

MANAGEMENT OF THE HIV-POSITIVE PREGNANT PATIENT WITH MARKED IMMUNODEFICIENCY AND MULTIPLE COMORBIDITIES


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Increasing HIV prevalence among women and growing numbers of HIV-positive patients who choose to become pregnant prompt a discussion of management strategies applied to such patients. In this work we analyze a case of a pregnant HIV-positive woman with marked immunodeficiency who started seeking medical advice only after she had developed severe life-threatening secondary conditions. We look at the progression of comorbidities that led to the death of the patient and her baby and evaluate the chosen treatment plan. We also propose recommendations for the management of patients with similar pathologies that include psychological care, vigilance against possible atypical progression of a comorbidity, such as tuberculosis, and extensive diagnostic evaluation.

Keywords: HIV-infection, pregnancy, expressed immunodeficiency, secondary diseases, tuberculosis

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ВЕДЕНИЕ БЕРЕМЕННОЙ ПАЦИЕНТКИ С ВИЧ-ИНФЕКЦИЕЙ И МНОЖЕСТВЕННЫМИ ВТОРИЧНЫМИ ЗАБОЛЕВАНИЯМИ НА ФОНЕ ВЫРАЖЕННОГО ИММУНОДЕФИЦИТА


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Возрастающее количество женщин, больных ВИЧ-инфекцией, и рост числа беременностей и родов среди них обуславливают актуальность изучения нетипичных случаев ведения таких пациенток. В настоящей статье проанализированы причины, приведшие к возникновению ситуации, когда беременная женщина с ВИЧ-инфекцией и выраженным иммунодефицитом обратилась за медицинской помощью только при возникновении тяжелых, опасных для жизни вторичных заболеваний. Рассмотрены особенности течения сочетанной с беременностью патологии, приведшей к гибели ребенка и матери. Дана оценка тактики ведения больной, разработаны рекомендации по ведению пациенток с подобными патологиями, а именно: обязательное психологическое сопровождение, настороженность в отношении возможного атипичного течения многих заболеваний, в частности, туберкулеза, максимальное расширение диагностического поиска.

Ключевые слова: ВИЧ-инфекция, беременность, выраженный иммунодефицит, вторичные заболевания, туберкулез

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In recent years, Russia has seen an increase in the number of HIV transmissions in heterosexual sexual contacts, and therefore the share of HIV-positive women grows. In this connection, the problem of pregnancy and HIV combined in one body becomes more urgent: more and more pregnant women from well-off families bear children and more and more HIV-positive women decide against abortion [1–3].

Treating such patients presents certain difficulties. Doctors need to reduce the risk of transplacental transmission of HIV and to keep the expectant mother relatively healthy. Moreover, the woman needs not only to give birth to a healthy baby but also to be able to bring it up. Therefore, women with HIV

undergo highly active antiretroviral treatment with the most advanced, effective and safe drugs and methods [1, 4–6].

Pregnancy is a difficult period in life of any woman, both from physiological and psychological points of view. This is when a woman is emotionally vulnerable and helpless and needs special care and support from others. HIV adds a number of mental state peculiarities and motives to safe the pregnancy to the mix [7]. In particular, research shows that HIV-positive pregnant women treat themselves negatively, believe their social role is low and have conflicting identities that make up the self-concept [8]. In addition, pregnancy in the presence of HIV often results in complications such as preeclampsia, chronic

intrauterine fetal hypoxia, anemia, threatened miscarriage, fetal growth retardation syndrome. For example, a research led by Yatsenko [9] shows that despite ongoing antiretroviral therapy (ART) such conditions were observed in 23.5, 55.0, 23.7, 20.0 and 7.0 % of cases, respectively. HIV-positive women also often deliver preterm and suffer from labor abnormalities. Surgical abdominal delivery, while reducing the likelihood of intrapartum HIV transmission to the child, significantly increases the risk of postpartum sepsis and boosted HIV development in mother's body [10]. Secondary diseases pose special problems. If a woman has a profound immunodeficiency, such diseases threaten both the life of the child and that of her own. Secondary infections are hard to treat, since the drugs chosen need to have the least negative impact on the fetus [11–14].

All in all, treatment strategy for HIV-positive pregnant women is well developed [1, 5, 6, 15, 16]. Its most cases, application of this strategy leads to the birth of a healthy child without harming the mother's health [1, 17]. But there are some complex cases that do not necessarily work out well. Below is a description of one of such cases.

Case description

Patient U., 31 years old, was admitted to hospital infection ward on May 28, 2016, complaints: fever up to 39 °C, weakness, malaise, cough with little phlegm, shortness of breath, loss of appetite, weight loss (6 kg per month), sweating.

Anamnesis shows the acute stage began in late April: fever, body temperature up to 39 °C, dry cough. The patient tried treating the condition with symptomatic drugs, to no effect. May 20–24 2016, patient was treated in hospital following the "community-acquired pneumonia" diagnosis: ceftriaxone, 2 g per day, intramuscularly and pathogenetic therapy. The treatment resulted in a slight improvement but the fever persisted. The patient left the hospital without permission. After 2 days, she started suffering from shortness of breath, fatigue and malaise became worse and May 28 the patient once again came to the hospital and was hospitalized.

Through the q&a session it became clear that patient was pregnant, 14 weeks, but she was not registered with the women consultancy. It was the first pregnancy, desired and in a marriage. In addition, in 2005 the patient was diagnosed with HIV, but, according to her, the hospital staff treated her dismissively and rudely so she reacted negatively and has grown afraid of medical care. Thus, she did not come monitoring examinations all these years and did not receive treatment. In 2015, before the marriage, the patient underwent HIV testing anonymously. According to her, the result was negative, but the report read "Reference value: "negative "; result of HIV RNA PCR: 104,607 copies/ml." That means the patient interpreted the results erroneously. She also had 4 surgeries for congenital abnormalities (cleft palate and lip), the last of which happened in 2005.

The patient's epidemiological anamnesis shows no aggravations.

When admitted to the hospital, her condition was considered moderately grave. The body mass was short (height — 169 cm, weight — 42 kg, BMI = 14.7 kg/m²). Pale skin, mucous oropharyngeal hyperemia, granular back wall. Lymph nodes (submandibular, cervical, axillary, inguinal) enlarged to 0.7 cm, painless, mobile. Respiratory system: sounds from lungs (percussion), hard breathing (auscultation), weak in lower sections, no wheezing. Muffled heart sounds. Coated tongue. Abdomen increased in size (due to pregnancy). Other organs and systems - no abnormalities. CBC revealed

signs of inflammation: neutrophilia (92 %), lymphopenia (6 %), high erythrocyte sedimentation rate (75 mm/h). Blood chemistry analysis revealed hypoproteinemia, small-scale hypertransaminasemia. UA revealed mild case of proteinuria (hereinafter, test results are shown on the figure). The diagnosis: "Viral infection, unspecified, moderately grave. Community-acquired pneumonia? Illness caused by HIV, with manifestations of infectious diseases. Stage 4B, progression without ART. Generalized lymphadenopathy. Cachexia. Pregnancy — 14 weeks." Patient received ceftriaxone 2 g per day intravenously and pathogenetic treatment (incl. infusion).

On May 30, patient's condition deteriorated, she suffered from aggravated shortness of breath, weakness. Liver size increased 2.5 cm. Glucocorticosteroids (dexamethasone 8 mg per day) were added to the treatment plan.

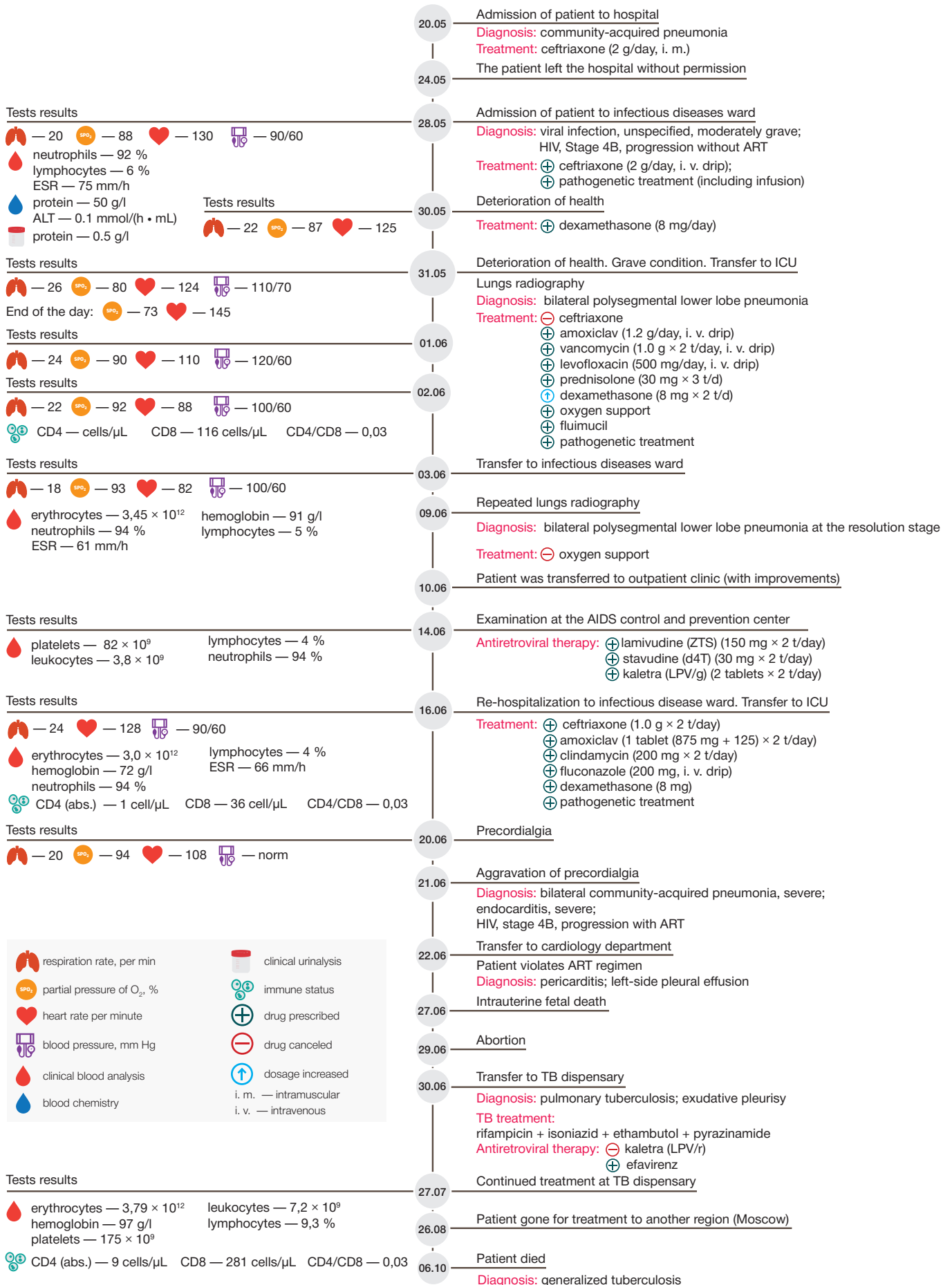
Next day, May 31, brought no alleviation: the patient was short of breath even at rest, suffered from rare dry cough and pains in the left part of the chest. Her condition was regarded as grave. Based on the chest radiograph, the diagnosis was bilateral polysegmental lower lobe pneumonia. Clarified clinical diagnosis was "Illness caused by HIV, with manifestations of bacterial and fungal infections. Stage 4B, progression without ART. Bilateral community-acquired polysegmental pneumonia (pneumocystis?), severe course. RF1. Cachexia. Orofacial candidiasis. Pregnancy — 14 weeks." Changes in the treatment plan: ceftriaxone canceled, prescribed: amoksiklav, vancomycin, levofloxacin, increased doses of corticosteroids, oxygen support, salbutamol inhalations, expectorants (Fluimucil), intensified infusion therapy (dosage and methods of administration are hereinafter shown on the figure). Additional tests were ordered, including sputum collection (no success). Through the day, the patient's condition continued to deteriorate: SpO₂ — 73 %, heartbeat — 145 BPM, urine output decreased to 500 ml/day. Aggravating cardiopulmonary failure brought the patient to intensive care unit.

June 1: patient complains about weakness and cough; condition remains grave but the trend is positive. June 2: body temperature normalized at 36.4 °C. Immunity and virus tests returned as follows: CD4⁺ T-lymphocytes — 4 cells/μL, CD8⁺ T-lymphocytes — 116 cells/μL, CD4/CD8 — 0.03; HIV RNA PCR — 1615358 copies/μL. Tests for markers of viral hepatitis returned negative. Additional consultations given by obstetrician-gynaecologist ("Pregnancy, 14 weeks. No indications for abortion") and phthisiologist ("More data supports bilateral nonspecific pneumonia"). Prescribed: tuberculin skin tests and sputum collection to find *Mycobacterium tuberculosis* (3 times). On June 3 the patient was transferred to the infectious disease ward. Sputum study was not performed due to lack of material.

On June 9 patient began complaining about cough and weakness again. Vital signs were normal, including body temperature. Repeated chest radiograph was the basis for diagnosed bilateral polysegmental lower lobe pneumonia at the resolution stage. Oxygen support was canceled. The next day, following the request of the patient she was transferred to outpatient clinic (with improvements).

On June 14 U. was examined by an infectiologist at the AIDS control and prevention center. The patient complained of dry cough, weakness and body temperature up to 38.5 °C from June 11. Gynecologist confirmed the patient was 16–17 weeks pregnant. CBC revealed thrombocytopenia, leukopenia, lymphopenia and neutrophilia. The patient was prescribed ART (figure). On June 15, her body temperature rose to 40 °C. U. was re-hospitalized at infectious disease ward.

Her condition was regarded as grave when she arrived there. Conditions found at the moment: tachycardia and



Brief clinical record of U., 31, female, pregnant, HIV-positive

low blood pressure; 2 cm liver protrusion from under the costal arch; decreased urine output; anemia, neutrophilia, lymphopenia; increasing lab immunodeficiency. The patient was transferred to the intensive care unit. Prescribed antibiotics — ceftriaxone, amoxiclav, clindamycin, antifungal fluconazole, dexamethasone, pathogenetic drugs. In the following days, the body temperature returned to normal, vital signs were stable, partial oxygen pressure was normal.

June 20: patient started feeling pains in the left part of her chest, body temperature increased again (38.2–38.6 °C). Electrocardiogram revealed sinus tachycardia. The next day, the pains in the chest became stronger. Chest radiograph was the basis for diagnosed bilateral polysegmental lower lobe pneumonia at the resolution stage. Diagnosis: "Bilateral community-acquired pneumonia, severe course. RF1. Infective endocarditis, severe course. Cardiopulmonary failure, stage I–II. Illness caused by HIV, with manifestations of bacterial, fungal infection, stage 4B, progression with ART in the background. Generalized lymphadenopathy. Cachexia. Expressed lab immunodeficiency. Hypochromic anemia. Pregnancy — 16–17 weeks." On June 22, the patient was transferred to cardiology department of somatic ward where the diagnosis was clarified: "HIV-infection, stage 4B, progression with ART in the background. Generalized lymphadenopathy. Bilateral polysegmental pneumonia, severe course. Pericarditis. Left-side pleural effusion. Body mass deficiency over 30 %. Cachexia. Expressed lab immunodeficiency. Hypochromic anemia. Thrombocytopenia. Pregnancy — 16–17 weeks." The patient continued ART course but complained about poor tolerance and was lax with the schedule.

On June 27, ultrasound revealed the fetus was dead. On June 29, the pregnancy was terminated (17–18 weeks). The patient continues to suffer from fever, leukocytosis increases in the blood because of stab cells.

Diagnosis of June 30: "Pulmonary tuberculosis. Pleural effusion." The patient was transferred to TB dispensary where she was prescribed first regimen specific therapy (rifampicin + isoniazid + ethambutol + pyrazinamide). Rifampicin forced a change in ART course: lopinavir/ritonavir was canceled and efavirenz prescribed.

On July 27, the patient continues to receive treatment in the TB dispensary. Clinical diagnosis: "HIV, stage 4B, remission with ART in the background. Disseminated pulmonary tuberculosis, infiltration and decay phase. AFB (–). Tuberculosis polyserositis. Pericarditis. Right-side exudate tuberculosis pleurisy. AFB (+) in exudate. Tuberculous papillitis. AFB (+) in urine. IA (MTB +), dispensary registry group, pneumocystis pneumonia in anamnesis. Persistent oral candidiasis. Expressed lab immunodeficiency." Immunity and resistance to virus-induced effects show a positive trend.

On August 26 the patient was reported to move to another region to seek treatment there (city of Moscow). Therefore, any further data on her disease are not available. However, patient's husband later sent a note stating U. died on October 6. Postmortem diagnosis: "Generalized tuberculosis." Diagnosis according to ICD X: "Illness caused by HIV, with manifestation of mycobacterial infection."

Case discussion

The case described above is not a typical one. From the social status point of view, the patient was quite well off, yet, being aware of her HIV status, she not only refused routine monitoring but postponed applying for medical assistance when it was needed direly. Denial, which is a natural psychological reaction

to expect from a person being informed of a positive HIV test (and which typically resolves into acceptance), stayed with U. for many years. Obviously, the reason behind the situation here is the first experience U. had with doctors, which was negative. Unfortunately, HIV-positive patients often suffer from the same attitude expressed by medical professionals. Our data indicates that up to 64 % of people living with HIV have faced unethical behavior of physicians and 21 % have to bear it often [18].

Same factor may have also contributed to the patient's refusal to register her pregnancy with the women consultancy, which is one of the reasons of its termination. Legislation secures the right of a woman to make decision about motherhood on her own. An HIV-positive woman, like any other, can give birth is she wants to [19]. But HIV imposes certain obligations on her: to bear a healthy baby, she must adhere to recommendations and, above all, take antiretroviral drugs [1, 5, 6]. In the case considered, while the pregnancy, though late, was conscious and desired, the woman was married, she violated the drug regimen. To improve her obedience to the ART regimen, a psychologist should have been invited to counsel U. Interdisciplinary approach to treatment of such patients implies having a psychologist on the team [1]. This patient's psycho-emotional problems were obvious and she needed psychological counseling. Unfortunately, hospitals rarely employ specialists of this profile. The patient received psychological support from her husband, physicians, employees of the medical university.

We believe that the ART regimen chosen in this case was justified. It was necessary not only to prevent vertical transmission of HIV, but also save life of the patient taking into account the marked immunodeficiency (CD4⁺ T lymphocytes — 4 cells/μL). One of the regimens that work well with pregnant women (including zidovudine, lamivudine and lopinavir/ritonavir) could not be applied due to anemia. That is why zidovudine was substituted with stavudine. This regimen belongs to the ART concept used for patients with initially low (less than 50 cells/μL) number of CD4⁺ T-lymphocytes. Choosing lopinavir over efavirenz, which the patient could not tolerate, was quite acceptable, since at this point U. was already in the 2nd trimester of her pregnancy. However, considering the fact that the patient also suffered from tuberculosis and had a low number of CD4⁺ (less than 100 cells/μL) from the outset, national guidelines for dispensary observation and treatment of HIV-positive patients could be followed and a fourth drug, enfuvirtide, added to the mix. It would not harm the fetus but could boost the effectiveness of ART [5, 6].

Pregnancy made the already complicated situation even worse. We believe that hormonal changes associated with pregnancy could exacerbate immunodeficiency, which resulted in further development of secondary infections. The most dangerous of them turned out to be tuberculosis, which lead to the death of the patient.

As is well known, tuberculosis takes an unusual course when there is immunodeficiency in the background [1, 20–22]. With CD4⁺ T-lymphocytes content below 500 cells/μL, the disease develops faster, its destructive forms are more difficult to identify, serous membranes get involved in the pathological process more often. When the content of CD4⁺ T-lymphocytes is below 350 cells/μL, pulmonary tuberculosis is associated with damaged pleura, pericardium, when it is below 200 cells/μL, there can be miliary lymphogenous dissemination with multiple organ lesions expressed through devastating syndrome, fever [1]. All of these symptoms have been observed in patient U. With profound immunodeficiency, (less than 100 CD4⁺ T-lymphocytes/μL) tuberculosis is often (up to 40 % of cases)

accompanied by development of other secondary diseases, which makes it even more difficult to make a diagnosis. Due to the almost complete loss of signs of granulomatous inflammation, in such patients tuberculosis morphologically and clinically resembles pneumonia. In 30 % of cases the clinical picture is 4–8 weeks ahead of dissemination, and in some patients radiography reveals no changes at all [1]. The case in question is a perfect example of such a turn of events. Since acute immunodeficiency makes radiography, tuberculin test and diaskintest uninformative, timely detection of TB requires morphological, direct microscopic and bacteriological, molecular genetic tests of biological fluids and biopsies. But, as this case shows, these tests also do not guarantee a quick result and sometimes simply cannot be performed. Difficulties with diagnostics and a high probability of generalization of tuberculosis when immunodeficiency is substantial indicate that patients with the CD4⁺ T lymphocytes content below 200 cells/ μ L need preventive treatment [6]. We believe that at the very beginning of treatment of patient U. there were good reason to assume she suffered from respiratory system disorders of mixed etiology, including tuberculosis (despite the absence of typical signs on radiographs), and thus consider treating her ex juvantibus.

Pulmonary tuberculosis, which remained unseen in the early stages, could have been boosted by concomitant lesions of *Pneumocystis jiroveci* etiology. Although *Pneumocystis jiroveci* were not found and the diagnosis was not confirmed in laboratory, clinical factors supporting presence of this pathology were gradually increasing respiratory distress (and scarcity of physical findings), high levels of ESR, low rates of the SpO₂ (to 73 %), and positive effect produced by clindamycin and glucocorticosteroids.

Serious polietiological damage to the lungs, namely hypoxia that followed cardiopulmonary disorder, was, in our opinion, one of the main causes of fetal death. An important role was also played by general exhaustion that manifested not only as a significant reduction in body weight, but also as asthenic syndrome, anemia, hypoproteinemia. The risk of spontaneous abortion in this case can be considered very high. But even if the pregnancy was saved, the risk of serious consequences for the health of the child was considerable. According to one study, posthypoxic CNS damage of varying degrees of severity were reported in 90.5 % of children, hematological changes in the form of anemia (mild to moderate) — 97.3 % of children [23]. In the case we are considering here, the woman could not save this pregnancy, regardless of how much she desired

it. The list of medical indications for abortion does not contain HIV, but in some cases, with all the risks taken into account and after a peer review, abortion is possible even after 12 weeks. On the other hand, in this case the operation can substantially harm health of the HIV-positive woman make the main diseases worse [24, 25]. In any case, it is the woman who always makes the choice. This is a difficult decision, and we believe in such situations psychological support is in order.

CONCLUSIONS

The case described above allows a number of conclusions.

Firstly, it is necessary to systematically work on making society treat HIV-positive individuals well. This is especially urgent in medical community, since such work can significantly increase the effectiveness of interactions between doctors and patients and prevent rejection of treatment by patients.

Secondly, treatment of patients with a complex mix of medical, psychological, ethical issues requires psychological support, so hospitals with infectious diseases wards should employ medics of the corresponding profile. Currently, physicians have to play the role psychologists and they do not always have the time and the necessary qualifications. As a recommendation, psychologists can be enlisted as volunteers from the circles of medical professionals, medical students (with the written consent of the patient), family members who are aware of the HIV-positive status of the individual.

Thirdly, successful treatment of HIV-positive pregnant women with severe immunodeficiency requires complete and rapid detection of secondary diseases and addressing them adequately. It is important to remember that very often immunodeficiency means that damage to organs has a number of reasons behind it and develops unusually. Doctors should always be on alert and maximize the spectrum of diagnostic search they perform and use all available methods. Treatment should be adequate. In cases when it is not possible to find the pathogen, the treatment should be empirical, with all the factors take into account. We believe that in some cases ex juvantibus therapy is a justified choice.

Finally, despite all the efforts medical professionals make, success is not always guaranteed. Pregnant women who are HIV-positive should be informed of the possible risks. To evaluate those risks, all the data available should be collected and analyzed. This task can be solved efficiently if the process of collection was automated and introduced to daily routine.

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