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DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIAL INFECTION

Annotation: After the discovery of the causative agent of tuberculosis by R. Koch, clinicians had the opportunity to diagnose it etiologically. The detection of the causative agent of Mycobacterium tuberculosis (MTB) in biological media is assessed as a reliable confirmation of the diagnosis of tuberculosis infection [1]. The material for verifying the diagnosis of pulmonary tuberculosis is respiratory (sputum, bronchoalveolar lavage fluid, BAL) and other (operational, biopsy) diagnostic material obtained from pathological Hearth. The main reason for the absence of the causative agent of tuberculosis in the respiratory material is its insignificant amount in the focus of inflammation. It should be noted that in a pathological process in the lungs not related to the bronchi, and/or in the presence of their structural deformities or obstruction, there is also an obstacle to the detection of the pathogen in the respiratory material. In such situations, it is difficult or impossible to obtain diagnostic material and pathogen for microbiological research using traditional methods, and to make a diagnosis, the doctor has to be guided mainly by epidemiological, clinical and radiological data, the results of biochemical, immunological and molecular genetic studies with an assessment of these changes in dynamics [2, 3]. Due to the importance of diagnosing pulmonary tuberculosis even in the absence of bacterial excretion in patients, we collected and analyzed literature data on additional methods and methods for obtaining samples of material for microbiological and other studies in order to detect tuberculosis. In the course of the literature search, an analysis of methods that allow indirectly judging the presence of the causative agent of tuberculosis (for example, immunological and radiation methods) was carried out. including the use of mathematical modeling. We have analyzed the methods and methods available in phthisiatric practice for diagnosing pulmonary tuberculosis with unproven bacterial excretion in the presence of clinical and radiological signs of the activity of the process in patients.

Key words: Tuberculosis, diagnosis, T-lymphocytes, clinical, immunological,

A search for publications was carried out and the results of scientific research on methods of diagnosing tuberculosis were analyzed, including a description of methods for obtaining biological material to search for an etiological factor. The search was carried out by keywords: tuberculosis diagnosis, unproven bacterial excretion, paucibacillary tuberculosis. Electronic databases of medical information were used: MEDLINE/PubMed and e-Library in the period from February 1 to April 1, 2021. The recommendations of the World Health Organization (WHO) on the possibility of using Xpert MTB/RIF Ultra in the diagnosis of pulmonary tuberculosis in the diagnosis of unproven bacterial excretion were studied [4] the term "paucibacillary tuberculosis" (oligobacillary tuberculosis) has been introduced in foreign publications. In the International Classification of Diseases, some clinical situations were coded as A16 (tuberculosis of the respiratory system, not confirmed bacteriologically and histologically) with subsequent clarification of their presence and results (A16.0 – A16.9). Particular attention was paid to situations coded as A15.2 and A15.3, in which the use of invasive diagnostic manipulations was justified. However, the slow growth of the tuberculosis pathogen and the long time it takes to determine the drug susceptibility of TB to antituberculous drugs pose problems both for the diagnosis and for the selection of optimal therapy [2]. According to the

federal statistical reporting (f. 33), in the Russian Federation in 2018, bacterial excretion was recorded in only 52.3% of patients with newly diagnosed tuberculosis. Among patients with human immunodeficiency virus (HIV) co-infection, pulmonary tuberculosis with negative sputum results based on cultured methods for the presence of MBT was found in every second registered case of the disease [5]. The proportion of such patients, depending on the quality of the bacteriological laboratory in the TB dispensary, varied from 18% to 30% [5]. In the practice of a phthisiologist the absence of bacterial excretion in pulmonary tuberculosis with clinical, laboratory and radiological signs of the activity of the process is explained by various reasons. The authors analyzed the terms and concepts that are used in foreign and domestic publications to differentiate situations depending on the reasons that explain the absence of bacterial excretion in the presence of signs of the activity of the tuberculosis process. As a result, two groups of clinical situations were formed: forms of pulmonary tuberculosis with unproven bacterial excretion in the presence of clinical, laboratory and radiological signs of the activity of the process and a negative result of sputum smear microscopy for MBT, but with positive results of cultural studies in the form of a scanty increase in MBT. In foreign literature, this situation corresponds to the terms: "paucibacillary tuberculosis" and "tuberculosis with oligobacillary isolation of MBT". In such situations, the pathological process developed with a sufficient potential of local immunity and a predominance of productive reactions in response to tissue damage [6]; forms of pulmonary tuberculosis with unproven bacterial excretion against the background of signs of activity of the process with a negative result of microscopic and cultural methods of examination, but in the presence of anatomical, functional features of the bronchopulmonary system, as well as with the localization of granulomas, which prevents (does not contribute) to the formation of a connection between the pathological focus and the environment. the use of invasive techniques. The fact of the absence of sputum or its weak production complicates the process of etiological confirmation of the diagnosis. In such cases, bronchoscopy is performed in combination with BAL. Sometimes, during bronchoscopy, a biopsy of tissue taken from the focus is additionally performed [7]. The liquid obtained in the BAL process was subjected to study, including the use of molecular genetic methods (for example, using the GeneXpert test), which made it possible to detect MBT DNA in the obtained material. For example, patients with negative sputum microbiological results during bronchoscopy with BAL from the affected area showed a 60% increase in the quality of etiological diagnosis (95% confidence interval (CI) 43.6–74.5), while in 14.3% of cases, multidrug-resistant/extensively resistant MBT (MDR/XDR) was detected [8] followed by a change in chemotherapy. Another method of obtaining material to confirm the presence of MBT was sputum induction performed by ultrasonic nebulization of hypertonic saline [9]. According to the authors' data [1], in HIV-infected patients with difficulties in sputum separation, the induction procedure provided a twofold increase in the number of cases of TB detection by culture. For the second type of clinical situations, the diagnosis was based on methods that made it possible to indirectly judge the infection, and in some situations it was necessary to resort to biopsy (surgery) in order to obtain material for subsequent studies. In vivo and in vitro immunological tests indirectly reflected the presence of the tuberculosis pathogen in the body by assessing the intensity of the production of interferon γ and T-lymphocytes in response to stimulation by specific proteins (ESAT-6, CFP-10). For this purpose, IGRA (interferon gamma release assay) tests (T-SPOT.TB and Quantiferon) were used, the introduction of which improved the quality of diagnosis of tuberculosis infection by 11% [6] in patients with immunocompromise, including in the absence of proven bacterial excretion. In the Russian Federation, a test with recombinant recombinant recombinant allergen (ATP) was created on the basis of recombinant ESAT-6 and CFP-10 proteins [7], the diagnostic efficiency of which reached 89.8% [8]. Comparison of immunological tests in vivo (ATP test) and in vitro (T-SPOT-TB and QFT) showed no significant differences in their diagnostic value

[6]. The method for the determination of ESAT-6 and CFP-10 peptides using NanoDisk-MS mass spectrometry (nanodisks) with negative microbiological test results had a specificity of 85.3% and a sensitivity of 88% [7]. Direct detection and quantification of serum antigens of MBT using NanoDisk-MS made it possible to quickly and accurately diagnose tuberculosis in adults and exceeded the quality of diagnostics based on microscopic and cultural methods [7].

The use of convolutional neural networks in a study on a model of tuberculosis in C3HeB/FeJ mice made it possible to create software capable of quickly recognizing and evaluating digital histopathological images obtained based on the classification of seven pathological signs and recognition of MBT in biological samples with a sensitivity of 97.94% and specificity of 83.65%. Approaches based on mathematical modeling methods and the use of artificial intelligence tools made it possible to develop computer programs and create algorithms for analyzing databases with the results of laboratory, radiation, histological and other research methods. This contributed to the improvement of indirect diagnostic methods in complex cases, including tuberculosis with unproven bacterial excretion .

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