

CLINICAL CASE

N.A. Gulyaeva, O.N. Ivanova, O.I. Gurieva, T.I. Kharitonova,
T.E. Burtseva

A CASE OF THE COMPLICATED COURSE OF DRUG-RESISTANT TUBERCULOSIS IN A 14-YEAR-OLD ADOLESCENT

DOI 10.25789/YMJ.2021.74.34

The article presents a clinical case of the development of drug-resistant tuberculosis in a teenager. The peculiarity of the clinical case is due to the fact that the adolescent was observed for local tuberculosis, was removed from the register for cure, but a year later he entered the anti-tuberculosis hospital with widespread tuberculosis with extensive drug resistance of mycobacterium tuberculosis (MBT) to 8 anti-tuberculosis drugs, with poor tolerance to chemotherapy. All these factors led to a complicated course of tuberculosis and was an indication for surgical treatment, for superior lobectomy with atypical resection of C6 of the left lung with decortication. In this regard, it is important to further improve the work of the general medical network among patients who have undergone tuberculosis, as well as the alertness of pediatricians on this pathology.

After the child was removed from dispensary observation, tuberculosis developed with a complicated course and extensive drug resistance of MBT to 8 anti-tuberculosis drugs, which led to upper lobectomy with atypical C6 resection of the left lung with decortication. Further improvement of the organization of anti-tuberculosis measures among patients with drug-resistant forms of tuberculosis is urgent. Pediatricians are advised to be wary of children who come into contact with people with drug-resistant TB.

Keywords: tuberculosis, adolescents, drug resistance, lobectomy, tuberculosis of the intrathoracic lymph nodes, X-ray examination.

Introduction. One of the serious problems of modern phthisiology is the increase in the incidence of tuberculosis caused by a drug-resistant pathogen - Mycobacterium tuberculosis (MBT). In 2010-2011, a multicenter study in 23 centers in 16 European countries found primary MDR MBT in 52.4% of cases. At the beginning of treatment, the tested MBT strains had resistance to pyrazinamide in 59.7%, to injectable drugs - in 26.6%, to fluoroquinolones - in 17.6%, to other anti-TB drugs - in 6.8% of cases.

In 2012-2014 in Saudi Arabia, MBT is mono-resistant to isoniazid in 1.8% of cases, to rifampicin - in 1.4%, to streptomycin - in 1.9%, to ethambutol - in 1.1% and to pyrazinamide - in 2.1%, primary MDR MBT was detected in 4% of cases.

The incidence rate of tuberculosis among children in the Russian Federation at the age of 0-14 years was 9.6 in 2017; 2018 - 8.3, per 100,000 children. Total in Russia in 2018 got sick for the first time - 65234 children (2017-70861 (-5627 cases) (2016 - 78121) (- 7261); including: 0-14 years old 2153 (2017-2475) (-322); (in 2016 -2865) (- 390), 15-17 years old: 765 (2017-868) (-103); (in

2016 - 964) (-96).

In the Republic of Sakha (Yakutia), according to the State Budgetary Institution of the Republic of Sakha (Yakutia) SPC "Phthisiology", the proportion of patients with multidrug resistance (MDR-MDR) among newly diagnosed patients with bacillary forms of TOD (respiratory tuberculosis) was 28.1% in 2019 (79 people), in 2018 - 29.8% (86 people), in 2017 - 32.8% (96 patients). In the Republic of Sakha (Yakutia), the incidence rates of tuberculosis in children aged 0-14 years remain higher than in the Russian Federation. In 2017, amounted to 17.3 per 100 thousand population. In 2018, amounted to 15.0 per 100 thousand population, which is also higher than in the Russian Federation. In 2019, the incidence in children was 14.1, which is 2 times higher than in the Russian Federation (14.1 per 100 thousand population)

The morbidity rate of the adolescent population during the study period decreased by 20.7% - from 51.1 to 40.5 per 100 thousand of the adolescent population, the average rate of decline was -0.6%. This indicator is characterized by the absence of a downward trend ($R^2 = 0.03$), and the rate of its growth (decline) fluctuated within significant limits - from 51.1% in 2017 to -29.1% in 2018 [6]

The most important indicator characterizing the quality of the organization of diagnosis and treatment of tuberculosis is the frequency of primary multidrug resistance (MDR) in newly diagnosed patients [1]. In contrast to the two above-mentioned indicators, the incidence of tuberculosis with MDR of the pathogen in the Republic of Sakha (Yakutia) over the past 5 years has not tended to decrease.

Tuberculosis of the intrathoracic

lymph nodes (IHLN) is the main clinical form of primary tuberculosis in children, adolescents and young people aged 18-24 years (up to 80-90% of cases) [4,5].

Most complications (up to 70%) are observed before the age of 3 years and in adolescence, in connection with the pubertal period, against the background of hormonal changes in the body [3]. The presence of close, long-term contact in the family, with relatives, patients with drug-resistant tuberculosis, in combination with unfavorable social factors, lead to the development of complicated processes in children and adolescents and to a positive dynamics in treatment [2].

Clinical example. Patient A. born in 2001 (14 years old) applied in May 2015. about the bend test Mantoux with 2 TE -9 mm. The Mantoux test was delivered at the school. The child was sent for X-ray examination. X-ray examination of the chest organs revealed changes in the intrathoracic lymph nodes.

Epidemic history: Family contact - with my mother in 1998. pulmonary tuberculosis was diagnosed, drug resistance of mycobacterium tuberculosis (MBT) was not revealed. Since 2000 to the present, the child's mother is not registered with the dispensary, on the chest X-ray from May 2017: metatuberculosis changes.

Anamnesis of life: A child from the 4th pregnancy, which lasted 1 half - toxocosis, in 2 - the threat of termination of pregnancy, Delivery on time, birth weight 4280g, height - 56 cm. Breastfeeding up to 1 year. Vaccinated at the maternity hospital, post-vaccination scar 5 mm.

Past diseases: chickenpox, acute respiratory viral infections.

He lives in a complete family, in a three-room comfortable apartment. Two

GULYAEVA Nadezhda Andreyevna - PhD in Medical Sciences, Assistant Professor MI NEFU of M.K. Ammosov, NAGulyaeva15@yandex.ru; **IVANOVA Olga Nikolayevna** - Doctor of Medicine, Prof. MI NEFU of M.K. Ammosov; **GURIEVA Olga Ivanovna** - Head of Dispensary No.2 SBI RS(Y) NPC 'Phthiziatra'; **KHARITONOVA Tamara Ignatyevna** - doctor of the children's anti-tuberculosis clinic SBI RS (Y) NPC «Phthiziatra»; **BURTSEVA Tatiana Egorovna** - Doctor of Medicine, Prof. MI NEFU of M.K. Ammosov, Senior visiting fellow, Head of YSC CMP

Table 1

Result of microbiological research

Material	Дата	By the "LM" KUM method	By seeding method	DNA research	Drug sensitivity
sputum	26.06.17	Detected 3+	3+	-	Stability H, R, Rb, S, E, Et, Am, OfI
sputum	13.09.17	single units	1+	-	-
sputum	10.10.17	negative	-	-	-
flushing from the nasopharynx	08.11.17	Not detected	Not detected	Not identified	-
flushing from the nasopharynx	09.11.17	Not detected	Not detected	Not identified	-
flushing from the nasopharynx	10.11.17	Not detected	Not detected	Not identified	-
flushing from the nasopharynx	13.12.17	Not detected	Not detected	Not identified	-
flushing from the nasopharynx	18.01.18	Not detected	Not detected	Not identified	-

*LM- luminescent microscopy

adults and three children live with the girl.

After collecting the anamnesis and analyzing the examination data, the girl was taken for dispensary registration in group III A with a diagnosis of Tuberculosis of the intrathoracic lymph nodes. Received treatment: isoniazid-0.6 (600 mg), ethambutol - 1.2 (1200 mg), pyrazinamide - 1.5 (1500 mg / kg), a total of 136 doses in the hospital of the department of pediatric tuberculosis No. 2. Withdrawn from dispensary registration in October 2016 with clinical cure.

06.03.17. there were complaints of increased body temperature up to 38.6, weakness, barking cough, I turned to a pediatrician, treatment was prescribed. I went to the doctor on 14.04.17 with complaints of a wet cough, runny nose, weakness, decreased appetite, was diagnosed with pharyngitis, treatment was prescribed. 20.04.17. I went to the pediatrician with complaints of pain in the chest, the girl's mother noticed a deformity in the sternum, turned to the traumatologist and pediatrician. The pediatrician has appointed a sputum test for acid-resistant *Mycobacterium tuberculosis* (KUM).

According to the radiograph from 28.06.17.: Deformity of the sternum at the point of transition to the handle, without signs of destruction. Infiltrative tuberculosis of the upper lobe and S-6 segment of the left lung in the phase of decay and seeding (Figure 1). Treatment was prescribed from 30.06.17. - 03.08.17. according to the IV chemotherapy regi-

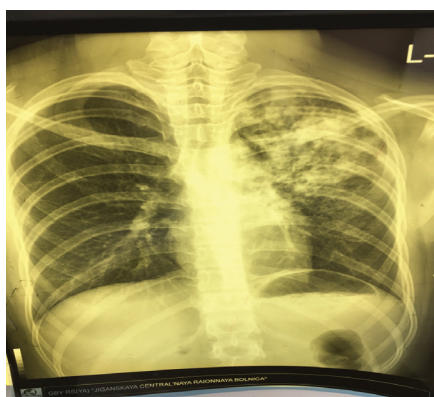


Fig. 1. Overview X-ray of the chest organs from 28.06.17.

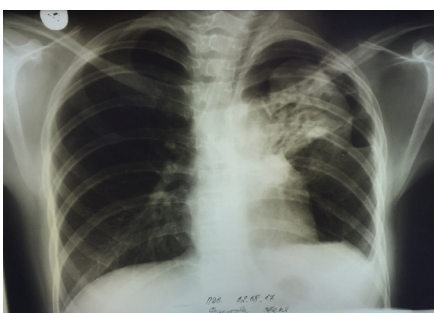


Fig. 2. Plain X-ray of the chest organs from 05.09.17.

men-pyrazinamide (Z) (1500 mg), amikacin (Am) (750 mg), levofloxacin (Lfl) (450 mg), prothionamide (Pto) (500 mg), cycloserine (Cs) (500 mg), PASC (9.0 g), received 35 doses. The condition worsened on 02.08.17. There were com-

plaints of pain in the side, an increase in body temperature to 38.0 - 38.5 C. On the repeated review radiograph of the chest organs from 02.08.17.: the upper lobe of the left lung, which collapsed due to the presence of air in the pleural cavity up to 1.5 cm. The upper lobe and S6 of the left lung are inhomogeneous and darkened with the presence of multiple different-caliber cavity shadows.

The right lung is transparent. The right root is structural, with the presence of calcifications. This picture corresponded to the picture of a partial pneumothorax on the left.

On the plain chest x-ray from 09/05/17. (Fig. 2): the upper lobe of the left lung is reduced in volume, unevenly darkened, with multiple dense shadows, in dynamics there is a partial improvement in the form of pathological changes. A small amount of air is retained apically in the pleural cavity. In S6 of the left lung, a decay cavity with a diameter of 1.5-2.0 cm with perifocal infiltration around is preserved. The lower lobe of the right lung is compensatory emphysematous sub-in-

Table 2

Dynamic of the patient's MANTOUX test, 2013-2016

year	Results
2013	Отр.
2014	10 mm
2015	9 mm
2016	14 mm

Table 3

Dynamics of the general blood test

Date	hemoglobin	red blood cells	ESR	white blood cells	rod-shaped	segmentonuclear	lymphocytes	monocytes	eosinophils	platelets
23.06.17.	87	4.13	9	12.73	10	68	9	12	-	664
13.11.17.	120	4.56	37	8.7	8	55	22	8	7	536
08.02.19.	83	4.5	26	6.2	1	51	35	9	4	551

Table 4

Dynamics of biochemical blood analysis

Date	Total bilirubin	Bilirubin direct	ALT	AST	creatinine	urea	glucose	calcium	potassium	chlorides
23.06.17.	7.1	3.72	17.5	2.16	-	-	-	-	-	-
09.01.17.	8.0	-	94.3	164.1	-	-	4.8	-	-	-
17.01.18.	7.0	-	125.6	176.1	51	2.3	-	2.73	108	4.4
18.02.19.	8.1	-	142.5	115.8	55	3.5	-	2.43	97	-

flated. Conclusion: Caseous pneumonia of the upper lobe and S6 of the left lung. Partial pneumothorax of the upper lobe of the left lung (Fig. 2).

According to the results of the ATR test in 2017, an increase in the size of the papule from 17 mm to 30 mm with necrosis was revealed, which is a sign of high sensitization of the body.

In the biochemical analysis of blood, the presented results show an increase in ALT from 17.5 units from 23.06.17 to 142.5 from 18.02.19, which indicates a hepatotoxic reaction to anti-tuberculosis drugs. According to the results of clinical, laboratory and X-ray examination (Tables 1-4 and Fig. 2), a consultation was held on 05.09.17 and a clinical diagnosis was made: Caseous pneumonia of the upper lobe and S6 of the left lung. Mycobacterium tuberculosis (+). Drug resistance to isoniazid, rifampicin, rifobutin, streptomycin, ethambutol, ethionamide, amikacin, ofloxacin (H, R, Rb, S, E, Et, Am, Of). Intoxication syndrome. Normochromic anemia 1 art.

The treatment was corrected. The condition has stabilized. In 22.09.17. medical documents were sent for correspondence consultation to the "Central Research Institute of Tuberculosis" to determine the further treatment tactics. Hospitalization in the adolescent department is recommended. Sputum analysis for Mycobacterium tuberculosis is negative from 09.10.17.

In the adolescent department of the Central Research Institute of Tuberculosis, taking into account the clinical, laboratory and radiological data of the examination, it was decided to conduct surgical treatment.

Treatment before surgery: individual chemotherapy regimen, taking into account XDR MBT (H, R, Rb, S, E, Et, Am, Of) and drug tolerance. Due to the increase in transaminases in the biochemical blood test from 09.11.17 g, hepatoprotective therapy was prescribed for 1.5 months (phosphogliv, 5% glucose). From 05.12.17 g - 11.12.17 g (8 doses): cycloserine 0.5 (500 mg); capreomycin 0.8 (800 mg) (lymphotropic); pyrazinamide 1.5 (1500 mg); PASC -9.0 g; zenix 0.6. From 22.12.17 - 04.07.18. (195 doses): cycloserine 0.5 (500 mg); pyrazinamide 1.5 (1500 mg); PASC 9.0; bedaquiline (according to the scheme-is prescribed

at a dose of 400 mg once a day daily for 2 weeks, then 200 mg 3 times a week for 22 weeks). A total of 201 doses were received before the operation. The tolerability of the drugs is unsatisfactory (hepatotoxic reaction to zenix; allergic reaction to capreomycin - eosinophilia in the hemogram of 18%).

05.07.18. the operation was performed-upper lobectomy with atypical resection of the C6 left lung with decortication. Computed tomography of the lungs from 06.07.18.: A picture of multiple tuberculomas in the progressive phase with moderate signs of tuberculosis inflammation activity. Bronchiectasis. Phe-



Fig. 3. Chest CT scan from June 27, 2019.

nomena of exogenous alveolitis. Tuberculous lymphadenitis.

Treatment after surgery according to an individual chemotherapy regimen: from 05.07.18. - 23.10.18. (111 doses) cycloserine 0.5 (500 mg); pyrazinamide 1.5(1500 mg); PASC 9.0; bedaquiline (according to the scheme). The total number of doses received in the adolescent department is 314. Pathogenetic therapy: prednisone –(7.5 mg per day); essentielle, methionine, glycine, glutamic acid; up to 30.07.18 g. - inhalation with ambrobene 2 r/day; ferrum lek. From 06.07.18. - 06.08.18. air insufflation into the abdominal cavity (800 ml) was performed – 4 procedures.

Clinical diagnosis: Tuberculosis of the intra-thoracic lymph nodes of the bronchopulmonary group on the right in the calcination phase, MBT (-), XDR (broad drug resistance) MBT (H, R, Rb, S, E, Et, Am, OfI). Condition after upper lobectomy with atypical resection of C6 of the left lung with decortication from 05.07.18 for caseous pneumonia of the upper lobe and C6 of the left lung.

Chest KT scan from June 27, 2019. The state of the VATS resection of the upper lobe of the left lung, in the basal part, the chain of the tantalum suture is determined. The lung is reduced in volume, the lower lobe is compensatorily pulled up, with the presence of fibrous strands. In the upper part of the upwardly displaced lower lobe, pneumosclerosis, small foci. The left root is deformed. The mediastinum is shifted to the left.

The right lung is in full volume, without focal and infiltrative changes. The bronchovascular pattern in the right lung is not changed. The bronchi are traced to the subsegmental level, their lumen is not changed. The right root with calcinate in the upper group of bronchopulmonary nodes.

In the upper mediastinum, enlarged lymph nodes are not detected. There is no free fluid in the pleural cavity.

Conclusion. Condition after VATS resection of the upper lobe of the left lung for caseous pneumonia. No recent tuberculosis changes were detected.

At this time, the patient is observed at the place of residence. Since 2018, there have been no relapses of the disease. He is under the supervision of a phthisiologist in the III group of dispensary registration, at the place of residence.

Conclusion. The problem of contact of children with patients with drug-resistant tuberculosis in the republic is quite relevant. We present a clinical example of the development of tuberculosis in a teenager with broad drug resistance of MBT to 8 anti-tuberculosis drugs (H, R, Rb, S, E, Et, Am, OfI), with unsatisfactory tolerability of anti-tuberculosis drugs in the form of increased transaminases in the biochemical blood test. All these factors led to a complicated course of the tuberculosis process and then to the surgical method of treatment - upper lobectomy with atypical C6 resection of the left lung with decortication. In this regard, it is important to further improve the work of the general medical network among patients who have suffered from tuberculosis, as well as the alertness of pediatricians for this pathology.

Литература

1. Винокурова М.К. Тенденции развития множественной лекарственной устойчивости у больных туберкулезом легких в РС(Я) / Винокурова М.К. //Актуальные проблемы и перспективы развития противотуберкулезной службы в РФ: мат-лы 1-го конгресса Национальной ассоциации фтизиатров.- СПб., 2012.-С. 97-98. [Vinokurova MK. Trends in the development of multiple drug resistance in patients with pulmonary tuberculosis in Republic Sakha (Yakutia). Actual problems and prospects for the development of anti-tuberculosis services in the Russian Federation: *Mater. 1st Congr. Assoc. 'National Association of Phthisiologists'*.-St. Petersburg, 2012; 97-98].
2. Гуляева Н.А. Особенности течения первичного туберкулеза у детей в зависимости от эпидемиологической ситуации в регионе / Гуляева Н.А., Винокурова М.К.// Предупреж-

дение распространения туберкулезной инфекции в циркумполярных регионах России. Актуальные проблемы сочетанных инфекций (ВИЧ/ТБ/гепатиты): мат-лы межрегион. науч.-практич. конф. - 2018:.-С. 36-37. [Gulyaeva NA, Vinokurova MK. Features of the course of primary tuberculosis in children depending on the epidemiological situation in the region. *Materials of the Interregional scientific and practical conference "Prevention of the spread of tuberculosis infection in the circumpolar regions of Russia. Current problems of combined infections (HIV/TB/hepatitis)"*. 2018; 36-37].

3. Кошечкин В. А. Туберкулез: учебное пособие / Кошечкин В. А., Иванова З.А. - 2017. [Koshechkin VA, Ivanova ZA. Tuberculosis, textbook: 2017].

4. Лугинова Е.Ф. Эффективность применения стандартных режимов химиотерапии у детей и подростков, больных туберкулезом органов дыхания / Лугинова Е.Ф., Гурьева О.И., Николаева Д.А. //Туберкулез и болезни легких. 2020;98(11):45-50. <https://doi.org/10.21292/2075-1230-2020-98-11-45-50> [Luginova EF, Gurieva OI, Nikolaeva DA. Efficiency of using standard chemotherapy regimens in children and adolescents, with respiratory tuberculosis. *Tuberkulez i bolezni legkih [Tuberculosis and lung disease]*. 2020; 98 (11): 45-50]. <https://doi.org/10.21292/2075-1230-2020-98-11-45-50>

5. Фтизиатрия / В. Ю. Мишин, С. П. Завражнов, А. В. Митронин [и др.].-2015. [Mishin VYu., Zavrazhnov SP., Mitronin AV., Grigoriev YG. Phthisiology., textbook; 2015].

6. Яковлева Л.П. Основные тенденции в динамике заболеваемости туберкулезом в Республике Саха (Якутия) в 2013-2018гг. / Яковлева Л.П., Кондратьева О.Д., Кондратьева М.Н. //Якутский медицинский журнал. - 2020. -№ 2 (70). -С. 59-62. [Yakovleva LP, Kondratieva OD, Kondratieva MN. Main trends in the dynamics of tuberculosis incidence in the Republic of Sakha (Yakutia) in 2013-2018. *Yakut Medical Journal*. 2020; 2 (70): 59-62.

7. M.M. Elhassan, H.A.Hemeg, M.A. Elmekki et al. Burden of multidrug resistant Mycobacterium tuberculosis among new cases in Al-Madinah Saudi Arabia Infect. *Disord. Drug Targets*. 2017; 17 (1): 14-23. doi: 10.2174/1871526517666161116104242.

8. G.Günther, F.van Leth, S.Alexandru et al. Multidrug-resistant tuberculosis in Europe, 2010. *Emerg. Infect. Dis*. 2015; 21 (3): 409-416. doi: 10.3201/eid2103.141343.

9. Y.Pang, J.Lu, F.Huo et al. Prevalence and treatment outcome of extensively drug-resistant tuberculosis plus additional drug resistance from the National Clinical Center for Tuberculosis in China: A five-year review. *J. Infect*. 2017; 5: 433-440. doi: 10.1016/j.jinf.2017.08.005.

