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Bedaquiline resistance in Mycobacterium tuberculosis during antimycobacterial therapy and its impact on clinical outcomes (clinical cases)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim. To analyze the nature of Bedaquiline (Bdq) resistance in Mycobacterium tuberculosis (MBT) during antimycobacterial therapy (AMBT) in patients with multidrug-resistant tuberculosis (MDR-TB), its impact on clinical outcomes and to detect risk factors for the Bdq drug resistance development on the example of own observed clinical cases.

Materials and methods. 2 clinical cases of own observations of the Bdq resistance development in MBT during AMBT in patients with MDR-TB who were treated at the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical University – Pulmonary Tuberculosis Department No. 2 of the Communal Non-profit Organization "Zaporizhzhia Regional Phthisio-Pulmonology Clinical Treatment and Diagnostic Center" are presented.

Results. The presented clinical cases confirm the literature data that the treatment effectiveness in patients with Rifampicin-resistant TB (RR-TB) and MDR-TB is associated with Bdq drug resistance. Regarding the reasons for the development of acquired Bdq drug resistance, the second clinical case, like the examples of other authors, demonstrates low adherence to treatment. There is no data in the literature about the lack of controlled treatment at the outpatient stage as a risk factor for Bdq drug resistance and negative clinical outcomes in patients with MDR-TB, which would complement the scientific experience in this problem.

Conclusions. In both clinical cases, Bdq drug resistance was acquired (secondary), and had an impact on the clinical outcomes of tuberculosis treatment. The risk factors for Bdq drug resistance and negative clinical outcomes were lack of controlled treatment at the outpatient stage in the first case and low adherence to treatment in the second one.

Key words: multidrug-resistant tuberculosis, bedaquiline, results.

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Резистентність мікобактерій туберкульозу до бедаквіліну під час антимікобактеріальної терапії та її вплив на клінічні наслідки (клінічні випадки)

О. М. Разнатовська, Р. М. Ясінський, О. С. Шальмін, А. В. Федорець, О. А. Світлицька

Мета роботи – на прикладі клінічних випадків власного спостереження у хворих на туберкульоз з множинною лікарською стійкістю (MDR-TB) проаналізувати характер резистентності мікобактерій туберкульозу (МБТ) до бедаквіліну (Bdq) під час антимікобактеріальної терапії (АМБТ), її вплив на клінічні наслідки та встановити фактори ризику виникнення лікарської стійкості до Bdq.

Матеріали та методи. Наведено 2 клінічні випадки власного спостереження виникнення резистентності МБТ до Bdq під час АМБТ у хворих на MDR-TB, які перебували на лікуванні у відділенні легеневого туберкульозу № 2 Комунального некомерційного підприємства «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» Запорізької обласної ради – клінічній базі кафедри фтизіатрії і пульмонології Запорізького державного медичного університету.

Результати. Наведені клінічні випадки підтверджують відомості фахової літератури про те, що ефективність лікування хворих на MDR-TB пов'язана з лікарською стійкістю до Bdq. Щодо причин виникнення набутої лікарської стійкості до Bdq, то у другому клінічному випадку показано низьку прихильність до лікування, і на це вказують багато авторів. Про відсутність контрольованого лікування на амбулаторному етапі як фактор ризику лікарської стійкості до Bdq і негативних клінічних наслідків у хворих на MDR-TB даних у науковій літературі немає, а отже це доповнить науковий досвід із цієї проблеми.

Висновки. В обох клінічних випадках лікарська стійкість до Bdq була набутою (вторинною) та впливала на клінічні наслідки лікування туберкульозу. Фактор ризику лікарської стійкості до Bdq та негативних клінічних наслідків у першому випадку – відсутність контрольованого лікування на амбулаторному етапі, у другому – низька прихильність до лікування.

Ключові слова: туберкульоз з множинною лікарською стійкістю, бедаквілін, результат.

Запорізький медичний журнал. 2023. Т. 25, № 1(136). С. 87-96

Increasing rate of drug-resistant tuberculosis (DR-TB) is a global health problem worldwide. 10 million people fell ill with tuberculosis in the world and 1,5 million died from it in 2020 according to the World Health Organization (WHO) [1,19]. Therefore, an important task of health care remains to search for ways of problem solving of improving effectiveness of DR-TB patient treatment. New regimens for the treatment of patients with multidrug-resistant tuberculosis (MDR-TB) have now been approved, including new anti-tuberculosis drugs, one of them is Bedaquiline (Bdq), which belongs to the antimycobacterial drugs from group A (the most highly effective drugs) [1,4,6,7,13,18]. Bdq-containing regimens of antimycobacterial therapy (AMBT) are associated with better outcomes and treatment safety [8,9,10,16,21,23].

Mishra G. P, Mulani J. [15] identified a mutation in the Rv0678 gene associated with resistance to Bdq and

possible cross-resistance to Bdq and clofazimine. Therefore, the authors recommend whole genome sequencing for the rapid diagnosis of resistance to Bdq for all patients with confirmed tuberculosis for the timely diagnosis of mutations in the Rv0678 gene.

The mutation in the Rv0678 gene in patients with MDR-TB who had not previously received Bdq, with cross-resistance to Bdq and clofazimine, was also indicated by W. He et al. [15] and J. Xu et al. [16]. Liu A. Y. et al. [22] detected, that patients with MDR-TB after Bdq-containing regimen treatment without this mutation had a high level of Clofazimine resistance.

Nguyen T. V. A. et al. [5] indicated the necessity of a standardized drug susceptibility test (DST) to Bdq developing, considering the identified mutations in the atpE, Rv0678, and pepQ genes.

Ismail N. et al. [12,14] performing in vitro whole genome sequencing of the stepwise mutations acquisition in the Rv0678, atpE, pepQ, and Rv1979c genes, hypothesized, that resistance to Bdq was first manifested by a mutation in the Rv0678 gene, mutation in the atpE gene followed later. Similar results were obtained by G. Degiacomi et al. [13].

Study results of Q. Guo et al. also evidenced the fact that mutations in the Rv0678 gene provided the primary mechanism of resistance to Bdq [23]. At the same time, the authors also identified a new gene, involved in Bdq resistance – glpK.

A study on resistance to Bdq in MBT isolates from Rifampicin-resistant (RR-TB) and MDR-TB patients who had not previously received Bdq was conducted by S. H. Wu et al. [17]. Sequencing with the determination of mutations in the atpE, Rv0678 and pepQ genes was performed according to Sanger. The authors identified 28 isolates with minimum inhibitory concentration (MIC) of Bdq <0.25 μg/mL and MIC ≥0.25 μg/mL among 65 randomly selected isolates. MBT isolates with MIC Bdq = 0.25 μg/ml were found to be resistant or sensitive to Bdq. At the same time, Bdq-resistant isolates also had mutations in the Rv0678 gene.

Liu Y. et al. [3], studying the dynamics of Bdq sensitivity in MBT isolates during AMBT obtained, that patients with MDR-TB and acquired Bdq resistance had a mutation in the Rv0678 gene. These patients were at greater risk of AMBT failure compared to initially Bdq resistant MDR-TB cases.

Saeed D. K. et al. [22] studied mutations in the Rv0678, pepQ, atpE, Rv1979c, mmpLS, and mmpL5 genes in whole genome sequencing to determine the sensitivity of MBT isolates to Bdq. The researchers found, that mutations in the RAV and Rv0678 genes were associated with Bdq resistance.

Gao J. et al. [11] have revealed the appearance of new populations of nontuberculous mycobacteria in 9 patients (3.1 %): *M. abscessus* (5 isolates), *M. fortuitum* (2 isolates), *M. avium* (1 isolate) and *M. intracellulare* (1 isolate) in a study on the effects of AMBT regimens that included Bdq in patients with MDR-TB. In the meantime, 3 out of 9 patients initially had resistance to Bdq, and 7 out of 9 patients achieved sputum conversion after 1 month.

We see that the frequency of Bdq resistance in MBT is growing rapidly throughout the world, and patients are at greater risk of AMBT failure, considering the literature data. At the same time, in patients with MDR-TB, both primary and acquired MBT resistance to Bdq is associated with mutations in the atpE, Rv0678, RAV, pepQ, and glpK genes, especially in the Rv0678 gene [5,12,14,15,17,20,22,23].

Aim

The aim was to analyze the nature of Bdq resistance in MBT during AMBT in patients with MDR-TB, its impact on clinical outcomes and to detect risk factors for the Bdq drug resistance development on the example of own observed clinical cases.

Materials and methods

Two clinical cases of own observations of the Bdq resistance development in MBT during AMBT in patients with MDR-TB who were treated in the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical University – Pulmonary Tuberculosis Department No. 2 of the Communal Non-profit Organization "Zaporizhzhia Regional Phthisio-Pulmonology Clinical Treatment and Diagnostic Center" of Zaporizhzhia Regional Council (CNO "ZRPPCTDC" ZRC) are presented.

Results

Clinical case 1

A patient O., female, 44 years old.

She was examined, when she came to her family doctor in March 2020 with complaints of a prolonged cough and subfebrile fever. MBT were detected in the sputum by both Ziehl–Neelsen staining (acid fast bacilli (AFB)) and molecular genetic (MG) methods, which were resistant to rifampicin (Rif): MBT+ AFB+ MG+ Rif+. Changes were detected on an X-ray examination of the chest cavity organs (chest X-ray) dated from March 24, 2020 (*Fig. 1*).

Diagnosis was made: RR-TB infiltrative of the left lung with contamination. Destruction+ MBT+ AFB+ MG+ Rif+. Histology 0 (a new case). Cohort 2 (2020).

On 07.04.2020, the growth of MBT culture (C) on a liquid medium and the result of the phenotypic drug sensitivity test (phDST) were obtained. The presence of MBT drug resistance (Resistance+) to isoniazid (H), rifampicin (R) and ethambutol (E) was detected. The susceptibility (Resistance-) of MBT to kanamycin (Km), capreomycin (Cm), levofloxacin (Lfx), moxifloxacin (Mfx) and protionamide (Pt) was remained.

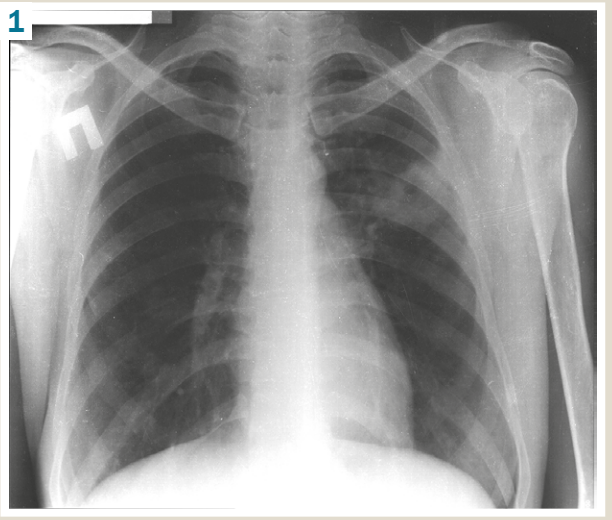
Considering DST, the diagnosis was changed: MDR-TB infiltrative of the left lung with contamination. Destruction+ MBT+ AFB+ MG+ Rif+ C+ phDST (HRE). Resistance- (Km Cm Lfx Mfx Pt) Histology 0 (a new case). Cohort 2 (2020).

The patient refused an inpatient treatment, therefore AMBT of MDR-TB, considering DST, was started on 21.04.2020 on an outpatient basis by a family doctor. The AMBT regimen was as follows: Lfx Bdq linezolid (Lzd) clofazimine (Cfz) Cm.

On May 20, 2020, due to a decrease in hemoglobin (Hb) and erythrocyte (Er) blood levels, Lzd was temporarily discontinued with a correction of the AMBT regimen: Lfx Bdq Cfz cycloserine (Cs) Cm.

During 3 months of treatment, the patient's condition progressively worsened. Radiologically, sharply negative dynamics was determined due to increased infiltration in the upper part of the left lung, increased size of the destruction and the appearance of new foci in S_6 of the right lung (*Fig. 2*).

In addition, bacterial smear and culture remained positive and the drug resistance profile of MBT was changed.



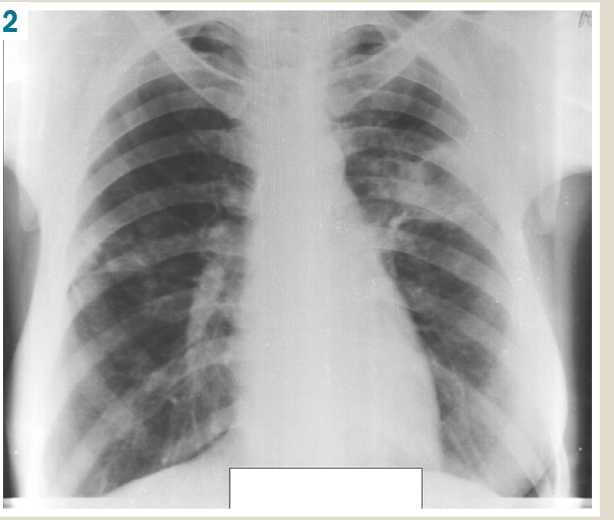


Fig. 1. Chest X-ray from 24.03.2020: There are an area of infiltration of a heterogeneous structure due to destructions from 1.5 cm to 2.0 cm in diameter and foci around it in S_{1+2} of the left lung. A wide path to the hilum. There are single foci in S_6 of the right lung.

Fig. 2. Chest X-ray from 30.07.2020: There are focal and infiltrative shadows with destruction up to 3,0 cm in diameter in the upper lobe of the left lung. Foci of contamination in S_6 of the right lung.

Sputum analysis from 05.08.2020: AFB+ C+ phDST (Lfx Mfx) Resistance- (Km Cm Pt).

Blood analysis from 10.08.2020: Hb – 76 g/l, Er – 2.71 × 10^{12}/l, leukocytes (WBC) – 5.86 × 10^9/l, platelets (pl) – 408 × 10^9/l, eosinophils (Ef) – 4 %, band neutrophils (b/n) – 4 %, segmented neutrophils (s/n) – 61 %, lymphocytes (Lf) – 20 %, monocytes (m) – 11 %, erythrocyte sedimentation rate (ESR) – 22 mm/h.

On August 10, 2020, the patient was hospitalized in a critical condition to CNO "ZRPPCTDC" ZRC.

The patient was examined by a therapist and concomitant diseases were diagnosed: Gastric ulcer disease. Postgastroresection syndrome (in 1998, she was operated on for gastric ulcer disease – a 2/3 resection of the stomach). Anemia of chronic disease (B12 and folate deficiency). Chronic toxic hepatitis, minimal activity.

Comprehensive treatment was prescribed, including the one recommended by the therapist for anemia. AMBT continued according to the scheme: Lfx Bdq Cfz Cs Cm.

Spirography from 11.08.2020: respiratory failure was not detected.

Electrocardiogram (ECG) from 11.08.2020: voltage was sufficient, sinus rhythm, heart rate – 74/min, heart electrical axis (HEA) was not deviated, early ventricular repolarization syndrome, QTcF = 404 msec.

Biochemical blood analysis from 12.08.2020: thymol test (ThT) – 14.17 units, alanine aminotransferase (AlAt) – 0.5 mmol/l/h, aspartate aminotransferase (AsAt) – 0.55 mmol/l/h, total protein (TP) – 69.3 g/l, glucose – 6,0 mmol/l, β-lipoproteins (BLP) – 23 units, creatinine – 97.1 μmol/l, urea – 3.61 mmol/l, residual urea nitrogen – 1.69 mmol/l, α-amylase – 6.8 g/l × h.

Enzyme-linked immunosorbent assay (ELISA) for HIV from 19.08.2020: negative.

Fibrobronchoscopy from 31.08.2020: infiltrative tuberculosis of B_{1+2} on the left side with stenosis of the 1st degree was detected.

After a month of inpatient treatment, the patient's condition was stably moderate-to-severe, bacterial smear and culture remained positive, and anemia persisted.

Sputum analyzes from 04.09.2020: AFB+ C+.

Blood analysis from 04.09.2020: Hb – 82 g/l, Er – 2.64 × 10^{12}/l, WBC – 8.4 × 10^9/l, pl – 438 × 10^9/l, Ef – 0 %, b/n – 1 %, s/n – 58 %, Lf – 25 %, m – 16 %, ESR – 21 mm/h.

Biochemical blood analysis from 12.09.2020: bilirubin – 10.7 mmol/l, ThT – 4.58 units, AlAt – 0.13 mmol/l/h, AsAt – 0.38 mmol/l/h, TP – 82.2 g/l, glucose – 5.61 mmol/l, BLP – 15.2 units, α-amylase – 7.15 g/l × h.

Sputum analyzes from 07.10.2020: AFB+ C-.

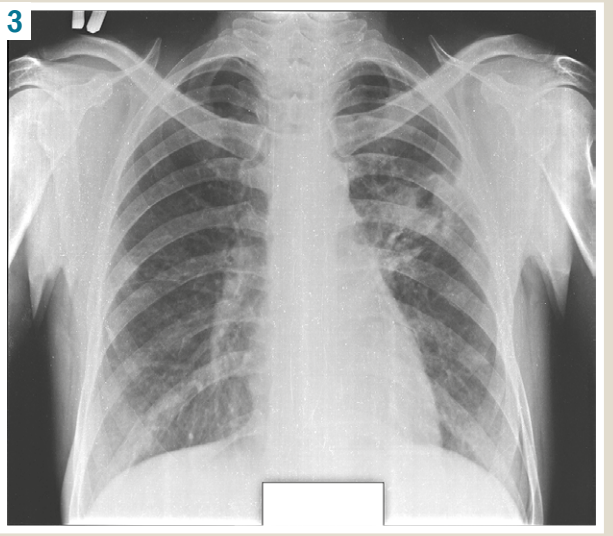
After 2 months of inpatient treatment (October 8, 2020), the AMBT scheme was corrected (Bdq Lzd Cfz Cs delamanid (Dlm)) because of an increase in the Hb level and obtaining updated data on DST with drug resistance to fluoroquinolones. A case of the disease was re-registered: tuberculosis with pre-extensively drug resistance (pre-XDR) infiltrative of the left lung with contamination. Destruction+ MBT+ AFB+ MG+ Rif+ C+ phDST (HRE), phDST II (Km Lfx Mfx). Resistance- (amikacin (Am) Cm Pt Bdq Lzd Cfz Dlm). Extra-pulmonary tuberculosis (EPTB), infiltrative tuberculosis of B_{1+2} on the left side with stenosis of the 1st degree. Histology 0 (a new case). Cohort 4 (2020).

After 3 months, bacterial smear and culture positivity persisted but susceptibility to Bdq remained on the background of positive X-ray dynamics (*Fig. 3*). Sputum test from 06.11.2020: AFB+ C+ phDST II (Km). Resistance- (Am Cm Pt Bdq Lzd Cfz Dlm).

Blood analysis from 16.11.2020: Hb – 91 g/l, Er – 2.96 × 10^{12}/l, WBC – 11.3 × 10^9/l, pl – 284 × 10^9/l, Ef – 2 %, b/n – 10 %, s/n – 72 %, Lf – 10 %, m – 6 %, ESR – 8 mm/h.

A thoracic surgeon recommended a surgical treatment, the patient did not consent.

After 4 months of the treatment, smear and culture conversion to negative was not documented, and the indicators of laboratory analyzes remained practically unchanged.



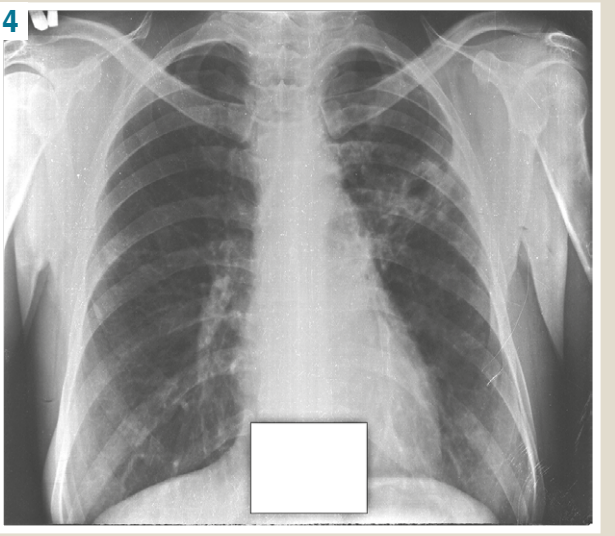


Fig. 3. Chest X-ray from 05.11.2020: in the upper lobe of the left lung, partial resorption of infiltration with the formation of a tuberculoma 5.0 × 3.5 cm in diameter with a destruction of 3.0 × 1.5 cm in diameter. All around are foci, fibrosis, a path to the root. In S_6 of the right lung – partially resolved foci of contamination. The hila are dense. The sinuses are free.

Fig. 4. Chest X-ray from 01.02.2021: in the upper lobe of the left lung, a partial resorption of the infiltration is noted, a tuberculoma up to 5.0 cm in diameter with a destruction up to 2.0 cm in diameter is formed. The path to the hilum gets narrower. There are perifocal fibrosis and polymorphic foci. The hila of both lungs are fibrously changed, deformed. In S_6 of the right lung, local fibrosis, isolated condensed foci are determined. The diaphragm domes are even, clear. The sinuses are free.

So, sputum test from 11.12.2020: AFB+ C+.

Blood analysis from 11.12.2020: Hb – 90 g/l, Er – 3.03 × 10^{12}/l, WBC – 8.1 × 10^9/l, pl – 420 × 10^9/l, Ef – 0 %, b/n – 3 %, s/n – 74 %, Lf – 17 %, m – 6 %, ESR – 24 mm/h.

Biochemical blood analysis from 11.12.2020: bilirubin – 12.3 mmol/l, ThT – 3.98 units, AlAt – 0.15 mmol/l/h, AsAt – 0.34 mmol/l/h, TP – 61.7 g/l, glucose – 5.52 mmol/l, BLP — 15.9 units, α-amylase – 10.8 g/l × h.

After 5 months, smear and culture conversion was not achieved (sputum analysis from 11.01.2021: AFB+ C+) and laboratory test results remained the same.

Rapid HIV test from January 25, 2021: negative.

Fibrobronchoscopy from 26.01.2021: partial resorption of infiltrative tuberculosis of B_{1+2} on the left side, left-sided partially limited purulent endobronchitis of the I–II degree.

After almost 6 months of the inpatient treatment, positive X-ray dynamics was determined (*Fig. 4*).

On 01.02.2021, the patient was re-examined by a thoracic surgeon with a recommendation for surgical intervention to remove the tuberculoma. That time, the patient consented to the re-proposed surgical treatment.

Diffuse changes in the liver and pancreas were detected during an ultrasound examination of the abdominal organs (US AO) from 02.02.2021.

Spirography from 02.02.2021: I degree respiratory failure, mixed type.

ECG from 02.02.2021: voltage was sufficient, sinus rhythm, heart rate – 73/min, HEA was not deviated, moderate diffuse changes in the myocardium of the ventricles, QTcF = 448 msec.

Blood analysis from 03.02.2021: Hb – 115 g/l, Er – 3.63 × 10^{12}/l, WBC – 11.7 × 10^9/l, pl – 597 × 10^9/l, Ef – 1 %, b/n – 5 %, s/n – 64 %, Lf – 21 %, m – 9 %, ESR – 30 mm/h.

Biochemical blood analysis from 03.02.2021: bilirubin – 11.6 mmol/l, ThT – 3.03 units, AlAt – 0.23 mmol/l/h, AsAt – 0.39 mmol/l/h, TP – 61.7 g/l, glucose – 4.24 mmol/l, BLP — 20.0 units, α-amylase – 5.32 g/l × h, creatinine – 110.6 μmol/l, urea – 4.12 mmol/l, residual urea nitrogen – 1.92 mmol/l.

Taking into account the planned surgical treatment on February 4, 2021, the AMBT scheme was corrected: Bdq Lzd Cfz Cs Dlm meropenem (Mpn) amoxicillin / clavulanic acid (Amx/Clv).

Repeated consultation by a therapist on February 5, 2021: Gastric ulcer disease, inactive phase. Postgastroresection syndrome. Anemia of mixed genesis.

Considering the planned surgical intervention, on February 10, 2021, a computed tomography of the respiratory system (Chest CT) was performed: in S_1 of the upper lobe of the left lung, cavity formations with thick walls of an irregular shape with uneven contours, 26 × 15 mm and 13 × 8 mm in diameter were determined. There were multiple dense foci from 2 to 9 mm in diameter, surrounded by areas of fibrosis; single dense foci of 2 to 5 mm in diameter in the S_3 of the right lung parenchyma (*Fig. 5.1, 5.2*).

On February 18, 2021, a surgery was performed due to a formed conglomerate tuberculoma with a destruction in the upper lobe of the left lung – thoracotomy on the left side of the chest, resection of the left upper lung lobe with the Bulau drainage.

Sputum test from 19.02.2021: AFB+ C+.

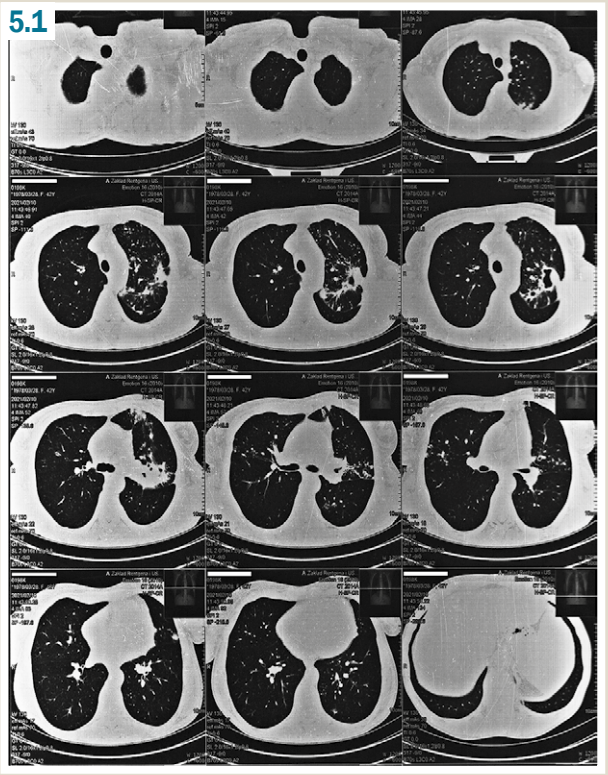
Fibrobronchoscopy from 19.02.2021: the stump of the left upper lobe bronchus. Condition after surgery. I–II degree bilateral diffuse purulent endobronchitis.

Fibrobronchoscopy from 26.02.2021: the stump of the left upper lobe bronchus. Hypertrophic endobronchitis.

After 8 months, the patient was only bacterial culture-positive (sputum test from 05.03.2021: AFB- C-).

Blood analysis from 16.03.2021: Hb – 125 g/l, Er – 3.96 × 10^{12}/l, WBC – 9.3 × 10^9/l, pl – 287 × 10^9/l, Ef – 5 %, b/n – 4 %, s/n – 60 %, Lf – 15 %, m – 16 %, ESR – 6 mm/h.

A complete conversion to negative and a normalization of laboratory analysis indicators were determined after 9 months.



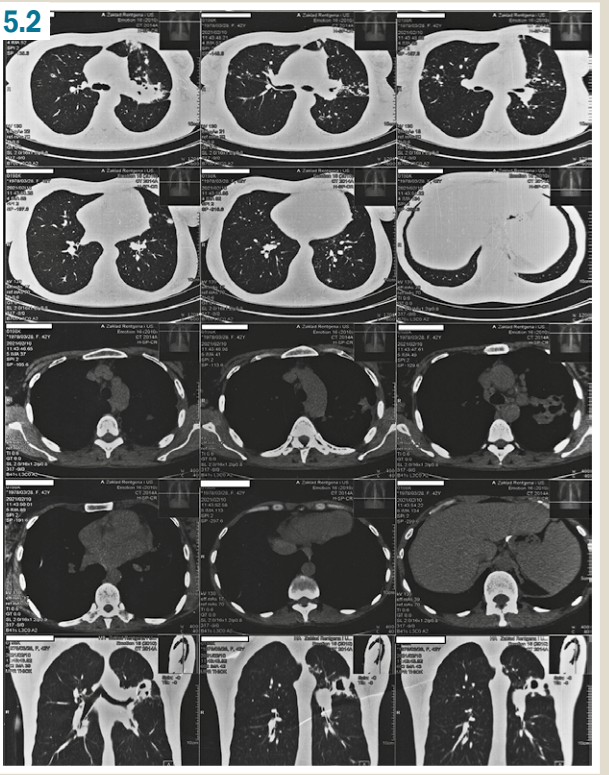
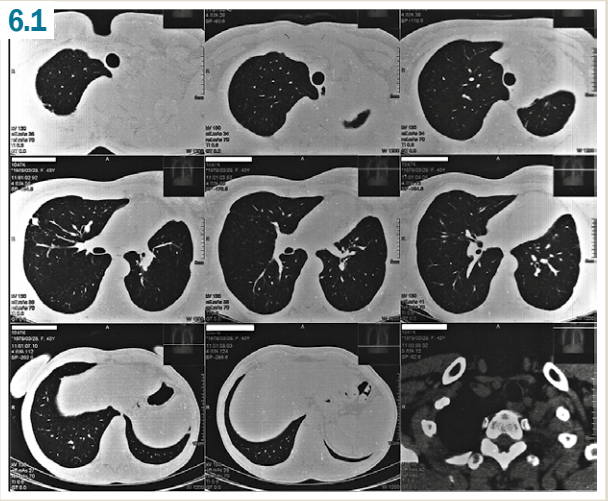


Fig. 5. Chest CT from 10.02.2021 before the surgical treatment.



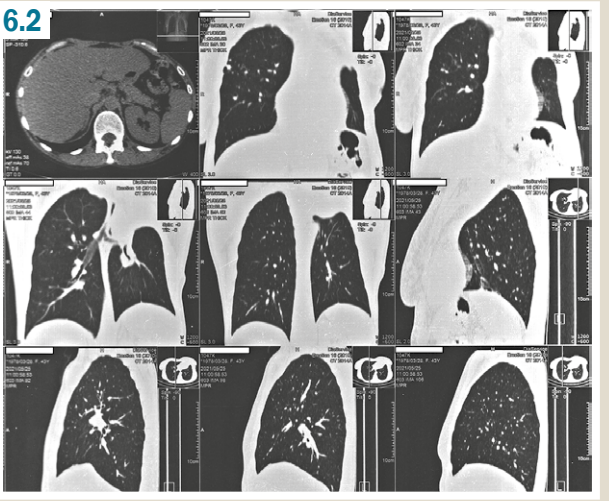


Fig. 6. Chest CT from 10.05.2021: condition after resection of the upper lobe of the left lung. There are bilateral single dense foci on the background of pneumofibrosis in the lower lung fields. The left hilum is pulled up. Pulmonary heart.

Sputum tests from 05.04.2021: AFB- C-.

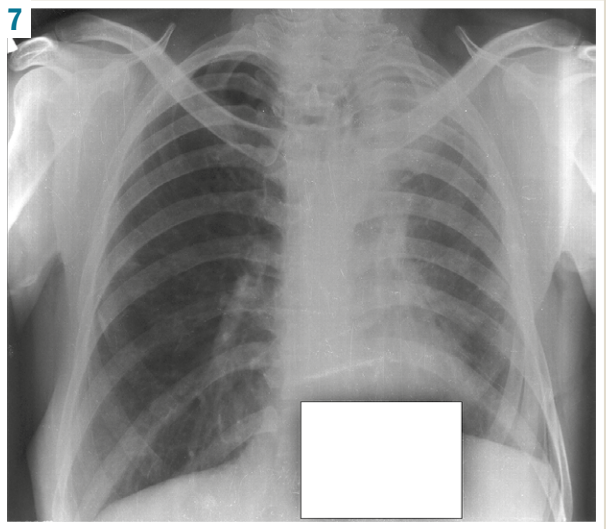
Blood analysis from 05.04.2021: Hb – 132 g/l, Er – 4.16 × 10^{12}/l, WBC – 9.4 × 10^{9}/l, pl – 298 × 10^{9}/l, Ef – 5 %, b/n – 5 %, s/n – 67 %, Lf – 13 %, m – 7 %, ESR – 20 mm/h.

Biochemical blood analysis from 05.04.2021: bilirubin – 10.15 mmol/l, ThT – 3.36 units, AlAt – 0.97 mmol/l/h, AsAt – 1.0 mmol/l/h, TP – 66.2 g/l, glucose – 5.69 mmol/l, BLP – 15.1 units, α-amylase – 4.84 g/l × h, creatinine – 122.5 μmol/l, urea – 3.41 mmol/l, residual urea nitrogen – 1.59 mmol/l.

Considering the positive dynamics, the general condition normalization and the conversion to negative, on the 10th month of treatment (06.04.2021), the patient was discharged from the hospital to continue outpatient treatment by a family doctor according to the AMBT regimen: Bdq Lzd Cfz Cs Dlm.

After 1 year of Bdq treatment, the patient had stable X-ray dynamics (*Fig. 6.1, 6.2*) without bacterial excretion (sputum tests from 06.05.2021: AFB- C-).

After 1 year and 1 month of Bdq treatment, positive MBT culture growth with drug resistance to all fluoroquinolones was obtained. Sputum tests from 10.06.2021: AFB- C+ phDST II (Lfx Mfx0,25 Mfx1,0), Resistasnce- (Am Cm Lzd Cfz Dlm).



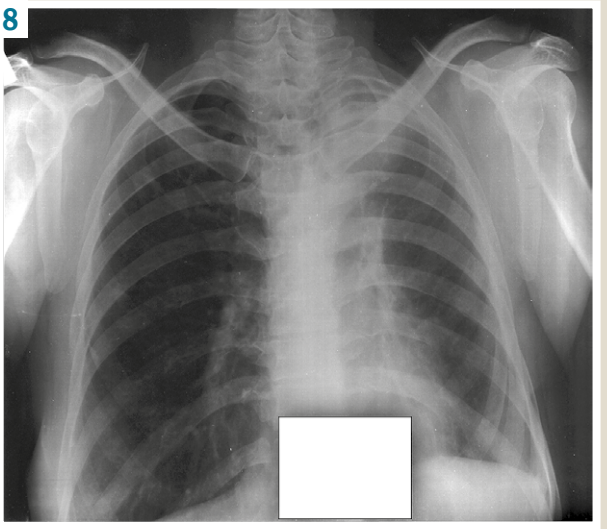


Fig. 7. Chest X-ray from 20.07.2021: condition after resection of the upper lobe of the left lung. The lung is expanded, there are fibrothorax, increased density of lung tissue, fibrosis in the upper fields. There are single dense foci on the background of bilateral pneumofibrosis in the lower fields. The left hilum is pulled up. Pulmonary heart.

Fig. 8. Chest X-ray from 08.10.2021: condition after resection of the upper lobe of the left lung. A fibrothorax is formed at the top of the left lung, the costo-diaphragmatic sinus is obliterated. There are fibrosis, dense small foci in the upper lobe of the right lung. Pulmonary heart.

After 1 year and 2 months of Bdq treatment, stable X-ray dynamics were determined (*Fig. 7*) without bacterial excretion (sputum analysis from 20.07.2021: AFB- C-).

During control examinations in August 2021 (after 1 year and 3 months of Bdq treatment), smear and culture reversion to positive was defined, DST was performed without Bdq (unavailability of tests). Sputum tests from 26.08.2021: AFB+ C+ Resistance- (Am Cm Lzd Cfz Dlm).

Blood analysis from 26.08.2021: Hb – 132 g/l, Er – 4.0 × 10^{12}/l, WBC – 7.6 × 10^{9}/l, pl – 290 × 10^{9}/l, Ef – 1 %, b/n – 14 %, s/n – 64 %, Lf – 18 %, m – 4 %, ESR – 4 mm/h.

During control examinations in October 2021 (after 1 year and 5 months of Bdq treatment), only culture reversion to positive was determined (sputum analysis from 08.10.2021: AFB- C+), X-ray – stable dynamics (*Fig. 8*). Fibrobronchoscopy from 08.10.2021: the stump of the left upper lobe bronchus.

During control examinations in December 2021 (after 1 year and 7 months of Bdq treatment), bacterial culture was positive and drug resistance to Bdq was diagnosed. Analysis of sputum from 01.12.2021: AFB- C+ phDST II (Bdq) Resistance- (Am Lzd Cfz Dlm). X-ray dynamics remained stable (*Fig. 9*). An increase in ESR, however, was detected. Blood analysis from 01.12.2021: Hb – 140 g/l, Er – 4.37 × 10^{12}/l, WBC – 8.4 × 10^{9}/l, pl – 292 × 10^{9}/l, Ef – 0 %, b/n – 8 %, s/n – 64 %, Lf – 19 %, m – 9 %, ESR – 38 mm/h.

Rapid HIV test from 01.12.2021: negative.

After obtaining the Bdq test results, DST was repeated in December 2021, and a repeated result with drug resistance to Bdq was obtained in January 2022.

On 13.01.2022, a case of treatment failure with extensive drug resistance (XDR) was registered, and the patient was transferred to a palliative treatment being diagnosed with XDR infiltrative of the left lung with contamination. Destruction+ MBT+ AFB+ MG+ Rif+ C+ phDST (HRE), phDST II (Km Lfx Mfx Bdq). Resistance- (Am Cm Pt Lzd Cfz Dlm). Histology+ (a new case), (palliative treatment – 01.2022). Cohort 4 (2020). Condition after surgery (18.02.2021) – upper left lobectomy.

The patient's general condition worsened dramatically 4 months after transfer to the palliative treatment (May 24, 2022). Due to further examination, negative X-ray dynamics with the appearance of a destructive process were revealed (*Fig. 10*), there was smear and culture reversion to positive and shortness of breaths, and an inflammatory reaction was increased:

– Sputum tests from 25.05.2022: AFB+ C+ Resistance- (Am Lzd Cfz Dlm);

– Spirography from 26.05.2022: II degree respiratory failure;

– Blood analysis from 26.05.2022: Hb – 118 g/l, Er – 3.8 × 10^{12}/l, WBC – 8.4 × 10^{9}/l, pl – 357 × 10^{9}/l, Ef – 0 %, b/n – 18 %, s/n – 69 %, Lf – 6 %, m – 7 %, ESR – 58 mm/h;

– ECG from 26.05.2022: Sinus tachycardia, heart rate 112/min, HEA is not deviated, incomplete blockade of the right branch of the bundle of His, hypertrophy of the right atrium, moderate diffuse changes in the myocardium, QTcF = 389 msec;

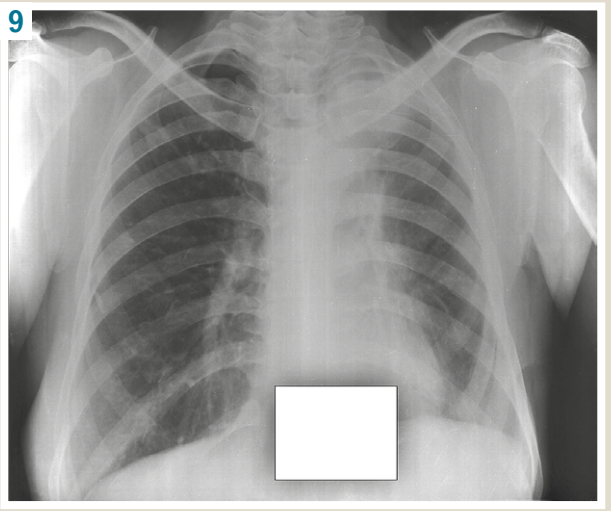
– Biochemical blood analysis from 27.05.2022: bilirubin – 12.05 mmol/l, ThT – 4.18 units, AlAt – 0.89 mmol/l/h, AsAt – 0.76 mmol/l/h, TP – 80.5 g/l, glucose – 4.05 mmol/l, BLP – 27 units, α-amylase – 6.83 g/l × h, creatinine – 100,4 μmol/l, urea – 3.02 mmol/l, residual urea nitrogen – 1.41 mmol/l.

Therapist consultation from 27.05.2022: Gastric ulcer disease, inactive phase. Postgastroresection syndrome. Chronic obstructive pulmonary disease (COPD), clinical group B, II degree, pneumofibrosis. II degree pulmonary failure (PF). Chronic pulmonary heart. I degree heart failure (HF). Anemia of mixed genesis.

Appropriate symptomatic therapy was prescribed.

6 months after transfer to the palliative care (20.07.2022), the patient's general condition continued to worse, smear and culture conversion to negative was not achieved.

Sputum analysis from 20.07.2022: AFB+.



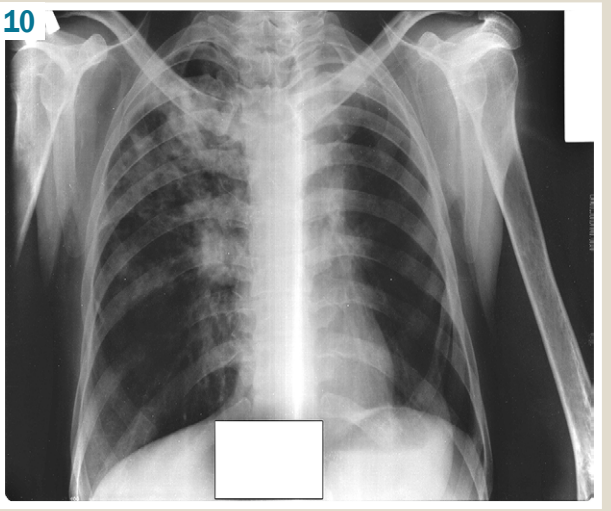


Fig. 9. Chest X-ray from 01.12.2021: condition after resection of the upper lobe of the left lung. Fibrothorax is formed at the top of the left lung, the costo-diaphragmatic sinus is obliterated. There are fibrosis, dense small foci in the upper lobe of the right lung. Pulmonary heart.

Fig. 10. Chest X-ray from 24.05.2022: Condition after resection of the upper lobe of the left lung. There are polymorphic foci and infiltrates with a decay cavity up to 3,0 cm in diameter in the upper lobe of the right lung. There are polymorphic foci and infiltrates of contamination in the upper fields of the left lung and in S_6 of the right lung. The hila are deformed, pulled up. The sinus on the left side is obliterated. Pulmonary heart.

Blood analysis from 20.07.2022: Hb – 118 g/l, Er – 3.75 × 10^{12}/l, WBC – 8.4 × 109/l, pl – 298 × 10^{9}/l, Ef – 3 %, b/n – 15 %, s/n – 64 %, Lf – 15 %, m – 3 %, ESR – 46 mm/h.

Spirography from 20.07.2022: Restrictive type of III degree respiratory failure. I degree obstructive disorders.

ECG from 11.07.2022: Sinus tachycardia, heart rate 102/min, HEA is not deviated, incomplete blockade of the right branch of the bundle of His, hypertrophy of the right atrium, moderate diffuse changes in the myocardium, QTcF = 391 msec.

It can be seen after the example we have demonstrated in case 1, the patient was newly diagnosed with tuberculosis on 24.03.2020, it was RR-TB and phDST with resistance to HRE. AMBT of MDR-TB was started on the outpatient basis by the family doctor, as the patient refused the inpatient treatment. AMBT regimen: Lfx Bdq Lzd Cfz Cm (21.04.2020–20.05.2020). Due to blood Hb and Er decreased levels, Lzd was temporarily discontinued with the AMBT regimen correction: Lfx Bdq Cfz Cs Cm (21.05.2020–09.08.2020). The patient's condition progressively worsened, there was persistent smear and culture positivity, and sharply negative X-ray dynamics was determined. Therefore, after 4 months of the outpatient treatment, she was hospitalized in a critical condition to CNO "ZRPPCTDC" ZRC. Complex treatment was prescribed in the hospital, including the one recommended by the therapist for anemia; AMBT continued according to the scheme: Lfx Bdq Cfz Cs Cm (10.08.2020–07.10.2020). The case was re-registered as pre-XDR after Hb increasing and receiving new DST results of resistance to fluoroquinolones and the AMBT regimen was corrected: Bdq Lzd Cfz Cs Dlm (08.10.2020–03.02.2021). The following correction of the AMBT scheme was done considering the planned surgical treatment: Bdq Lzd Cfz Cs Dlm Mpn Amx/Clv (04.02.2021–06.04.2021).

Given the positive dynamics, the general condition normalization and the smear and culture conversion, on the 10th month of treatment (06.04.2021), the patient was discharged from the hospital to continue outpatient treatment by the family doctor according to the AMBT regimen: Bdq Lzd Cfz Cs Dlm. During the control examination in August 2021 (after 1 year and 3 months of Bdq treatment), smear and culture reversion to positive was defined again, DST was performed without Bdq (unavailability of tests). After Bdq tests became available, DST was repeated in December 2021, and the repeated result with drug resistance to Bdq was obtained in January 2022. On 13.01.2022, a case of treatment failure with XDR was registered, and the patient was transferred to the palliative treatment.

It should be noted that after 7 months of Bdq treatment, MBT were still susceptible to it. Drug resistance to Bdq was detected after 1 year and 7 months of treatment. Bdq drug resistance may have developed earlier, but it was impossible to be detected because of Bdq test unavailability in the hospital. During the entire time of AMBT, the patient continued to be smear and culture positive with the progression of tuberculosis inflammation. The patient's general condition improved only in the hospital, and stabilization of the process occurred after surgery, but it lasted for 5 months, and smears and cultures were negative for only 3 months. The patient's general condition worsened dramatically 4 months after transfer to the palliative treatment: negative X-ray dynamics with the destructive process development, bacterial excretion, shortness of breaths and increased inflammatory reaction. A risk factor for drug resistance to Bdq was the lack of controlled treatment at the ambulatory stage.

Clinical case 2

A patient A., male, 47 years.

From the anamnesis: Tuberculosis was firstly detected in 2002. He received AMBT. Relapse of tuberculosis (RTB) was in 2009, he received treatment in places of deprivation of liberty. The treatment was completed with the results – cured in both cases.

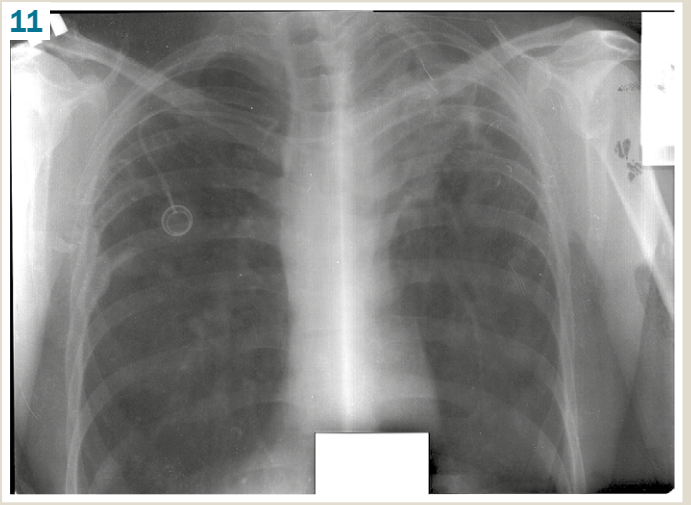


Fig. 11. Chest X-ray from 24.05.2019: there are focal-infiltrative changes from high to low intensity with destructions (up to 1.5 cm in diameter in the left lung and up to 1.0 cm in the right lung) in the upper lobes and S_6 of both lungs on the background of significant fibro-dystrophic changes. The left apex with signs of hypoventilation. The left hilum is enlarged, poorly structured and pulled up.

He came to his family doctor in May 2019 with complaints of a prolonged cough, shortness of breath, and night sweats. After additional examinations, MBT resistant to rifampicin were found in the sputum: MBT+ AFB+ MG+ Rif+. Sputum analyzes from 24.05.2019: AFB+ C+ phDST I (HR pyrazinamide (Z) E), phDST II (Km). Resistance-(Cm Pt Lfx Mfx Lzd Cfz). Chest X-ray from 24.05.2019 (*Fig. 11*) showed changes.

The following diagnosis was made: Pulmonary MDR-TB, disseminative. Destruction+ MBT+ AFB+ MG+ Rif+ C+ phDST I (HRZE), phDST II (Km). Histology 0 (RTB). Cohort 2 (2019).

The AMBT regimen was prescribed: Z Cm Lfx Pt Cs para-aminosalicylic acid (Pas).

ELISA for HIV from 03.06.2019: negative.

Spirography from 03.06.2019: Restrictive type of III degree respiratory failure.

ECG from 03.06.2019: voltage is sufficient, sinus rhythm, heart rate 75/min, HEA is not deviated, QTcF = 417 ms.

Blood analysis from 04.06.2019: Hb – 146 g/l, Er – 4.46 × 10^{12}/l, WBC – 8.1 × 10^9/l, pl – 470 × 10^9/l, Ef – 5 %, b/n – 2 %, s/n – 57 %, Lf – 28 %, m – 8 %, ESR – 40 mm/h.

Biochemical blood analysis from 05.06.2019: bilirubin – 9.44 mmol/l, ThT – 5.53 units, AlAt – 0.22 mmol/l/h, AsAt – 0.27 mmol/l/h, TP – 70.7 g/l, glucose – 4.76 mmol/l, BLP – 22.0 units, creatinine – 91.9 μmol/l, urea – 3.94 mmol/l, residual urea nitrogen – 1.84 mmol/l.

Until December 2019, the patient was only sputum smear positive (bacterioscopically AFB+, C-). He was not treated regularly and repeatedly skipped antimycobacterial drug-taking. Control DST revealed drug resistance to fluoroquinolones in January 2020: AFB+ C+ phDST II (Km Lfx Mfx0,25) Resistance- (Cm Pt Mfx1.0 Lzd Cfz). Based on that, a case of treatment failure was registered.

Negative radiological dynamics was noted in March (chest X-ray from 10.03.2020): numerous polymorphic infiltrates and foci from high to medium intensity on the background of fibrosis in the upper lobes and S_6 of both lungs are determined. There are destructions up to 2,0 cm in diameter in S_{1+2} of the left lung and up to 1,0 cm in diameter in S_6 of the right lung. The hila are structural, the left one is pulled up. The sinuses are free.

Smear and culture conversion was not achieved. Analysis of sputum from 10.03.2020: AFB+ C+ phDST II (Km Lfx Mfx0.25 Mfx1.0). Resistance- (Cm Am Lzd Dlm).

On 11.03.2020, the case was re-registered: pulmonary pre-XDR-TB, disseminative. Destruction+ MBT+AFB+ MG+ Rif+ C+ phDST I (HRZE), phDST II (Km Lfx Mfx0.25 Mfx1.0). Resistance- (Cm Am Lzd Dlm). Histology 0 (Repeated course). Cohort 1 (2020). A repeated AMBT course was prescribed according to the scheme: Bdq Lzd Cfz Dlm Mpn Amx/Clv.

The patient was defined to be sputum smear and culture negative during the one-month monitoring due to the prescribed treatment for 10 months (March – December), and positive radiological dynamics was diagnosed in August 2020. Chest X-ray from 27.08.2020: bilateral partial resorption of focal-infiltrative shadows on the background of fibrosis. The cavity in the upper field of the left lung is reduced to 1.5 cm in diameter. The left hilum is deformed and pulled up.

The patient was non-adherent to the treatment, he repeatedly skipped antimycobacterial drug-taking. Control bacterioscopic and bacteriological tests revealed sputum smear and culture reversion to positive in January 2021 (sputum analysis from 23.01.2021: AFB C+ phDST II (Lfx Mfx0.25), Resistance- (Cm Pt Mfx1.0 Lzd Cfz).

Persistent sputum smear and culture positivity was defined since January during the treatment by AMBT regimen, which included Bdq. Drug resistance to Bdq was detected for the first time in March (sputum analysis from 02.03.2021: AFB+ C+ phDST II (Mfx1,0 Bdq). Resistance- (Cm Am Lzd Cfz Dlm).

Radiologically significant dynamics were also not determined (Chest X-ray from 30.03.2021: bilateral polymorphic focal-infiltrative shadows in the upper lobes and S_6 with destructions in the left upper lobe up to 2.0 cm in diameter, in S_6 of the right lung – up to 1.0 cm in diameter. The hila are pulled up. Pulmonary heart.

The patient continued to be non-adherent to the treatment, he repeatedly skipped antimycobacterial drug-taking.

In April 2021, DST result with drug resistance to Bdq was obtained again (sputum analysis from 08.04.2021): AFB- C+ phDST II (Mfx1.0 Bdq). Resistance- (Cm Am Lzd Cfz Dlm).

The case was re-registered as XDR, a case of repeated treatment failure – the patient was transferred to a palliative treatment: pulmonary XDR-TB, disseminative. Destruction+ MBT+ AFB+ MG+ Rif+ C+ phDST I (HRZE), phDST II (Km Lfx Mfx0.25 Mfx1.0 Bdq). Resistance- (Cm Am Lzd Dlm). Histology 0 (Repeated course). Cohort 1 (2020).

Blood analysis from 08.04.2021: Hb – 144 g/l, Er – 4.51 × 10^{12}/l, WBC – 9.5 × 10^9/l, pl – 297 × 10^9/l, Ef – 5 %, b/n – 4 %, s/n – 53 %, Lf – 34 %, m – 3 %, ESR – 29 mm/h.

Biochemical blood analysis from 08.04.2021: bilirubin – 7.2 mmol/l, ThT – 4.34 units, AlAt – 0.54 mmol/l/h, AsAt – 0.24 mmol/l/h, TP – 83.9 g/l, glucose – 4.2 mmol/l, BLP – 20 units, creatinine – 114 μmol/l, urea – 5.43 mmol/l, residual urea nitrogen – 2.54 mmol/l.

ECG from 08.04.2021: voltage is sufficient, sinus tachycardia, heart rate – 92/min, HEA is not deviated, signs of impaired intra-atrial conduction, moderate changes in the myocardium, QTcF = 404 ms.

It can be seen from the example which has been demonstrated in case 2, the patient had been suffering from tuberculosis since 2002: new case (2002), RTB (2009). Since May 2019, he received AMBT of MDR-TB according to the scheme: Z Cm Lfx Pt Cs Pas. He was treated irregularly and repeatedly skipped antimycobacterial drug-taking. The control sputum analysis revealed sputum smear and culture reversion to positive and DST diagnosed drug resistance to fluoroquinolones in January 2020. Due to this, the case of treatment failure was registered. In March 2020, the case was re-registered as pre-XDR and the repeat course of AMBT was prescribed according to the regimen: Bdq Lzd Cfz Dlm Mpn Amx/Clv. The patient continued to be non-adherent to the treatment and repeatedly skipped antimycobacterial drug-taking. The control bacterioscopic and bacteriological tests revealed reversion of sputum smear and culture positivity in January 2021. In April 2021, the DST result with drug resistance to Bdq was obtained. The case was re-registered as XDR, the case of repeated treatment failure – the patient was transferred to the palliative treatment. The risk factor for drug resistance to Bdq was low adherence to treatment.

Discussion

The presented clinical cases confirm the literature data that the treatment effectiveness for patients with RR-TB and MDR-TB is associated with drug resistance to Bdq. So, G. P. Mishra, J. Mulani [15], studying the low efficacy of AMBT in patients with Rifampicin-resistant TB (RR-TB), have found that it was associated with resistance to Bdq. Liu Y. et al. [3], studying the dynamics of the MBT isolates sensitivity to Bdq during AMBT, have obtained, that these patients were at greater risk of AMBT failure compared to initially resistant to Bdq MDR-TB cases. Mallick J. S. et al. in a systematic review [2] have determined that in order to prevent the development of acquired resistance in MBT isolates to Bdq during AMBT, treatment regimens should include drugs with high and early bactericidal activity.

At the same time, the number of disturbing reports on both primary and acquired MBT resistance to Bdq has been increasing for the last few years, according the literature, which could lead to a rapid loss of this new drug. Regarding the reasons for the development of acquired drug resistance to Bdq, the second clinical case, as examples of other authors, has demonstrated low adherence to treatment. Mallick J. S. et al. [2], Liu Y. et al. [3], Guglielmetti L. et al. [4] indicate the reasons of this outcome: the prescription of Bdq to patients with initially low adherence to treatment, a high frequency of self-discontinuation of AMBT by patients.

There is no data in the literature about the lack of controlled treatment at the outpatient stage as a risk factor for Bdq drug resistance and negative clinical outcomes in patients with MDR-TB, which could complement the scientific experience in this problem.

Conclusions

In both clinical cases, drug resistance to Bdq was acquired (secondary), and had an impact on the clinical outcomes of tuberculosis treatment. The risk factors of drug resistance to Bdq and negative clinical outcomes were the lack of controlled treatment at the outpatient stage in the first case, and low adherence to treatment in the second one.

Prospects for further research. Further study on MBT resistance to new antimycobacterial drugs during AMBT and its impact on clinical outcomes.

Conflicts of interest: authors have no conflict of interest to declare.
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