hemopoiesis lineages with haemorrhaging.

According to the postmortem examination results, the cause of death (primary disease) was adenocarcinoma of the tail of the pancreas T3bN1M1 with degradation, invasion of parapancreatic cellular tissue and splenic hilum, with numerous metastases to regional lymph nodes, liver; concurrent diseases — acute infective endocarditis of the aortic valve. Immediate cause of death: sepsis caused by cancer intoxication.

Discussion

This case study describes myeloid LR associated with verified advanced adenocarcinoma of the tail of the pancreas and a concurrent disease — acute infective endocarditis. The patient who was admitted to the hospital with neurological symptoms was diagnosed with signs of severe multiple organ failure, systemic inflammation reaction, septicopyaemia in the form of severe bilateral multisegmental pneumonia, hepatic abscesses, signs of type 2 myocardial infarction and marked leukocytosis 60×10^9/L with left shift to myeloblasts.

The postmortem examination showed high-grade ductal adenocarcinoma of the tail of the pancreas with degradation and metastases to lymph nodes and liver, related to acute infective endocarditis, involving the aortic valve, with sepsis in the form of septicopyaemia and thromboembolism in the systemic and lesser circulation. The resulting severe combined pathology with a potential paraneoplastic component caused the development of a neutrophilic myeloid reaction with a marked left shift and an increase in the relative banded neutrophil count to 94.5 %.

In this case study, it is not possible to make a firm conclusion about the onset of infective endocarditis (IE) and its variant. At the same time, given the extent of the tumour, presence and aggravation of leucocytosis from day 1 of hospitalisation, acute IE is possible, taking into account LR development with patient's condition worsening.

In the absence of life-time signs of vegetation on aortic valve cusps, incomplete correlation of the clinical pattern with the modified Duke criteria, a differential diagnosis of IE includes non-bacterial thrombotic endocarditis (NBTE). Life-time diagnosis of NBTE is challenging, postmortem examinations reveal NBTE only in 1.2–3.4 % of cases [7]. According to retrospective studies, NBTE is diagnosed in 4 % of all patients with advanced solid malignancies; however, its exact incidence is unknown [8]. In a majority of cases, NBTE is associated with adenocarcinoma of lungs, pancreas, stomach and ovaries [9].

The differential diagnosis of NBTE and IE is crucial for optimal management; however, there are no pathognomonic signs which can reliably differentiate between these two conditions. It is essential to take into account a comorbidity or concurrent disease, which can increase the risk of NBTE, especially malignancies. Nevertheless, very often cancer patients have poor immunity as a result of drug therapy or progressing tumour and are at high risk of IE due to frequent vein catherisation. Therefore, the diagnosis of NBTE should include assessment of individual risk factors, clinical, laboratory and instrumental data in order to rule out other pathologies, particularly infective endocarditis and endocarditis with negative blood culture.

Despite the fact that a majority of LR are associated with solid tumours, LR in pancreatic cancer has been

described in a few case studies [10–12]. Patients with paraneoplastic syndrome can have fever, which makes differential diagnosis of LR more difficult and impels to search for an infectious pathology as the most common cause of LR. Various infections should be ruled out in the first place, not only because they are more common than paraneoplastic LR, but because they can limit further therapy of cancer [13].

If a malignancy has no clinical manifestations, tumour-associated leucocytosis can be interpreted as an infection or myeloproliferative disorder, thus resulting in unnecessary diagnostic procedures, including bone marrow biopsy and molecular genetic testing. Reduction in leucocytosis with antitumour therapy can be an indirect sign of therapy efficacy, or can be used as a marker of disease progression in these patients if LR aggravates [14].

Infective endocarditis is very rarely a separate cause of LR. Such LR cases are described in patients with infective marantic (initially non-infective thrombotic) endocarditis related to an oncological disease [11]. At the same time, in the absence of a progressing malignancy, the most common cause of LR is a systemic infectious process. In a retrospective cohort study conducted in a hospital in Porto Alegre (Brazil), among 105 patients, LR was associated with infection in 55 % of cases (mostly infections of lower respiratory tract and urinary tract) [15]. Israeli researchers presented similar results of an assessment of outcomes in 173 hospitalised patients: an infectious process was a cause of LR in 48 % of cases, including sepsis in 9 % of patients [16]. Independent predictors of death were age (odds ratio 2.5, $p = 0.014$) and diagnosed sepsis (odds ratio 3.8, $p < 0.001$) [16].

In microbiological examination of blood samples taken from patients with LR, the most common finding is gram-negative microorganisms; however, a potential pathogen can be Micobacterium tuberculosis in disseminated tuberculosis [17]. In a number of clinical observations, a clostridial infection, including pseudomembranous colitis, was also described as one of the causes of LR [18, 19]. Large retrospective analyses of patients with LR were conducted before COVID-19; however, the novel coronavirus infection can also cause LR, particularly in patients with severe COVID-19 [20].

Conclusion

Therefore, the diagnostic search in LR patients, including elderly and old patients, with initially unclear origin should include cancer alertness; however, it should not neglect assessments for other possible causes, including IE and NBTE, requiring a multidisciplinary approach in intricate diagnostic situations. Prognosis in patients with LR is greatly dependent on the course of the primary disease, and is very poor in cancer-associated LR.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Резник Е.В. (ORCID ID: https://orcid.org/0000-0001-7479-418X): научное руководство, разработка концепции, написание текста рукописи, сбор данных и обработка материала

Батов М.А. (ORCID ID: https://orcid.org/0000-0002-3780-4358): разработка концепции, написание текста рукописи, сбор данных и обработка материала, взаимодействие с редакцией в процессе подготовки публикации и печати

Апарина Т.В. (ORCID ID: https://orcid.org/0000-0001-8431-4397X): доработка текста, итоговые выводы, критический пересмотр статьи на предмет важного интеллектуального содержания

Ким О.В. (ORCID ID: https://orcid.org/0000-0001-8366-555X): сбор данных, доработка текста, итоговые выводы, критический пересмотр статьи на предмет важного интеллектуального содержания

Шурдумова М.Х. (ORCID ID: https://orcid.org/0000-0003-4639-7237): анализ научной работы, доработка текста, итоговые выводы, предоставление иллюстративного материала

Михалева Л.М. (ORCID ID: https://orcid.org/0000-0003-2052-914X): научное руководство, анализ научной работы, доработка текста, итоговые выводы, критический пересмотр статьи на предмет важного интеллектуального содержания

Смирнов А.П. (ORCID ID: https://orcid.org/0000-0002-9979-4140): научное руководство, критический пересмотр статьи на предмет важного интеллектуального содержания

Голухов Г.Н. (ORCID ID: https://orcid.org/0000-0002-0161-005X): научное руководство, организационно-административная деятельность

Author Contribution:

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

Reznik E.V. (ORCID ID: https://orcid.org/0000-0001-7479-418X): scientific supervision, conceptualisation, manuscript writing, data collection and processing

Batov M.A. (ORCID ID: https://orcid.org/0000-0002-3780-4358): conceptualisation, manuscript writing, data collection and processing, liaising with the editorial team in preparation for publication and printing

Aparina T.V. (ORCID ID: https://orcid.org/0000-0001-8431-4397X): revision of the text, final conclusions, critical revision of the article for important intellectual content

Kim O.V. (ORCID ID: https://orcid.org/0000-0001-8366-555X): collecting data, refining the text, finalising conclusions, critically revising the article for important intellectual content

Shurdumova M.Kh. (ORCID ID: https://orcid.org/0000-0003-4639-7237): analysing the research paper, finalising the text, final conclusions, providing illustrative material

Mikhaleva L.M. (ORCID ID: https://orcid.org/0000-0003-2052-914X): academic supervision, analysis of the research paper, revision of the text, final conclusions, critical revision of the article for important intellectual content

Smirnov A.P. (ORCID ID: https://orcid.org/0000-0002-9979-4140): academic supervision, critically reviewing the article for important intellectual content

Golukhov G.N. (ORCID ID: https://orcid.org/0000-0002-0161-005X): academic supervision, critically reviewing the article for important intellectual content, organisational and administrative support

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