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MYCOBACTERIOSES: STUDY OF DRUG RESISTANCE OF NON-TUBERCULOSIS MYCOBACTERIA TO ANTI-TB DRUGS

Abstract. Non-tuberculosis mycobacteria are widely prevalent in the environment (water, ground, etc.) as saprophytes, but in certain cases they can be agents of serious diseases with heavy course. i.e. mycobacterioses. Differentiation the mycobacteriosis and pulmonary tuberculosis is rather difficult because both diseases have similar clinical and roentgenological manifestations and presence in the sputa acid fast bacteria. Identification of cultures obtained from patients by method GenoType®Mycobacterium CM/AS was conducted, and 68 non-tuberculosis mycobacteria out of 412 cultures investigated. In 58 cases out of them there were isolate the slowly growing non-tuberculosis mycobacteria (M.celatum – 54, M.avium – 2, M.malmoense – 1, M.*lentiflavum – 1). In* 82.3% (56 patients) cases drug sensitivity to anti-TB drugs of the 1st line was preserved, in 18.6% (12 patients) cases drug resistance observed. Out of 12 resistant cultures in 13.2% (9 patients) cases there was multiple drug resistance (to isoniazid, rifampicine, streptomycin, ethambutol), 2.9% (2 patients) cases had the extensive drug resistance (to amikacin, capreomycin, ofloxacin and ethionamid).

Keywords: mycobacteriosis, non-tuberculosis mycobacteria, diagnostics, drug resistance.

Initial reference to the diseases caused by nontuberculous mycobacteria (NTMB) occurs in the first half of the XX century. NTMB were considered as virtually non-pathogenic to humans, and up to 50-ies in the world press have met only sporadic case reports of diseases caused by these organisms [1, 2]. Mycobacteriosis etiological factor is the non-tuberculous mycobacteria. Since then, the situation has changed in the direction of a minor growth of a number of Mycobacterium species of the genus, and, consequently, the emergence of patients with mycobacteriosis. NTMB are widely distributed in the environment as saprophytes, but in some cases they may be etiologic factors of severe (even fatal) disease [3-6]. Unlike Mycobacterium tuberculosis that are obligate pathogens, NTMB - saprophytes, ordinary residents of different environments, such as water, soil, etc. However, these microorganisms have potential pathogenicity and can cause disease processes in humans.

Antibiotics suppressing the vital activity of the causative agent in the treatment process is not spared drug-sensitive representatives of the normal microflora of the human body. Survivors or trapped outside the drug-resistant bacteria are in favorable conditions and can be cause of disease development. In particular, these microorganisms are NTMB, characterized by a wide range of drug resistance [7].

At the present stage phthisiological service started to increasingly face with the pathology caused by nontuberculous mycobacteria. For example, in Russia in comparison with other countries there are more often lungs mycobacterioses. This clinical and radiographic changes in the lungs are similar to those of tuberculosis. Unfortunately, there is no single clinical feature characteristic of this disease. Symptoms usually do not differ from those of tuberculosis. They are varied and nonspecific chronic productive cough with little sputum predominantly mucous character, coughing up blood, a slight shortness of breath, malaise, fatigue, fever, weight loss, loss of appetite, night sweats [5, 8].

According to the classification proposed in 1959 by E.Runyon, mycobacteria are divided into 4 groups according to their growth rate and ability to form a yellow or orange pigment colonies: 1) photochromogenous (forming carotenoid pigments in light), 2) scotochromogenous (forming carotenoid pigments in dark), 3) nonphotochromogenous (not forming pigment), 4), the fast-growing, acid-fast saprophytes [9].

At present time various aspects of the problem of mycobacteriosis caused by NTMB are studied, in particular, a very important issue is to study the stability of the NTMB to the anti-TB drugs (ATD). According to the literature, NTMB often have a natural resistance to anti-TB drugs. In fact, it may be resistance associated with the use of chemotherapeutic agents at the respective other pathology. It should be borne in mind that for the treatment of mycobacteriosis there are applied not only to products that are used in tuberculosis, so the stability of mycobacteria is known a little [10-12]. To determine the stability of NTMB to chemotherapy drugs it is used in basically the same methods for determining the DST and the environment, as for Mycobacterium tuberculosis.

Materials and methods. In the National reference-laboratory of the National Center of TB problem it was investigated resistance of mycobacteria to the ATD of 1 layer (streptomycin, isoniazid, rifampicin and ethambutol) and 2 layer (ofloxacin, amikacin, capreomycin, ethionamide) on solid Lowenstein-Jensen medium by method of proportions and a liquid medium to automated microbiological analyzer BACTEC MGIT-960. For studying it was taken the culture of mycobacteria isolated from different pathological material (sputum, bronchial lavage, pus, etc.).

Results. Totally 412 patients over 3 years (2013-2015) were investigated. Of these, by method of genotyping GenoType®Mycobacterium CM/AS in 83.5% (344 patients) cases it is highlighted Mycobacterium.complex, which confirms the presence of tuberculous process, and in 16.5% (68 patients) were identified NTMB: of them M.celatum - 13,1% (54 pers.), M.gordone - 1,7% (7 pers.), M.avium-0,5% (2 pers.), isolated cases of M.malmoense, M.fortuitum, M.lentiflavum , M.absceccuss, M.phlei - 0,2% (1 pers.).

Among the 54 cultures M.celatum (slow-growing NTMs) in 83.3% (45 cases), there is sensitivity to the major ATB drugs (isoniazid, rifampicin, ethambutol and streptomycin), in 14.8% (8 cases) - resistance to HRSE, 1 8% (1 case) resistance to HS.

Among the 7 cultures M.gordone (scotochromogenous) in 85.7% (5 cases) there is sensitivity to the major ATB drugs (isoniazid, rifampicin, ethambutol and streptomycin), 14.2% (1 case) - resistance to HRSE, 14,2% (1 case) resistance to S.

Of the 2 cultures M.avium 1 culture was sensitive to anti-TB drugs, 1 culture is resistant to isoniazid. The remaining NTMB (slow-growing and fast-growing): M.malmoense, M.fortuitum, M.lentiflavum, M.absceccuss, M.phlei were sensitive to major ATD of 1 layer.

Also NTM stability to ATD of 2 layer has been studied: amikacin, capreomycin, ethionamide, and ofloxacin. Most of isolated NTM in 96.2% (66 patients) was sensitive to the ATD of 2 layer, and only in 2.9% (2 patients) of representative of slow-growing NTM M.celatum was simultaneous resistance to amikacin, capreomycin, ethionamide, and ofloxacin.

Conclusions:

1. Diagnosis of mycobacteriosis is constantly faced with certain difficulties, since NTM cause human disease similar to tuberculosis and require additional identification of mycobacteria isolated molecular genetic tests.

2. Of the 412 cultures studied by genotyping GenoType®Mycobacterium CM/AS, in 83.5% of cases it was highlighted Mycobacterium.complex, 16.5% - NTM.

3. In most cases, the NTM (from 83.3% to 96.2%) are sensitive to ATD of 1 and 2 layers respectively.

4. Among the slow-growing NTM M.celatum in 14.8% of cases it was mounted simultaneous resistance to all four major ATD of 1 later (isoniazid, rifampicin, ethambutol and streptomycin) and in 1.8% of cases of isoniazid and streptomycin. Also, in 2.9% (2 patients) with NTM M.celatum it was simultaneous resistance to second-line drugs: amikacin, capreomycin, ethionamide, and ofloxacin.

REFERENCES

[1] Ellis S.M., Hansell D.M. Imaging of nontuberculosis (atypical) mycobacterial pulmonary infection ,*Clin.Radiol*, **2002**, 57,661-669 (in Eng.).

[2] Obrien D.P., Currie B.J., Krause V.L. Nontuberculous mycobacterial disease in northern Australia: a case series and review of the literature. *Clin.Infect.Dis.*,**2000**, 31, 985-967(in Eng.).

[3] Litvinov V.I., MakarovaM.V., KrasnovaM.A.Nontuberculousmycobacterial . – M.:MNPCBT,**2008**, 256p (in Russ.).

[4] MakarovaM.V. Isolation and identification of nontuberculous mycobacteria TB patients institutions : Author. dis.kand.med.nauk .M.,**2010**,49p. (in Russ.).

[5] Otten.T.F., VasilevA.V. Mycobacterioses - SPb. Medical press,**2005**, 9p. (in Russ.).

[6] MarrasT.K., WallaceR. J. Jr., KothL.L.etal. Hypersensitivity pneumonitis reaction to Mycobacterium avium in household water.*Che*st, **2005**, 664-671(in Eng.).

[7] ZikovM.P., IlinaT.B. Potentially pathogenic mycobacteria and laboratory diagnosis of mycobacteriosis-M.,**1978**, 175 p (in Russ.).

[8] Brown-Elliot B.A., Wallace R. J. Jr. Infections caused by nontuberculous mycobacteria. In Mandell G.L., Bennett J.E. Dolin R. eds. Principles and practice of infection disease. *Philadelphia, PA: Elsevir Churchill Livingstone*, **2004**, 2909-2916 (in Eng.).

[9] Daley C.L., Griffith D.E. Pulmonary non-tuberculous mycobacterial infections.*Int. J. Tuberc. LungDis.,* **2010**, 14, 6, 665-671(in Eng.).

[10] MakarevichN.M. Sensitivity to various atypical mycobacteria TB drugs // Coll. Scien .tr., **1976**, 20, 148-150 (in Russ.).

[11] Griffith D. Therapy of nontuberculous mycobacterial disease.*Curr.Opin.Infect.Dis.*,**2007**, 20, 198-203 (in Eng.).

[12]Heifets L., Jenkins P. Speciation of micobacteria in clinical laboratories,InGangadharam P.R. Jenkins P.A. Mycobacteria. Vol.I. *Basic Aspects. New York:Chapman a Hall (Inf. Thompson Publishing)*, **1998**, 308-350 (in Eng.).

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МИКОБАКТЕРИОЗЫ: ИЗУЧЕНИЕ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ НЕТУБЕРКУЛЕЗНЫХ МИКОБАКТЕРИЙ К ПРОТИВОТУБЕРКУЛЕЗНЫМ ПРЕПАРАТАМ

Аннотация. Нетуберкулезные микобактерии широко распространены в окружающей среде (вода, почва и др.) как сапрофиты и в некоторых случаях могут вызывать тяжело протекающие заболевания – микобактериозы. Дифференцировать микобактериоз и туберкулез легких бывает весьма сложно, поскольку оба заболевания имеют сходные клинико-рентгенологические проявления и обнаружение в мокроте кислотоустойчивых бактерий. Проведена идентификация культур пациентов методом генотипирования GenoType®MycobacteriumCM/AS, выделено 68 нетуберкулезных микобактерий из 412 исследованных культур. Из них в 58 случаях выделены медленнорастущие нетуберкулезные микобактерии (M.celatum - 54, M. avium - 2, M. malmoense 1, M.*lentiflavum-1). В* 82,3% (56 пациентов) случаях сохранена лекарственная чувствительность к противотуберкулезным препаратам первого ряда, в 18,6% (12 пациентов) – наблюдалась лекарственная устойчивость. Из 12 устойчивых культур в 13,2% (9 пациентов) случаях наблюдалась множественная лекарственная устойчивость (к изониазиду, рифампицину, стрептомицину, этамбутолу), в том числе в 2,9% (2 пациента) случаев имели широкую лекарственную устойчивость (к амикацину, капреомицину, офлоксацину и этионамиду).

Ключевые слова: микобактериоз, нетуберкулезные микобактерии, диагностика, лекарственная устойчивость.

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МИКОБАКТЕРИОЗДАР: ТУБЕРКУЛЕЗ ЕМЕС МИКОБАКТЕРИЯЛАРДЫҢ ТУБЕРКУЛЕЗГЕ ҚАРСЫ ДӘРІЛЕРГЕ ТҰРАҚТЫЛЫҒЫН ЗЕРТТЕУ

Аннотация. Туберкулез емес микобактериялар қоршаған ортада (су, топырақ) сапрофиттер ретінде кеңінен тараған. Кейде олар ауыр ағыммен өтетін микобактериоз ауруын тудыруы мүмкін. Микобактериоз бен өкпе туберкулезін ажырату қиынға соғады, себебі екеуінің клинико-рентгенологиялық көріністері бірдей және қақырықта қышқылға тұрақты бактериялар табылады. GenoType®Mycobacterium CM/AS генотиптеу әдісімен талдау арқылы науқастардың қақырығынан өсіп шыққан 412 дақылдан 68 туберкулез емес микобактери бөліп алынды. Олардың ішінде 58 жағдайда жай өсетін туберкулез емес микобактерилер (M.celatum - 54, M. avium - 2, M. malmoense 1, M.lentiflavum-1) бөлініп алынды. 82,3% (56 науқас) жағдайда бірінші қатардағы туберкулезге қарсы препараттарға дәрілік төзімділік сақталған, ал 18,6% (12 науқас) – дәрілік төзімділік сақталмаған. 12 дәріге тұрақты дақылдардың 13,2% (9 науқас) жағдайда көп дәріге тұрақтылық (изониазидке, рифампицинге, стрептомицинге, этамбутолға), соның ішінде 2,9% (2 науқас) жағдайда дәрілерге кеңінен тараған тұрақтылық (амикацинге, капреомицинге, офлоксацинге, этионамидке) байқалған.

Түйін сөздер: микобактериоз, туберкулёз емес микобактериялар, диагностика, дәрілерге тұрақтылығы.