Specificities of Clinical Manifestations of Generalized Tuberculosis in Contemporary Conditions

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Abstract: Despite pronounced positive changes in the epidemiology of tuberculosis, generalized forms are still encountered, which pose considerable threat to a patient's life. Similar forms include damage to the lungs and other organs. A significant contribution to the generalization of the tuberculosis process is made by combined effect of tuberculosis and HIV infection. Our goal was to study the clinical manifestations, dynamics and outcomes of treating the generalized forms of tuberculosis as one of the most severe varieties of the tuberculosis process, as well as their relationship with concomitant HIV infection. Sixty-six patients with generalized forms of tuberculosis, who were treated at the state healthcare institution of Saratov Regional Clinical Tuberculosis Hospital from 2016 to 2019, were examined. Medical examination results showed that among patients with generalized forms, HIV-infected young men with newly diagnosed tuberculosis predominated. Of the lung lesions, disseminated and infiltrative forms of pulmonary tuberculosis were most frequently encountered. In patients without HIV infection, generalization of the tuberculosis process was observed mainly in patients with disseminated forms and fibrous cavernous tuberculosis. In patients with concomitant HIV infection, generalization was observed primarily in case of disseminated and infiltrative tuberculosis. In addition to the lungs, the central nervous system and abdominal organs were most frequently affected. Among the lesions of the central nervous system, the most common manifestation was tuberculous meningitis. Multiple lesions (three or more process localization) were diagnosed more often in patients with HIV infection. Most observed cases were drug-resistant tuberculosis. Treatment of patients with generalized tuberculosis lesions was not sufficiently effective.

Keywords: tuberculosis, generalized process, HIV infection, clinical manifestations, forms of tuberculosis, drug resistance, treatment effectiveness.

Introduction

Despite the positive changes in the epidemiology of tuberculosis in the Russian Federation, generalized forms of the process are still encountered, which pose a considerable threat to the patient's life. Similar forms include damage to the lungs and other organs. Over recent years in Russia, there has been an increase in the number and proportion of the patients with HIV-associated tuberculosis. In 2018, they amounted to 25.1%; while in a number of territories, the proportion

of newly diagnosed patients with a combination of tuberculosis and HIV infection reached 44 % [1,2,3]. In particular, there is an increase in the number of tuberculosis patients with advanced HIV infection. Mortality rates in these patients reach high values [4,5]. At the end of 2018, the Saratov region was among 30 regions of the Russian Federation with the highest number of patients, having a combination of tuberculosis and HIV infection (396 people).

The total number of patients with combined HIV-TB pathology in these regions was 88.2 % of all registered in Russia [1]. The combination of tuberculosis and the late stages of HIV infection changed the pathogenesis of the tuberculosis process, shifting it towards alternative inflammation with the loss of typical clinical and radiological symptoms and the development of generalized processes of hematogenous and lymphogenous origins [6]. In recent years, especially in connection with the increase in HIV-associated tuberculosis, tuberculosis with multiple damage to organs and systems is often diagnosed [8]. The most frequent lesion in patients with generalized forms of tuberculosis is localized in the respiratory system (91.4 % of cases) [7]. The situation is aggravated by the spread of drug resistance in the pathogen, especially multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), leading to a decrease in the effectiveness of treatment and an increase in mortality. The clinical recovery rate for patients with active tuberculosis in the Russian Federation is not sufficiently high enough, amounting to 37.3 % [1].

The objective of our research was to study the clinical manifestations, dynamics and outcomes of treatment of tuberculosis generalized forms as one of the most severe varieties of the tuberculosis process, as well as their relationship with associated HIV infection.

Materials and Methods

We observed 66 patients with generalized forms of tuberculosis who received treatment at the state healthcare institution of Saratov Regional Clinical Tuberculosis Hospital from 2016 to 2019. The examination included X-ray and tomographic methods for assessment of respiratory and osteoarticular systems. Computed tomography of the respiratory system, spine, joints, along with magnetic resonance imaging of the brain were performed in accordance with clinical indications. If abdominal organs were suspected for lesions, laparoscopy was used. In the presence of hydrothorax, thoracoscopy and ultrasound of the pleural cavity were performed.

To establish the diagnosis of tuberculosis, a substrate study was used: sputum; lavage fluid; fistulous discharge from the affected lymph nodes; cerebrospinal and pleural fluids. These substrates were examined bacterioscopically (by simple microscopy with Ziehl-Neelsen staining and luminescent method), bacteriologically (culture on solid nutrient media – for example, Löwenstein-Jensen medium, and liquid nutrient media using the BD BACTEC™ method), as well as by means of molecular genetics method (Gene Xpert™ test) with investigation of drug resistance in the pathogen. The diagnosis was verified histologically (affected peripheral lymph nodes, abdominal organs, pleura, and brain substance).

Results and Discussion

Among the examined patients, 41 (61.5 %) people were HIV-infected (study group I), whereas remaining 25 (38.5 %) did not have HIV infection (study group II).

Age distribution of the patients was the following: 20 years old and under (n = 1) person, 21–30 yo (n = 12), 31–40 yo (n = 30), 41–50 yo (n = 15), 51 yo and older (n = 8). In group I, patients with HIV, young people up to 40 years old prevailed (82.5 %), while in group II, on the contrary, the majority of patients (64.0 %) were over 40 years old. By gender, men dominated in both groups, constituting 72.0 % (group I – 72.5 %, group II – 72.0 %). Most patients were first identified (75.3 %). However, number of first identified in group I was higher (87.5 %, *vs.* 56.0 % in group II. Relapses amounted to 12.3 % (5 % in group I *vs.* 24.0 % in group II). Patients with a chronic course of the disease averaged 12.3 % (7.5 % in group I *vs.* 20.0 % in group II).

Distribution by forms of pulmonary tuberculosis was as follows: disseminated tuberculosis prevailed in both groups (on the average – 48.5 %). In group I, it was 46.3 %, while in group II, 52.0 %. Moreover, miliary tuberculosis (4 cases, or 12.5 %) was found only among HIV-infected people. Infiltrative tuberculosis ranged second by frequency of occurrence (31.8 %), but constituted 41.5 % of the patients in group I, while 2.5 times less, or 16.0 %, in group II ($\chi^2 = 4.64$, $df = 1$, $p < 0.05$). In group II, fibrous cavernous tuberculosis predominated (24.0 %), while

in group I, it was observed in 4.9 % of cases. Focal pulmonary tuberculosis and caseous pneumonia tuberculosis occurred at 3.0 % of cases each, whereas tuberculomas were found in 1.5 % of the patients.

The pulmonary process was complicated in 22.7 % of cases: exudative pleurisy was diagnosed in 18.1 % of patients, and tuberculosis of the bronchi and larynx was diagnosed in 4.5 % of cases.

Extrapulmonary lesions were represented by the following localizations. Besides lungs, the first place in the frequency of occurrence was taken by a tuberculous lesions of the central nervous system (47 %): tuberculous meningitis / meningoencephalitis (29 cases) and cerebral tuberculomas (2 cases), followed by abdominal tuberculosis (19.7 %), tuberculosis of peripheral lymph nodes (12.1 %), tuberculosis of bones and joints 10.6 %), and pericarditis (4.5 %).

Extrapulmonary damage to a single organ was observed in 67.6 % of cases: 62.5 % in group I *vs.* 76.0 % in group II. Multiple organs' involvement in the tuberculosis process, besides the lungs, was observed in every third patient (32.2 %). However, multiple lesions (3 localizations) prevailed in patients with HIV infection: 37.5 % in group II *vs.* 24.2 % in group II.

Pulmonary destruction was detected in 38.4% of the cases, moreover, in the group of HIV-infected people, two times less often (27.5%) than in group II (56%), ($\chi^2 = 4.65$, $df = 1$, $p < 0.05$).

Excretion of bacteria was observed in 56.9 % of patients: 1.5 times less often (47.5 %) in HIV-infected patients than in the comparison group (72.0 %).

Drug-resistant strains of MTB (*Mycobacterium tuberculosis* Zopf 1883) prevailed: only 12.3 % were drug-sensitive (11.1 % in the group with HIV infection, 14.2 % in group II), while 28.1 % (33.3 % in group I, 21.4 % in group II) were drug-resistant. The combined number of MDR-TB and XDR-TB cases accounted for 59.3 % of the entire patient pool: 55.5 % of HIV-infected people, and 64.2 % of those without HIV.

The length of hospital stay averaged 78 bed-days: 107 in group I and 31 in group II.

The treatment outcomes were as follows: 26.9 % of the patients recovered (i. e. were effectively treated), improvement was observed in 7.6 % of cases, treatment was not effective in 25.0 % (no improvement), every third patient died (34.6 %), and 5.7 % prematurely interrupted treatment.

Conclusion

Among patients with generalized forms, HIV-infected young men with newly diagnosed tuberculosis predominated. Of the lung lesions, disseminated and infiltrative pulmonary tuberculosis were most frequently encountered. In patients without HIV infection, generalization of the tuberculosis process was observed mainly in patients with disseminated forms and fibrous cavernous tuberculosis. In patients with concomitant HIV infection, generalization was observed mainly in case of disseminated and infiltrative tuberculosis.

Besides lungs, the central nervous system and abdominal organs were most often affected. Of the CNS lesions, the most common manifestation was tuberculous meningitis or meningoencephalitis. Multiple lesions (three or more localizations of the process) were diagnosed more often in patients with HIV infection. Most cases were drug-resistant tuberculosis. Treatment of patients with generalized tuberculosis lesions was not sufficiently effective.

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