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Management Tactics for Patients with Combined Cavernous Tuberculosis with Multidrug Resistance/Extensive Drug Resistance and Macleod Syndrome (Clinical Case)

Our own observation of a case of combined cavernous tuberculosis with multidrug resistance (MDR-TB) and extensively drug resistance (XDR-TB) and MacLeod syndrome is presented. Our aim was to determine the managing tactics of such patients. MDR-TB with a cavity in the upper lobe of the left lung was first diagnosed in the patient 5 years ago and MacLeod syndrome was diagnosed in the right lung (a thin-walled emphysematous bulla measuring 88.5 × 54.2 × 45.2 mm in diameter in the upper third of the subpleural mediastinal pleura). At the end of the intensive phase, after 6 months of treatment, the patient developed massive bacterial excretion and additionally developed resistance to ethambutol. X-rays revealed the formation of fibro-cavernous tuberculosis in the upper lobe of the left lung (several destructions with thickened walls, some of them deformed, with significant fibrous changes around them); bullous dystrophy with several dense foci was detected in the right lung. Considering the negative dynamics, the patient was operated on: left upper lobectomy, atypical resection of S6 of the left lung. The patient completed treatment with residual changes in the form of metatuberculous fibro-focal changes in the lungs and the condition after surgery. No actions were taken regarding MacLeod syndrome. The patient had stable clinical and radiological dynamics for 5 years, which indicated the high effectiveness of surgical intervention in addition to antimycobacterial therapy (AMBT). COVID-19 provoked reactivation of a specific process after 5 years, which turned into XDR-TB due to additional resistance (bacterial excretion was one-time, and foci were identified on the X-ray). At the same time, the patient still had grade II pulmonary insufficiency, as 5 years ago, and the number of emphysematous bullae increased, measuring 7—46.6 mm in diameter on the anterior surface in the right lung. Considering the negative dynamics of MacLeod syndrome, the patient needs to undergo an operation to reduce the volume of the upper third of the right lung. Thus, the management tactics for patients with a combined course of cavernous MDR-TB/XDR-TB and MacLeod syndrome , when AMBT fails, are as follows: in the presence of bacterial excretion after 4—6 months of treatment and a cavernous process, consider the possibility of additional surgical intervention (lobectomy, resection, etc.); in the presence of MacLeod syndrome, consider the possibility of additional surgery to reduce the volume of the affected part of the lung.

Keywords

Tuberculosis, multidrug resistance, extensive drug resistance, cavern, MacLeod syndrome, surgical intervention.

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are serious public health problems worldwide today [3, 11, 12]. Without a doubt, the main method of treatment for these forms of tuberculosis is antimycobacterial therapy (AMBT) according to drug susceptibility testing (DST) data.

Cavernous tuberculosis is one of the risk factors for an adverse outcome of tuberculosis [7] due to the fact that AMBT alone does not provide sterilisa-

tion of fibrous caverns, which is the cause of reactivation and chronicity of the specific process. Therefore, additional surgical removal of such cavities in MDR-TB and XDR-TB can provide sterilising cure in the long term, which increases the effectiveness of treatment in this category of patients [9, 10].

G.Y. Marfina et al. [7] indicate that thoracic surgery should be considered as an important element of the complex treatment of patients with cavernous MDR-TB and XDR-TB, as it contributes to the cessation of bacterial excretion after a month of surgery (including lung resection) in 68.8 % of MDR-TB and 45.5 % of XDR-TB and after 20—36 months — in 95.5 and 65.7 %, respectively. According to other researchers [4—7, 12], in cases of destructive MDR-TB and XDR-TB, surgical intervention (partial lung resection, lobectomy, etc.) in addition to AMBT helps reduce the bacterial load, which , as a result, significantly increases the chances of cure in a significant part of patients and reduces the mortality rate.

According to the results of the research by M.S. Opanasenko et al. [1], it was determined that the optimal timing of surgical treatment of patients with MDR-TB and XDR-TB of the lungs is 4—6 months after the start of AMBT. Researchers have found that performing lung resections with corrective AMBT allows for a 7.3 % increase in effectiveness of surgical interventions by 16.1 % and a decrease in postoperative mortality by 10.1 %. Lobectomy and segmental resection are the most effective among resection interventions, the use of which allows for a 7.3 % increase in effectiveness a 1.9-fold reduction in the mortality rate, and an 8 % reduction in the level of postoperative complications.

MacLeod syndrome [2] (unilateral pulmonary emphysema, vanishing lung, bullous emphysema of the lungs) is a special form in which one lung is affected. Men who suffer from frequent respiratory diseases are affected more often. Valvular obstruction of small bronchioles is important in the pathogenesis of MacLeod syndrome. Histologically, emphysema with individual subpleurally located bullae, reduction of pulmonary capillaries and dilation of small bronchi with hypoplastic changes in the walls are determined. There are no clinical manifestations (long asymptomatic course) in most patients; in others, the leading symptom is shortness of breath. It is caused by the fact that the emphysematous lung causes the mediastinum to shift to the opposite side and occupies most of the volume of the chest cavity, which leads to pronounced ventilation disorders of the normally developed lung, which provides gas exchange. Radiological manifestations of MacLeod syndrome include a sharp increase in the transparency of the affected lung, weakening of the pulmonary pattern and large bullae. Spirography results indicate signs of emphysema. According to research [2], it has been found that the triggering mechanism of bullous emphysema of the lungs (MacLeod syndrome) may be residual changes after a tuberculosis process in the past. It is well known that the predominant localisation of tuberculosis is the upper parts of the lungs, which is characterised by the duration of the process, the toxic effect of *Mycobacterium tuberculosis* (MBT) on the lungs, lymphostasis and the development of fibrosis. Fibrosis leads to uneven resistance of the alveolar walls to airflow, which leads to the formation of a cavity associated with the bronchioles, the collapse of which causes the formation of a valve mechanism that ensures the gradual entry of air into this cavity. Relapses of tuberculosis can lead to bronchiolar obliteration and further stretching of the alveolar cavity, leading to impaired perfusion of the alveolar walls with their further destruction.

According to M.S. Opanasenko et al. [8], the treatment method for bullous lung disease is lung volume reduction surgery (removal of the least functional part of the lung to improve airflow, diaphragmatic mechanics, chest wall function and alveolar gas exchange in the remaining lung), which allows for achieving treatment effectiveness in 100 % of cases after 3 months, and in 89.9 % after 2 years.

Thus, additional surgical intervention for cavernous MDR-TB and XDR-TB is a relevant issue today. At the same time, the treatment of MacLeod syndrome, regardless of the nature of its origin, also requires surgical intervention. In the available literature, we did not find descriptions of the combined course of cavernous MDR-TB/XDR-TB and MacLeod syndrome.

Objective — to indicate the tactics of managing patients with a combined course of cavernous MDR-TB/XDR-TB and MacLeod syndrome in the case of ineffectiveness of AMBT, using the example of our own observation.

Clinical case

Patient: *Stanislav,* 59 years old.

From anamnesis. He suffered a chest injury in 2002 (fractured ribs, left lung damage). From 2002 to 2004, he was in prison. There was tuberculosis contact with his son: firstly diagnosed tuberculosis (FDTB) in 2004, relapse of tuberculosis (RTB) in 2009, Pre-XDR-TB (2010) fibro-cavernous form of tuberculosis of the lungs, Destruction+ MBT+, smear (M)+, culture (C)+, phenotypic drug susceptibility test (phDST) (isoniazid (H), rifampicin (R), ethambutol (E), streptomycin (S), kanamycin (Km), amikacin (Am), capreomycin (Cm), ofloxacin (Ofx), ethionamide (Et), para-aminosalicylic acid

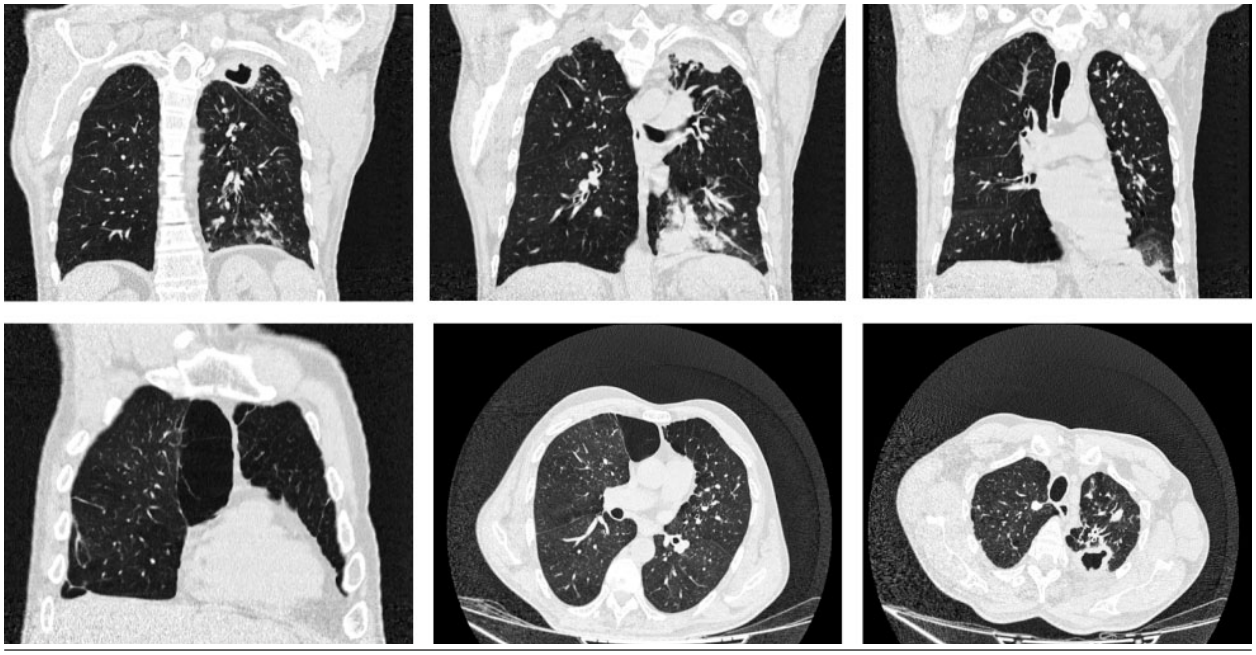

Fig. 1. **CT scan of the thoracic cavity dated 3 September 2019**

(Pas)) — died due to pulmonary haemorrhage in November 2011.

The patient worked at a company, where he underwent a fluorography examination every year (the last was in March 2019). At the beginning of September 2019, his condition deteriorated (cough with purulent sputum, body temperature up to 39 °C), he was consulted by his family doctor. During computed tomography of the thoracic cavity (CT scan), the following changes were detected (Fig. 1): A series of tomograms in axial, sagittal and frontal projections showed a thin-walled emphysematous bulla measuring 88.5 × 54.2 × 45.2 mm in diameter in the upper third of the subpleural-mediastinal pleura of the right lung. The apical pleura is thickened to 22.3 mm. Subpleurally, a cavity formation with unevenly thickened walls up to 4.5 mm, with undermined tuberous inner and indistinct radiant outer contours, with signs of connection to the draining subsegmental bronchus, measuring 41.5 × 32.5 mm in diameter, is determined in the upper lobe of the left lung. Also, some dense foci with a diameter of 3 to 11.5 mm, mainly subpleurally, are detected in the upper lobe of the right lung. Throughout the left lung, foci are identified as dissemination and they merge into a large conglomerate measuring 70.5 × 31.8 mm in diameter in the lower lobe.

Considering the CT scan data and the presence of tuberculosis contact in the anamnesis, the patient was referred for consultation to a phthisiologist, where he was further examined. Thus, in the sputum analysis of 6 September 2019, both microscopically and by molecular genetic method (MG), MBT resistant to rifampicin was detected: M(1+) MG+ Rif+. BACTEC culture showed growth of foreign non-specific flora, and nontuberculous mycobacteria grew on Lowenstein—Jensen medium (ID test negative, sodium salicylate test positive). A week later (13 September 2019), increased bacterial excretion (M (3+)) in the sputum analysis was detected and culture revealed resistance to HR and pyrazinamide (Z) with preserved sensitivity to: Km, Cm, levofloxacin (Lfx), moxifloxacin (Mfx), linezolid (Lzd), clofazimine (Cfz) and prothionamide (Pt).

During fibrobronchoscopy (FBS), infiltrative tuberculosis of segment B1+2 on the left side and limited purulent endobronchitis of the upper lobe bronchus (grade I—II) were revealed.

The rapid HIV test was negative. Blood and urine biochemical parameters were within normal limits. The white blood cell count showed mild leukocytosis.

Spirography results indicated grade II ventilatory failure.

Based on the results of additional examinations, the following diagnosis was established: Multidrug resistant tuberculosis (MDR-TB) (09/2019) infiltrative form of the upper lobe of the left lung with dissemination. Destruction+. MBT+ MG+ Rif+ M+ C+ phenotypical DST (phDST) (HRZ) Resistance-(KmCmLfxMfxLzdCfzPt). Extrapulmonary tuberculosis (EPTB) infiltrative of B1+2 on the left. Histology 0 (FDTB). Grade II pulmonary insufficiency (PI).

A short-term treatment regimen STR, «Bangladesh regimen» was prescribed: 6 months — H(0.6) EZKmMfx(0.8)PtCfz/5 months — EZMfx(0.8)Cfz.

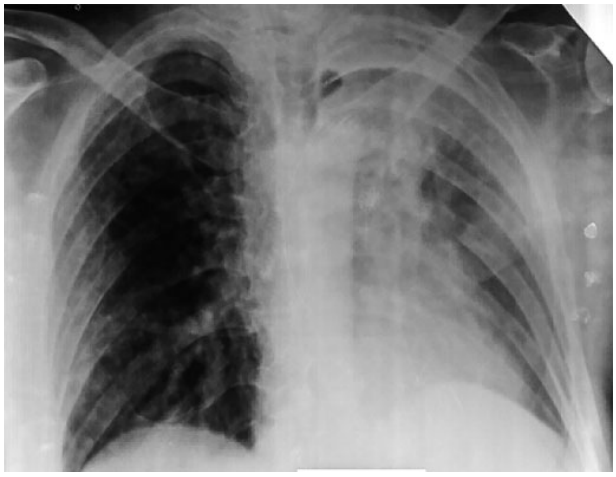

Fig. 2. **Chest X-ray dated 19 February 2024, taken in the infectious diseases hospital**

Cessation of bacterial excretion was achieved after 3 months of treatment. After 4 months, the patient's X-ray showed positive changes (January 2020): there is an area of pleuro-pneumocirrhosis of heterogeneous structure due to a deformed cavity measuring 3 × 1.5 cm in diameter at the apex of the left lung; there are few mostly intense foci in the upper lobes and S6 of both lungs.

After 5 months, a decrease in the volume of the upper lobe of the left lung was determined radiographically, which was compacted and infiltrated, and showed several areas of destruction with thickened walls, some of them deformed, with significant fibrous changes around them; bullous dystrophy with several dense foci was detected in the right lung.

After 6 months of treatment, the patient developed massive bacterial excretion (M(3+)) and additionally developed resistance to ethambutol. At the same time, the patient had heart problems, so he was examined and checked by a physician. Consultant physician's conclusion: Idiopathic arrhythmia — paroxysmal atrial fibrillation, normosystolic form. Heart failure (HF) grade 1.

Considering the presence of bacterial excretion after completing the intensive phase of treatment, the patient underwent left-sided thoracotomy, upper lobectomy, atypical resection of S6 of the left lung and drainage of the left pleural cavity according to Bülau. The intensive phase of STR was extended by another 2 months.

Radiologically, 2 weeks after the surgical intervention, the following was observed: condition after resection of the upper lobe of the lung; the lung is expanded, there are two small horizontal levels in the subclavian zone, there is a chain of postoperative sutures in the projection of the left root, the left root is pulled up, there is a homogeneous shadow with an oblique, unclear contour originating from the 6th rib; there is fibrosis in the right lung, focal shadows at the apex and in the lower parts and the sinus is obliterated by adhesions.

Stable cessation of bacterial excretion after the surgical intervention was determined until the end of chemotherapy.

In August 2020, the patient completed treatment with residual changes (RCTB) in the form of metatuberculous fibro-focal changes in the lungs; condition after surgery (04/2020) — upper lobectomy and atypical resection of S6 of the left lung.

The patient was under the supervision of a phthisiologist and responsibly underwent all preventive examinations. From August 2020 to February 2024, he had no complaints about his health, there was no bacterial excretion, and a stable radiological picture was observed.

The patient's condition deteriorated sharply after hypothermia on 16 February 2024 (catarrh, cough and fever with an increase in body temperature to 40 °C). The next day, after progressive shortness of breath at rest had appeared, the patient was hospitalised in a serious condition by the ambulance team to the regional infectious diseases hospital with a diagnosis of COVID-19 and bilateral pneumonia. After further examination, the patient's COVID-19 Ag Cito-test was negative, COVID-19 was not detected by PCR, but rifampicin-resistant MBT (MG+ Rif+) were identified. On the chest X-ray (Fig. 2): the post-surgical condition of the left lung is noted; the left lung is reduced in volume, there is homogeneous intensive shadow; there are polymorphic focal shadows throughout the entire lung field on the right; the mediastinal organs are shifted to the left; the sinuses are clear.

The patient was treated for pneumonia caused by COVID-19 in the infectious diseases hospital. After receiving the results, the patient was consulted by a phthisiologist, and on the third day of inpatient treatment, he was transferred to the regional tuberculosis dispensary with a diagnosis of RTB/rifampicin-resistant TB (RifTB).

The patient underwent further examination at the regional tuberculosis dispensary.

Biochemical and general blood and urine tests were within normal limits. Sputum analysis from 21 February 2024: gDST (HLfxMfx) M(–). Culture examination: Löwenstein-Jensen medium — growth observed; BACTEC — MBT positive, phDST (HRZ).

The patient was consulted by a physician, who diagnosed ischaemic heart disease (IHD). Cardiosclerosis with rhythm disturbance — atrial fibrillation, tachysystolic form, permanent variant. HF, grade II A.

Based on additional examination data, the next diagnosis was established: Pre-XDR-TB (02/2024)

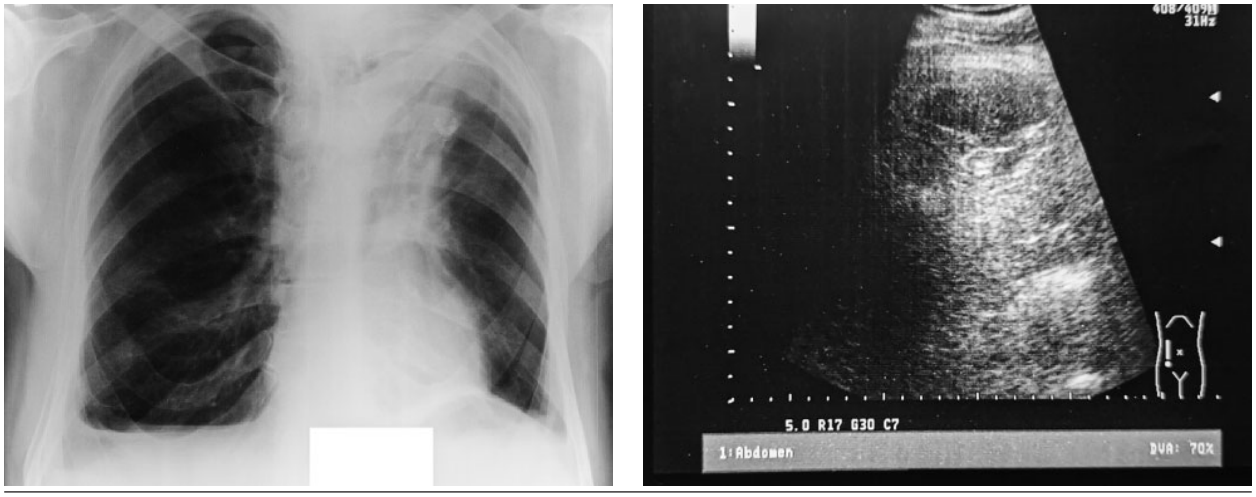

Fig. 3. **Chest X-ray and ultrasound of the left side along the posterior axillary line (20 ml of encapsulated liquid) dated 5 March 2024.**

focal of the upper lobe of the right lung. Destruction–. MBT+ M– MG+ Rif+ gDST (HLfxMfx) phDST (HRZ) Resistance– (AmLfxMfxBdqLzd CfzDlm). Histology 0 (RTB). Status post surgery (14 April 2020): upper lobectomy and atypical resection of S6 of the left lung. Pneumofibrosis of the left lung. PI, grade II. IHD. Cardiosclerosis with rhythm disturbance: atrial fibrillation, tachysystolic form, permanent variant. HF, class II A.

Given that the patient was initially treated for bilateral pneumonia (COVID-19) in an infectious diseases hospital, a follow-up chest X-ray was performed 2 weeks later. The X-ray dated 05/03/2024 showed positive changes compared to that from 19/02/2024 (Fig. 3). The condition after surgery on the left (resection of the upper lobe and S6); the left lung is reduced in volume due to gross pneumofibrosis, fibrothorax has formed; pleural layerings in the postoperative suture area; the hilum is fibrotically deformed and retracted; the dome of the diaphragm is deformed by pleuro-diaphragmatic adhesions; the costophrenic sinus is narrowed, with pleural thickenings and a small amount of fluid; there is fibrosis in the upper lobe, with dense and intense foci; the sinus is partially obliterated, pleural layerings; the right edge of the spine is visible; the mediastinal structures are displaced to the left. Ultrasound revealed 20 ml of encapsulated fluid along the left posterior axillary line.

Considering that a thin-walled emphysematous bulla measuring 88.5 × 54.2 × 45.2 mm in diameter was detected in the upper third of the right lung in the subpleural mediastinal pleura on the CT scan of the upper lung dated 3 September 2019, it was decided to perform a control CT scan of the upper lung to assess its dynamics. Thus, on the CT scan of the thoracic cavity dated 6 March 2024, CT signs of upper lobectomy, atypical resection of S6 of the lower lobe of the left lung; emphysematous bullae, calcified focal formation of the upper lobe of the right lung, several calcifications and dense foci of the lung parenchyma were determined (Fig. 4). There are a calcified focal formation measuring 10.9 × 9.3 × 8.4 mm in diameter in S1 of the upper lobe of the right lung, small calcifications measuring 3.2—4.0 mm in diameter in S2, an area of gross fibrosis measuring up to 9.6 mm in S3, a single calcification measuring up to 2.1 mm in diameter in S6 of the lower lobe, multiple dense foci measuring 1.9—3.0 mm in diameter in S8—S9 and emphysematous foci measuring 7.0—46.6 mm in diameter on the anterior surface. There is a chain of metal sutures and significant apical stratifications at the apex of the right lung, there are few dense foci with a diameter of 1.5—3.2 mm in the lower part. The vascular pattern is diffusely enhanced, thickened and deformed.

From 23 February 2024, the patient received treatment according to the BPaL scheme.

Detection of MBT was a one-time event by MG method (MG+ Rif+ gDST (HLfxMfx)), a culture examination was carried out from the sample for BACTEC — MBT positive, phDST (HRZ).

Discussion

As we see, firstly diagnosed MDR-TB with a cavity up to 41.5 × 32.5 mm in diameter in the upper lobe of the left lung against the background of multiple foci throughout the left lung, that merged into a large conglomerate measuring 70.5 × 1.8 mm in diameter in the lower lobe, were detected in the patient 5 years ago. MacLeod syndrome in the right lung was first described: a thin-walled emphysematous bulla measuring 88.5 × 54.2 × 45,2 mm in diameter in the upper third of subpleural mediastinal pleura. Also, some dense foci measuring 3.0 to

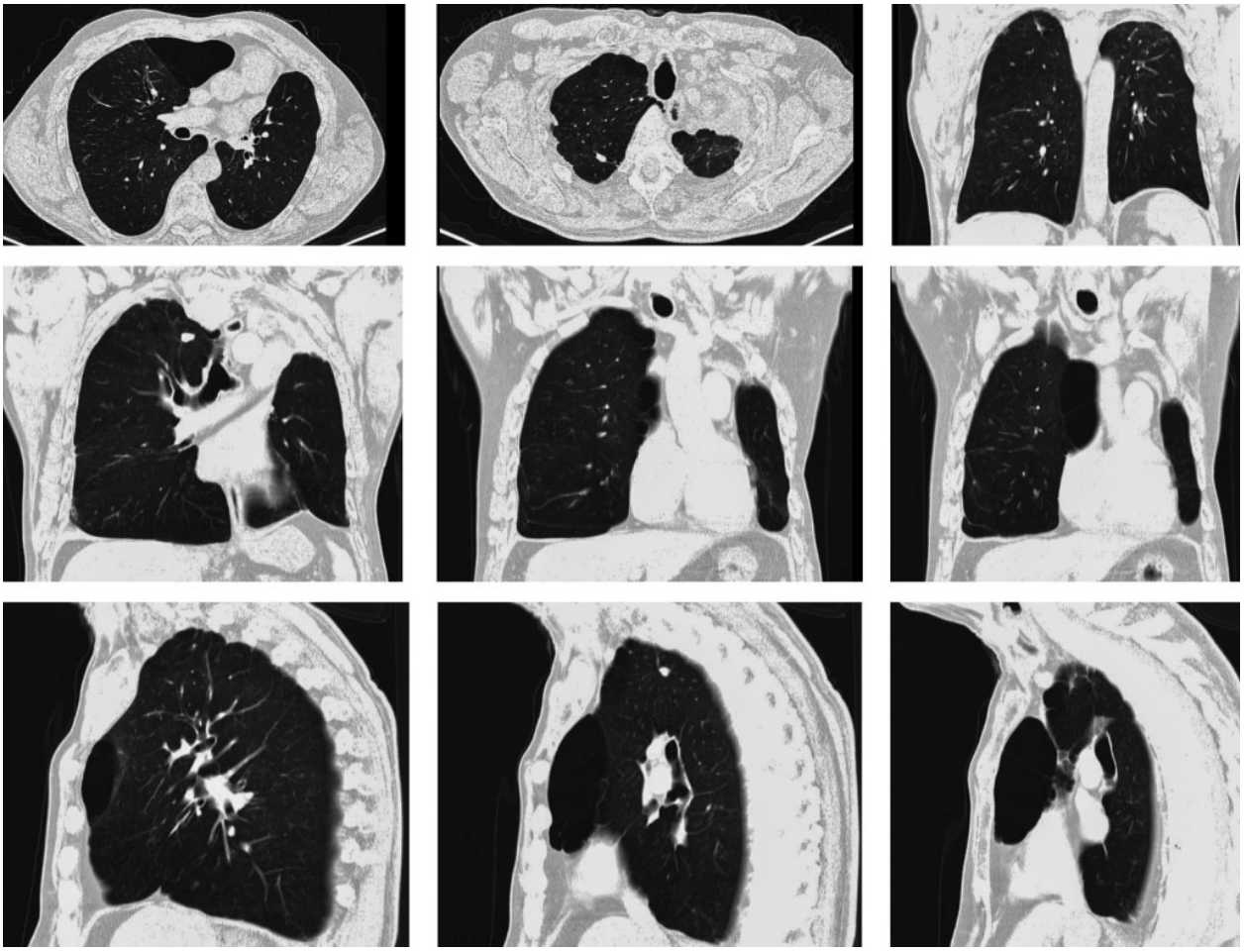

Fig. 4. **CT scan of the thoracic cavity dated 6 March 2024**

11.5 mm in the upper lobe of the right lung, mainly subpleurally, were detected, indicating a previous tuberculosis process, which the patient denied. Perhaps it was spontaneously cured tuberculosis, as the patient had contact with his son who died from XDR-TB. Therefore, it can be assumed that the triggering mechanism for the development of MacLeod syndrome was the tuberculous process.

Clinically, the patient had pulmonary insufficiency of the second degree. At the end of the intensive phase, after 6 months of treatment, the patient developed a massive bacterial excretion and additionally developed resistance to ethambutol. X-rays revealed the formation of fibro-cavernous tuberculosis in the upper lobe of the left lung (several destructions with thickened walls, some of them deformed, with significant fibrous changes around them); bullous dystrophy with several dense foci was detected in the right lung.

Considering the negative dynamics, the patient was operated on: left upper lobectomy, atypical resection of S6 of the left lung. The patient completed treatment with residual changes in the form of metatuberculous fibro-focal changes in the lungs, the condition after surgery. No actions were taken regarding MacLeod syndrome with an emphysematous bulla measuring 88.5 × 54.2 × 45.2 mm in diameter.

The patient had stable clinical and radiological dynamics for 5 years, which indicated the high effectiveness of surgical intervention in addition to AMBT.

COVID-19 provoked reactivation of a specific process after 5 years, which turned into XDR-TB due to additional resistance (bacterial excretion was one-time, and foci were identified on the X-ray). At the same time, the patient still had grade II pulmonary insufficiency , as 5 years ago, and the number of emphysematous bullae increased, measuring 7.0—46.6 mm in diameter on the anterior surface of the right lung. Considering the negative dynamics of MacLeod syndrome, the patient needs to undergo an operation to reduce the volume of the upper third of the right lung.

Conclusions

Thus, the management tactics for patients with a combined course of cavernous MDR-TB / XDR-

TB and MacLeod syndrome when AMBT fails are as follows:

- in the presence of bacterial excretion after 4–6 months of treatment and a cavernous process, consider the possibility of additional surgical intervention (lobectomy, resection, etc.);
- in the presence of MacLeod syndrome, consider the possibility of additional surgery to reduce the volume of the affected part of the lung.

There is no conflict of interest.
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Тактика ведення пацієнтів із поєднаним перебігом кавернозного туберкульозу з множинною/широкою лікарською стійкістю на тлі синдрому Маклеода (клінічний випадок)

Представлено власне спостереження випадку поєднаного перебігу кавернозного туберкульозу з множинною лікарською стійкістю (МЛС-ТБ) та широкою лікарською стійкістю (ШЛС-ТБ) на тлі синдрому Маклеода. У пацієнта 5 років тому уперше виявлено МЛС-ТБ із каверною у верхній частці лівої легені, а у правій легені діагностовано синдром Маклеода (субплеврально у медіастинальній плеврі у верхній третині тонкостінна емфізематозна булла розміром 88,5 × 54,2 × 45,2 мм). По завершенні інтенсивної фази через 6 міс у пацієнта виникло масивне бактеріовиділення та додатково з'явилася резистентність до етамбутолу. Рентгенологічно визначалося формування фіброзно-кавернозного туберкульозу верхньої частки лівої легені (кілька деструкцій із потовщеними стінками, деякі з них деформовані, навколо значні фіброзні зміни), у правій легені — бульозна дистрофія з поодинокими щільними вогнищами. З огляду на негативну динаміку пацієнта прооперовано (лівобічна верхня лобектомія, атипова резекція S6 лівої легені). Пацієнт завершив лікування із залишковими змінами у вигляді метатуберкульозних фіброзно-вогнищевих змін легень, стан після операції. З приводу

синдрому Маклеода не вжито жодних заходів. Протягом 5 років у пацієнта визначалася стабільна клінічно-рентгенологічна динаміка, що вказувало на високу ефективність хірургічного втручання, проведеного додатково до антимікобактеріальної терапії. Через 5 років коронавірусна хвороба-2019 спровокувала реактивацію специфічного процесу, який завдяки додатковій резистентності перейшов у ШЛС-ТБ (бактеріовиділення було одноразовим, а рентгенологічно процес виявився вогнищевим). Як і 5 років тому, у пацієнта зберігалася легенева недостатність II ступеня, а в правій легені по передній поверхні кількість емфізематозних був збільшилася, вони були діаметром 7,0 × 46,6 мм. З огляду на негативну динаміку синдрому Маклеода пацієнту необхідно виконати операцію зі зменшення об'єму верхньої третини правої легені.

Отже, у пацієнтів із поєднаним перебігом кавернозного МЛС-ТБ/ШЛС-ТБ на тлі синдрому Маклеода за неефективності антимікобактеріальної терапії, наявності бактеріовиділення через 4—6 міс та кавернозного процесу слід розглянути можливість проведення оперативного втручання (лобектомія, резекція тощо), за наявності синдрому Маклеода — можливість проведення операції зі зменшення об'єму відповідної частини легені.

Ключові слова: туберкульоз, множинна лікарська стійкість, широка лікарська стійкість, каверна, синдром Маклеода, хірургічне втручання.

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