X-RAY DIAGNOSTICS OF TUBERCULOSIS IN THE SCREENING OF PATIENTS WITH HIV INFECTION

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ABSTRACT

Background. *The main method of screening of patients with HIV infection to detect pulmonary tuberculosis is X-ray diagnostics. A comparative assessment of changes in lung tissue in different methods of X-ray diagnostics and at different levels of $CD4^+$ cells seems relevant.*

The aim of the study. *To compare plain radiography and computed tomography of the lungs as screening methods for detecting tuberculosis in patients with HIV infection at various stages of immunosuppression.*

Material and methods. *396 patients with HIV registered at the AIDS Center were examined using plain lung radiography (PLR) and computed tomography (CT). To search for mycobacterium tuberculosis, we used bacterioscopy of a smear with Ziehl – Neelsen staining; HAIN-GenoType MTBDRplus technique; inoculation of BACTEC MGIT 960 liquid media; inoculation of Löwenstein – Jensen dense medium. Statistical processing of numerical material was carried out using the Statistica 5.5 program with a significance level $p \leq 0.05$; Pearson χ^2 criterion was used for the analysis of qualitative features.*

Results. *When comparing the results of PLR and CT, the differences were found. When using PLR, the focal lung lesions were described more often ($\chi^2 = 40.79$; $p = 0.00001$), according to CT data, they turned out to be fibrosis ($\chi^2 = 2.33$; $p = 0.1269$). When comparing the PLR and CT data, the differences were obtained in the reporting of pulmonary fibrosis ($\chi^2 = 20.78$; $p = 0.00001$), focal lung lesions ($\chi^2 = 40.79$; $p = 0.00001$), dissemination ($\chi^2 = 9.16$; $p=0.0025$).*

Conclusion. *When screening HIV-infected patients (at the standard of using plain radiography twice a year) it should be taken into account that CT provides more precise differentiation of focal lung lesions and pulmonary fibrosis, earlier detection of dissemination syndrome and ground-glass, especially at severe immunodeficiency with a decrease in $CD4^+$ T lymphocytes down to 200 cells and less. Timely appointment of CT study will improve the effectiveness of tuberculosis detection at the stage of screening in AIDS centers.*

Key words: *plain radiography, computed tomography, tuberculosis, HIV infection*

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ЛУЧЕВАЯ ДИАГНОСТИКА ТУБЕРКУЛЁЗА В СКРИНИНГЕ ПАЦИЕНТОВ С ВИЧ-ИНФЕКЦИЕЙ

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РЕЗЮМЕ

Обоснование. *Основным методом скрининга ВИЧ-инфицированных пациентов для выявления туберкулёза лёгких является лучевая диагностика. Сравнительная оценка изменений в лёгочной ткани при различных методах лучевой диагностики и различном уровне $CD4^+$-клеток представляется актуальной.*

Цель исследования. *Сравнить обзорную рентгенографию и компьютерную томографию лёгких как методы скрининга по выявлению туберкулёза у пациентов с ВИЧ-инфекцией с различными стадиями иммуносупрессии.*

Материал и методы. *Методами обзорной рентгенография лёгких (ОРГ) и компьютерной томографии (КТ) обследованы 396 пациентов с ВИЧ, состоящих на учёте в СПИД-центре. Для поиска микобактерий туберкулёза применялись бактериоскопия мазка с окраской по Цилю – Нильсену; методика по HAIN-GenoType MTBDRPlus; посев на жидких средах BACTEC™ MGIT™ 960; посев на плотных средах Левенштейна – Йенсена. Статистическую обработку числового материала проводили с использованием программы Statistica 5.5 с уровнем значимости $p \leq 0,05$; для анализа качественных признаков использовали критерий χ^2 (Пирсона).*

Результаты. *При сопоставлении результатов ОРГ и КТ отмечены различия. При ОРГ чаще описывались очаговые тени ($\chi^2 = 40,79$; $p = 0,00001$), которые по данным КТ оказались фиброзом ($\chi^2 = 2,33$; $p = 0,1269$). При сравнении данных ОРГ и КТ получены отличия в описании фиброза лёгочной ткани ($\chi^2 = 20,78$; $p = 0,00001$), очаговых теней ($\chi^2 = 40,79$; $p = 0,00001$), диссеминации ($\chi^2 = 9,16$; $p = 0,0025$).*

Заключение. *При проведении скрининга ВИЧ-инфицированных пациентов (при стандарте применения обзорной рентгенографии 2 раза в год) необходимо учитывать, что КТ позволяет чётче дифференцировать очаговые тени и фиброз лёгочной ткани, раньше выявлять синдром диссеминации и «матовое стекло», особенно при выраженном иммунодефиците при снижении $CD4^+$ Т-лимфоцитов менее 200 клеток. Своевременное назначение КТ позволит повысить эффективность выявления туберкулёза на этапе скрининга в центрах СПИД.*

Ключевые слова: *обзорная рентгенография, компьютерная томография, туберкулёз, ВИЧ-инфекция*

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OBJECTIVES

The HIV infection epidemic situation in Russia, with an emerging trend towards improvement, still remains dramatic [1–2]. Significant achievements in reducing population morbidity and mortality from tuberculosis (TB) with a high prevalence of HIV infection in Russia reduce the stabilization rate of the tuberculosis situation [3]. HIV infection has become the most significant risk factor for activation of latent tuberculosis infection caused by *M. tuberculosis* [4]. This situation is largely proven by the spread of tuberculosis among HIV-infected people (TB/HIV). During the period from 2005 to 2018, the incidence of TB/HIV in Russia increased 4 times – from 2.1 to 8.5 per 100 thousand population – and was accompanied by a significant increase in the number of deaths, which was due to the late detection of HIV infection, when the course of the disease acquired a severe and sometimes irreversible character [5].

Currently, the majority of patients with HIV infection are observed in the AIDS centers, where check-ups allow for the timely tuberculosis detection. In general healthcare centers, when dealing with symptoms of lung disease, both tuberculosis and HIV infection can be detected for the first time [6, 7].

A method of tuberculosis screening in patients with HIV infection is X-ray diagnostics, carried out twice as often as in the general population (twice a year). Radiologic changes are still the most informative, since they allow detecting local forms of tuberculosis in varying degrees of severity and localization in 100 % of cases when examining the lungs. Increasingly, in AIDS centers, computed tomography (CT) is currently being used as screening, which makes it possible to increase the informative value of the study. The revealed during X-ray diagnostics changes are not specific and may be characteristic of other lung diseases. If changes are detected on the X-ray and/or CT, a diagnostic minimum examination for tuberculosis is performed. It is important to prove the specificity of the process by detecting *Mycobacterium tuberculosis* (MBT) [7–10].

Clinical and radiological manifestations of the tuberculosis process in patients with HIV infection depend on the degree of immunosuppression. At advanced stages of immunodeficiency, the nature of inflammation changes, and generalization of the process is possible [11–13].

Tuberculosis combined with HIV infection is characterized by atypical manifestations, including X-ray ones, which complicates diagnosis [14, 15]. In severe immunodeficiency (CD4 < 100 cells/μL), clinical symptoms are 4–8 weeks ahead of the appearance of dissemination; in most patients, changes characteristic of tuberculosis cannot be detected on the X-ray [3].

During the initial exam of X-ray images, the radiologist suspects tuberculosis in 34.5 % of cases; at the same time, characteristic changes for the early process stages are noted only in 20.7 % of patients [5, 16].

The features of HIV-associated tuberculosis are constantly being studied by both Russian and foreign authors. There are contradictions about the frequency of bacterial excretion in such patients; most authors note difficulties in verifying the diagnosis [17]. Determining the role of X-ray diagnostics among the methods of detecting tuberculosis in HIV-positive individuals is considered as an important aspect [18].

THE AIM OF THE STUDY

To compare plain radiography and computed tomography as screening methods for detecting tuberculosis in HIV infected-patients with various stages of immunosuppression.

MATERIALS AND METHODS

Study design. A retrospective non-randomized study was performed within 2019–2020. The subjects of the study were 396 patients of both genders meeting the inclusion criteria, aged 25 to 65 years (average age – 40.95 ± 8.02 years).

Compliance criteria. The inclusion criteria for this study were: age 18 and older, diagnosis of HIV infection, and follow-up care at the AIDS center.

Procedure situation. The study included patients undergoing follow-up care at the Samara Regional Center for the Prevention and Control of AIDS and Infectious Diseases.

Recording outcomes methods. The study included patients consulted by a phthisiatrician at the AIDS Center. A standardized questionnaire including data on HIV infection and tuberculosis infection was filled out by all patients (by continuous sampling method), and the results of annual plain lung radiography (if available) were taken into account. Before the study, all patients underwent plain lung radiography (PLR) in two anatomical projections and computed tomography. MBT was searched in sputum and/or bronchoalveolar fluid (in case of bronchoscopy) of the patient. To detect MBT in all patients, sputum smear bacterioscopy techniques (BALG, bronchoalveolar lavage) with Ziehl – Neelsen staining, a molecular genetic method based on hybridization technology (HAIN-GenoType MTBDRplus), liquid media inoculation in the automated BACTEC™ MGIT™ 960 system, inoculation of Löwenstein – Jensen dense medium were used. Data for the analysis were entered into an MS Excel spreadsheet (Microsoft Corp., USA) and did not contain any personal data of the study subjects [19].

Ethical review. Written informed consent was obtained from each study participant before performing the procedures. The research protocol was approved by the Bioethics Committee of the Samara State Medical University of the Ministry of Health of the Russian Federation (Protocol No. 211 dated October 7, 2020).

Statistical analysis. Statistical data processing was carried out using Statistica 10 software package (StatSoft Inc., USA). Normality verification of the quantitative parameters distribution was carried out using the Kolmogorov – Smirnov test. For quantitative parameters in the compared groups, the arithmetic mean and root-mean-square (standard) errors of the mean (M ± m) were estimated,

and confidence interval limits (CI) were calculated. Qualitative features were analyzed by examining their frequencies through contingency tables using a chi-squared test χ^2 (Pearson's test). The critical value of the statistical significance level when testing the null hypotheses was taken to be 0.05. If the achieved level was exceeded, the null hypothesis was accepted.

RESULTS

A survey of 396 HIV-infected patients who had been registered at the AIDS Center for at least a year was conducted. A quarter of them (24.24 %) were with severe immunosuppression – the number of $CD4^+$ cells < 50 cells/μL (Table 1).

TABLE 1

DISTRIBUTION OF PATIENTS WITH HIV INFECTION BY LEVEL OF $CD4^+$ T LYMPHOCYTES

Level of $CD4^+$ T-cells, cells/μL	Total	
	abs.	%
< 50	96	24.24
50–99	53	13.38
100–199	75	18.94
200–349	76	19.19
350–499	28	7.07
> 500	68	17.17

The phthisiatrician consulted 396 patients. Male were the majority – 263 (66.4 %); female – 133 (33.6 %); average age – 40.57 ± 0.39 years (95% CI: 39.80–41.34). 250 (63.1 %) were unemployed of working age, 52 subjects had a profession and worked in their own specialist areas (13.1 %); the rest had casual employment. The most frequent route of HIV infection is through the injecting drugs use (IDU) – 57.6 % of all cases ($\chi^2 = 18.18$; $p = 0.00001$).

The limitation of HIV infection detection within three years was registered in 55 % of all cases ($\chi^2 = 8.08$; $p = 0.0045$); in other patients — more than three years. The majority of patients (75 %) were registered in the last 3 years ($\chi^2 = 70.32$; $p = 0.00001$).

When comparing the results of the plain lung radiography with the computed tomography data, differences in the reporting were noted. Focal lung lesions ($\chi^2 = 40.79$; $p = 0.00001$) were more often described during the plain lung radiography, which, according to CT data, in some cases were assessed as limited fibrosis ($\chi^2 = 2.33$; $p = 0.1269$). The preliminary diagnosis of focal tuberculosis with the reporting of a focal lung lesion on the X-ray was cancelled after CT examination in 12 patients. According to the CT, some changes interpreted as focal lung lesions were assessed as normal or fibrosis. As per the CT, the dissemination syndrome was detected much more often ($\chi^2 = 9.16$; $p = 0.00.259$) (Table 2). When comparing X-ray and CT data, statistically significant differences were obtained in the reporting of pulmonary fibrosis ($\chi^2 = 20.78$; $p = 0.00001$), focal lung lesions ($\chi^2 = 40.79$; $p = 0.00001$), dissemination ($\chi^2 = 9.16$; $p = 0.0025$ (Pearson's test)).

Patients examined for tuberculosis were classified depending on changes in lung tissue according to CT scans of the chest organs (chest CT) and CD4 cell levels (Table 3). Lung tissue dissemination was observed in 39 % of cases in patients with level of CD4 cells < 50 cells/μL; in half of the cases, changes in the X-ray were not detected due to low contrast. When reported on chest CT, these changes were interpreted as "ground-glass", which is a "signal" of the dissemination syndrome. As the level of CD4 cells increased, lung tissue dissemination was less common. Lung tissue changes in the form of infiltration focus were found in 30 % of cases ($n = 43$) in patients with CD4 cells < 50 cells/μL level. At follow-up diagnosis, 72.1 % of patients from this group ($n = 31$) were diagnosed with pulmonary tuberculosis. The majority of patients (73.5 %; $n = 50$) from the group with CD4 cells > 500 cells/μL

TABLE 2

RESULTS OF PLAIN RADIOGRAPHY AND COMPUTED TOMOGRAPHY

Changes in lung tissue	PLR	CT	Pearson's test (χ^2; p)
Focal lung lesion	91 (22.98 %)	27 (6.82 %)	$\chi^2 = 40.79$; $p = 0.00001$
Limited dimming (focus)	167 (42.17 %)	146 (36.87 %)	$\chi^2 = 2.33$; $p = 0.1269$
Lung tissue dissemination	22 (5.56 %)	51 (12.88 %)	$\chi^2 = 9.16$; $p = 0.0025$
Rounded lesion in the pulmonary field	3 (0.76 %)	3 (0.76 %)	$\chi^2 = 0.00$*; $p = 1.0000$
Pleural effusion	6 (1.52 %)	6 (1.52 %)	$\chi^2 = 0.00$*; $p = 1.0000$
Limited fibrosis	37 (9.34 %)	83 (20.96 %)	$\chi^2 = 20.78$*; $p = 0.00001$
Norm (without pathology)	70 (17.68 %)	80 (20.20 %)	$\chi^2 = 0.82$*; $p = 0.3645$
Total	396	396	

Note. * – Pearson's chi-square test with Yates' correction for continuity.

level were not diagnosed with pulmonary tuberculosis upon further examination.

According to the results of a complete physical examination by a phthisiatrician, 174 patients were diagnosed with tuberculosis. Among the active forms of pulmonary tuberculosis, infiltrative – 63.8% of cases ($\chi^2 = 17.66$; $p = 0.00001$) and disseminated – 26.4% of cases ($\chi^2 = 58.00$; $p = 0.00001$) were more common (Table 4).

TABLE 3

DISTRIBUTION OF CHANGES IN LUNG TISSUE ON CHEST CT BY THE LEVEL OF CD4 CELLS IN PATIENTS EXAMINED FOR TUBERCULOSIS

Changes in lung tissue according to chest CT	Level of CD4⁺ T-cells, cells/μL					
	< 50	50–99	100–199	200–349	350–499	> 500
Focal lung lesion (*n* = 27)	7 (26.0 %)	2 (7.4 %)	4 (14.8 %)	10 (37.0 %)	–	4 (14.8 %)
Limited dimming (focus) (*n* = 146)	43 (29.0 %)	20 (13.7 %)	38 (26.0 %)	15 (10.8 %)	10 (6.8 %)	20 (13.7 %)
Lung tissue dissemination (*n* = 51)	20 (39.2 %)	13 (25.5 %)	7 (13.7 %)	10 (19.6 %)	1 (2.0 %)	–
Rounded lesion in the pulmonary field (*n* = 3)	–	–	1 (33.3 %)	–	–	2 (66.7 %)
Pleural effusion (*n* = 6)	–	3 (50.0 %)	1 (16.7 %)	1 (16.7 %)	1 (16.7 %)	–
Limited fibrosis (*n* = 83)	12 (14.5 %)	5 (6.0 %)	12 (14.5 %)	23 (27.7 %)	9 (10.8 %)	22 (26.5 %)
Without pathology (*n* = 80)	14 (17.5 %)	10 (12.5 %)	12 (15.0 %)	17 (21.3 %)	7 (8.7 %)	20 (25.0 %)
Total (*n* = 396)	96 (24.2 %)	53 (13.4 %)	75 (18.9 %)	76 (19.2 %)	28 (7.1 %)	68 (17.2 %)

TABLE 4

CLINICORADIOLOGIC DIAGNOSES

Total	Diagnosis	abs. (*n* = 396)	%
Active pulmonary tuberculosis (*n* = 174)	Disseminated tuberculosis	46	26.44
	Infiltrative tuberculosis	111	63.79
	Focal tuberculosis	17	9.77
No evidence of pulmonary tuberculosis (*n* = 222)	Residual changes of tuberculosis (calcifications, pneumofibrosis)	13	5.86
	Community-acquired pneumonia	53	23.87
	Pleurisy	6	2.70
	Fibrosis	70	31.53
	Without pathology	80	36.04

TABLE 5

DISTRIBUTION OF LUNG TISSUE INJURY VOLUME ON CT BY THE LEVEL OF CD4 CELLS IN PATIENTS WITH CONFIRMED PULMONARY TUBERCULOSIS

Lung tissue injury volume according to chest CT	Level of CD4⁺ T-cells, cells/μL					
	< 50	50–99	100–199	200–349	350–499	> 500
Bilateral lesion (*n* = 84)	38 (45.2 %)	13 (15.5 %)	14 (16.7 %)	13 (15.5 %)	1 (1.2 %)	5 (5.9 %)
Destruction (*n* = 57)	23 (40.4 %)	9 (15.8 %)	8 (14.0 %)	8 (14.0 %)	1 (1.8 %)	8 (14.0 %)

TABLE 6

RESULTS OF DIAGNOSTIC METHODS OF MYCOBACTERIUM TUBERCULOSIS DETECTION

Methods (number of studies)	Number of positive results	
	abs. (*n* = 116)	%
Bacterioscopy of a smear with Ziehl – Neelsen staining (*n* = 396)	44	37.93
HAIN-GenoType MTBDRPlus (*n* = 396)	56	48.28
Bactec™ MGIT™ 960 (*n* = 396)	99	85.34
Inoculation of Löwenstein – Jensen dense medium (*n* = 396)	97	83.62

According to chest CT, bilateral lung lesion prevailed (45.2 %; *n* = 38) in patients with the level of CD4 cells < 50 cells/μL (Table 5). This group also had the largest number of cases of lung tissue destruction – 40.4 % (*n* = 23) – in patients who had not been examined for more than 3 years (16.2 %).

The diagnosis was considered verified in case of confirmation of MBT presence by various methods in 116 (66.6 %) patients (Table 6).

DISCUSSION

HIV-infected patients are a medical risk group for tuberculosis, with adolescents and adults required to undergo fluorography examination twice a year. In HIV-infected subjects, X-ray changes in the lungs with tuberculosis may be similar to other secondary and opportunistic diseases, making it difficult for radiologists to interpret the skiagram [3].

The manifestation and course of tuberculosis in patients with HIV infection differ significantly from its onset and course in subjects with a healthy immune system. As the number of $CD4^+$ lymphocytes decreases to a level of < 200 cells/μL, active fluorographic detection of respiratory tuberculosis is not justified; tuberculosis often has a generalized nature with synchronous lesions of several systems and organs. HIV-associated immunosuppression is characterized by a pleuropneumonia-like clinical picture, often with an acute onset, rapid and intensive disease development. The sensitivity of immunological tests also decreases in proportion to the degree of immunodeficiency.

When monitoring patients with HIV infection, difficulties in diagnosing tuberculosis often appear at stage 4. The level of immunosuppression is important in characterizing changes in the lungs. According to the majority of authors, when the level of CD4 lymphocytes is > 200 cells/μL, compared with the level of CD4 ≤ 200 cells/μL, the frequency of such radiological signs characteristic of the tuberculosis process during computed tomography of the chest organs as alveolar infiltration, destruction of lung tissue decreases, and the frequency of atypical manifestations increases (interstitial changes similar to "ground glass") [7]. According to the results of the study, all identified syndromes were assessed as characteristic of the tuberculosis process. In case of severe immunodeficiency, the volume of lung tissue injury increases in the form of a manifestation of bilateral dissemination and destruction, which indicates the process progression.

To detect pulmonary tuberculosis in adults, the most informative screening method is still plain lung radiography. Its insufficient information content in HIV-infected patients with severe immunosuppression can lead to the omission of pathology, especially with negative bacterioscopy data. Computed tomography as a more highly informative method allows to improve the quality, but given the high economic component for screening, it can be used differentially at the level of the AIDS center before referral to the TB dispensary, which can reduce the number of unjustified referrals and reduce the risks of infection of patients without tuberculosis and, conversely, accelerate the appointment of in-depth diagnostics in the specialized TB service. An integrated approach at the screening stages will prevent the development of progressive forms of tuberculosis in patients with HIV infection.

CONCLUSION

According to the Order of the Ministry of Health of the Russian Federation dated 21.03.2017 No. 124n "On approval of the procedure and timing of preventive medical examinations of citizens to detect tuberculosis", persons with HIV infection are classified to the group subject to preventive examination twice a year. To date, X-ray diagnostics in HIV-infected patients remains the key method of screening, forming a group for in-depth diagnosis of pulmonary tuberculosis. Computed tomography is mandatory if there is any doubt concerning the interpretation of changes on the plain lung radiography, especially in febrile HIV patients with severe immunosuppression in the absence of changes on the plain lung radiography of the chest organs and $CD4^+$ lymphocyte levels below 200 cells/μL.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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ЛИТЕРАТУРА

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