

Features of the simultaneous course of pulmonary aspergillosis and tuberculosis on the background of type 1 diabetes mellitus (clinical case)

O. M. Raznatovska^{id}*A,D,E,F, Yu. V. Myronchuk^{id}C,D, O. S. Shalmin^{id}E,F,
A. V. Fedorets^{id}A,B, O. A. Svitlytska^{id}B,C

Zaporizhzhia State Medical University, Ukraine

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*E-mail:

raznatovskaya@gmail.com

Aim. To analyze the features of the simultaneous course of pulmonary aspergillosis and multidrug-resistant pulmonary tuberculosis (MDR-TB) on the background of type 1 diabetes mellitus, on the example of a clinical case of our practice.

Materials and methods. Clinical case of our practice of simultaneous pulmonary aspergillosis and MDR-TB on the background of type 1 diabetes mellitus in a patient, who was treated in Pulmonary tuberculosis department No. 2 of clinical base of Phthisiatry and Pulmonology Department of Zaporizhzhia State Medical University at Communal Non-Commercial Enterprise of the "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthisiatry and Pulmonology" of Zaporizhzhia Regional Council.

Results. In the presented clinical case, the patient had been suffering from diabetes mellitus for 8 years and had been receiving insulin therapy for all these years. One year before the TB disease, he had contact with an index patient, but he categorically refused a course of preventive chemotherapy. Also, the patient did not make a comparison X-ray TCO after 6 months, as a contact person. MDR-TB and aspergilloma of the left lung of the patient were diagnosed simultaneously on the background of severe condition with decompensated form of type 1 diabetes mellitus, severe intoxication syndrome and inflammatory process, massive hemoptysis. Aspergilloma of the left lung was diagnosed using X-ray TCO and cultural examination of bronchial aspirate for *Aspergillus*, which was not difficult to diagnose. Diagnosis of MDR-TB was also not difficult, because the patient had MBT, which contributed to the timely and correct appointment of antimycobacterial therapy. Surgery for aspergilloma of the left lung was contraindicated, as the type 1 diabetes was in decompensation. Persistent hyperglycemia remained, despite the fact of antifungal therapy and constant correction of insulin therapy prescribed for the patient. Endocarditis quickly developed in the patient, which was the reason of patient's death.

Conclusions. The decompensated form of type 1 diabetes mellitus caused persistent hyperglycemia, which was the reason of immune disorders and this made the patient's body susceptible to bacterial (MDR-TB) and fungal (aspergillosis) infections, which led to the development of the complication of endocarditis and death. A big mistake in his case, was a categorical refusal by the patient to receive a course of preventive chemotherapy, as a contact person with an index patient. In view of this, in the presence of type 1 diabetes, the patient should have not neglected it. And as a result, the patient had a MDR-TB, one year after. At the same time, the patient did not make a comparison X-ray TCO, after 6 months, as a contact person, which was a possible reason for the missing of early diagnosis of pulmonary aspergilloma. That's why, a correct treatment of type 1 diabetes mellitus and timely preventive radiological examination of the thoracic cavity organs are especially important, as the diabetes mellitus is the most common premorbid background for TB and aspergillosis.

Ключові слова:

легеневий аспергілез, мультирезистентний туберкульоз, цукровий діабет 1 типу.

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Особливості одночасного перебігу легеневого аспергілезу та туберкульозу при цукровому діабеті 1 типу (клінічний випадок)

О. М. Разнатовська, Ю. В. Мирончук, О. С. Шальмін, А. В. Федорець, О. А. Світлицька

Мета роботи – на клінічному випадку власного спостереження проаналізувати особливості одночасного перебігу легеневого аспергілезу та мультирезистентного туберкульозу (МР ТБ) при цукровому діабеті 1 типу.

Матеріали та методи. Наведено клінічний випадок власного спостереження одночасного перебігу легеневого аспергілезу та МР ТБ у пацієнта з цукровим діабетом 1 типу, який перебував на лікуванні у відділенні легеневого туберкульозу № 2 на клінічній базі кафедри фтизіатрії і пульмонології Запорізького державного медичного університету КНП «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» ЗОР.

Результати. Пацієнт, клінічний випадок якого наведено, мав цукровий діабет 1 типу протягом 8 років, отримував терапію інсуліном. За рік до захворювання на МР ТБ мав контакт з індексним пацієнтом, але від курсу профілактичної хіміотерапії категорично відмовився. Також хворий не зробив контрольну рентгенограму органів грудної порожнини (РГ ОГП) як контактна особа через 6 місяців. МР ТБ та аспергілезу лівої легені в пацієнта діагностували одночасно на тлі важкого стану з декомпенсованою формою цукрового діабету 1 типу, вираженим інтоксикаційним синдромом і запальним процесом, масивним кровохарканням. Аспергілезу лівої легені виявили за результатами РГ ОГП та культурального дослідження аспірату з бронхів на *Aspergillus*, під час діагностики труднощі не виникли. Діагностика МР ТБ також не складна, оскільки пацієнт був бактеріовиділювачем. Це сприяло своєчасному і правильному призначенню антимікобактеріальної терапії. Оперативне втручання з приводу аспергілезу лівої легені було протипоказане через декомпенсований стан цукрового діабету 1 типу. Незважаючи на те, що пацієнтові призначили протигрибкову терапію, постійно здійснювали корекцію інсулінотерапії, зберігалася стійка гіперглікемія. У хворого швидко розвинувся ендокардит, що спричинив смерть.

Висновки. Декомпенсована форма цукрового діабету 1 типу призвела до стійкої гіперглікемії, що стало наслідком порушення імунітету та зробило організм пацієнта сприйнятливим до бактеріальної (МП ТБ) та грибової (аспергілез) інфекції, спричинивши виникнення ускладнення (ендокардит) і смерті. Категорична відмова пацієнта від курсу профілактичної хіміотерапії (контактна особа з індексним хворим) стала у цьому випадку великою помилкою. Враховуючи наявність цукрового діабету 1 типу, пацієнт не мав цим нехтувати. Оскільки необхідних заходів не вжито, пацієнт через рік захворів на МП ТБ. Ба більше, хворий не зробив контрольну РГ ОГП як контактна особа через 6 місяців, можливо, це стало причиною того, що аспергілема легені не була діагностована на ранніх етапах захворювання. Особливо важливим є правильне лікування цукрового діабету 1 типу, а враховуючи, що цукровий діабет – найчастіший преморбідний фон для ТБ, і аспергілези, необхідне своєчасне профілактичне рентгенологічне дослідження органів грудної порожнини.

Aspergillosis is the most common mycosis of the lungs, caused by mold fungi of the genus *Aspergillus* [8]. Aspergilloma is a cavitary lesion with clearly delineated walls, which isolates spores of fungi of the genus *Aspergillus* from the mechanical purification and immune eradication [3]. The clinical picture of pulmonary aspergillosis is determined by the interaction between the fungus *Aspergillus* and the host [9].

Pulmonary aspergilloma is often associated with tuberculosis (TB) and is found in residual tuberculous cavities, as sufficient oxygen and caseous necrosis contribute its growth in this location [4].

The main methods of aspergillosis diagnostics are radiological (X-ray examination of the thoracic cavity organs (TCO)), but computed tomography (CT) of the TCO is recommended, if possible), cultural examination of sputum for fungi of the genus *Aspergillus* and histopathological examination of samples of the affected tissue. Thus, J. A. Maertens et al. [8] indicate a high frequency of negative cultural results, which significantly complicates the differential diagnosis. Also, identification of galactomannan antigen in serum and bronchoalveolar lavage samples [12] and *Aspergillus*-specific IgE, is recommended for diagnosis of aspergillosis [13]. And for the diagnosis of endobronchial aspergilloma, which is diagnosed in various diseases (cancer with metastases, TB, bronchiolitis, etc.), the timely use of fibero bronchoscopy (FBS) is recommended [5–7, 14, 15].

Kosmidis C. and Denning D. W. [9] indicated, that invasive aspergillosis develops in patients with severe immunodeficiency, and chronic pulmonary aspergillosis affects patients without immune disorders, but with concomitant lung diseases, such as: chronic obstructive pulmonary disease, sarcoidosis, previous or concomitant TB, mycobacteriosis.

Horiuchi K. et al. [13] observed a clinical case of simultaneous course of allergic bronchiogenic aspergillosis and aspergilloma in a patient, who had had TB in the past. Despite massive hormone and antifungal therapy, the patient continued to have respiratory symptoms, which were the reason of lobectomy of the upper lobe of the right lung, where aspergilloma was localized. However, the patient's condition worsened with increasing respiratory symptoms 23 months after treatment stopped. Visualization revealed bronchiectasis, cavities with mucoid obstruction in the lower part of the right lung indicating recurrence of aspergillosis. The patient's condition slightly improved only after 5 years of hormonal and antifungal therapy. Therefore, the authors addressed the severity of aspergillosis and recommended long-term patients monitoring, as this condition may recur, even after surgery and remission.

Liang C. N. et al. [2] observed a patient, who had acute mediastinitis on the background of the simultaneous detection of rifampicin-resistant tuberculosis (Rif TB), endobronchial tuberculosis and pseudomembranous aspergillosis tracheobronchitis. However, despite the performed complex treatment, the patient died of massive hemoptysis on the 10th day after hospitalization. The authors suggested that acute mediastinitis in immunosuppressed patients with central respiratory tract damage, namely, with concomitant endobronchial tuberculosis and pseudomembranous aspergillosis tracheobronchitis were the potential cause of death.

Diabetes mellitus is one of the most common premorbid backgrounds for *Aspergillus* invasion of the bronchi [1].

Nugroho G. M. S. and Wulandari L. [11] in their clinical case described the diagnosis of aspergilloma of the left lung in a woman with type 2 diabetes mellitus, who was admitted to the hospital with chronic hemoptysis. The diagnosis of aspergillosis was confirmed culturally (*Aspergillus* was found in sputum). The patient had thoracotomy with left upper lobectomy. The authors believed, that type 2 diabetes was the risk factor for *Aspergillus* infection, as hyperglycemia caused immunodeficiency. And timely removal of aspergilloma and maintenance of blood glucose levels could provide a good prognosis.

Soewondo W. et al. [4] observed a patient with type 2 diabetes mellitus who was diagnosed of aspergilloma in the upper left lung, after 9 months of ineffective antimycobacterial therapy (AMBT). The patient also underwent a lobectomy, after which a positive effect was achieved on the background of AMBT and antifungal therapy with blood glucose control.

Like the previous authors [4], A. A. Kumar et al. [10] described a clinical case of their own observation of triple pathology: multidrug-resistant pulmonary tuberculosis (MDR-TB) and aspergilloma of the upper lobe of the right lung on the background of type 2 diabetes mellitus. A 50-year-old woman with a long history of type 2 diabetes mellitus, who had been receiving AMBT irregularly for 2 years, for MDR-TB complained of productive cough and hemoptysis for the past 2 months. The X-ray TCO revealed a cavity with thick walls in the upper right lobe with constant aspergilloma. The patient underwent resection of her upper right lobe of the lung, and biopsy and culture of the resected specimen showed concomitance of *Aspergillus fumigatus* and multidrug-resistant *Mycobacterium tuberculosis* (MBT). And as in the previous case, after the surgery on the background of AMBT and antifungal therapy with control of blood glucose levels, treatment success was achieved.

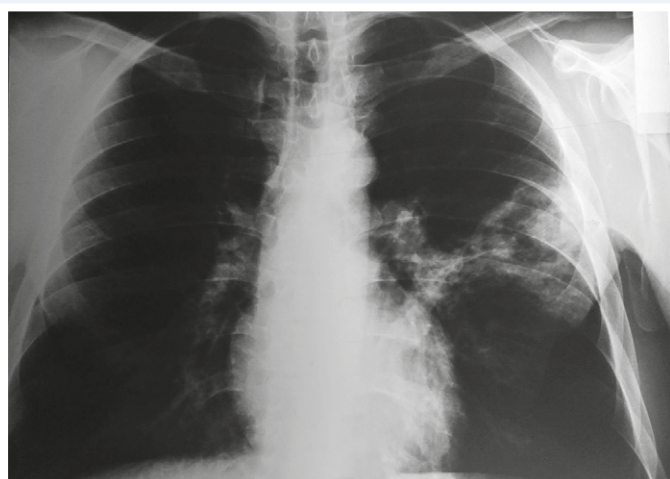


Fig. 1. X-ray TCO at hospitalization in the CNE "ZRCDPP" ZRC.

As we can see from the literature review, pulmonary aspergillosis is a serious disease per se, and in combination with tuberculosis (both sensitive and MDR-TB) and type 2 diabetes, the condition worsens significantly. In all cases, aspergilloma of the lungs required surgery to remove it, and the main clinical symptom was hemoptysis. However, we did not find in the literature a description of a clinical case of the simultaneous course of pulmonary aspergillosis and tuberculosis on the background of type 1 diabetes mellitus, which became the reason for writing this article.

Aim

To analyze the features of the simultaneous course of pulmonary aspergillosis and MDR-TB on the background of type 1 diabetes mellitus, on the example of a clinical case of self-observation.

Materials and methods

Clinical case of self-observation of simultaneous pulmonary aspergillosis and MDR-TB on the background of type 1 diabetes mellitus in a patient, who was treated in the pulmonary tuberculosis department No. 2 of clinical base of Phthisiatry and Pulmonology Department of Zaporizhzhia State Medical University at Communal Non-Commercial Enterprise of the "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthisiatry and Pulmonology" of Zaporizhzhia Regional Council (CNE "ZRCDPP" ZRC).

Results

Clinical case

Patient K., 37 years old. From the anamnesis: type 1 diabetes mellitus was first diagnosed in 2012, and he has been receiving regular insulin therapy since then. He has not had a tuberculosis before. In October 2019, the patient had contact with his wife's brother, who had TB. At the time of the follow-up examination, as a contact

person with the index patient, changes in the lungs on the X-ray TCO were not found. After 6 months, the patient did not do a comparison X-ray. He categorically refused a course of preventive chemotherapy.

In October 2020, he went to his family doctor with complaints of cough with sputum, massive hemoptysis, subfebrile fever, weight of loss, excessive urination, thirst, rapid fatigability, numbness of fingertips, skin itching, nausea and vomiting. The following changes were revealed at the X-ray TCO (Fig. 1): in S1 + 2/S6 of the left lung a deformed destruction cavity to 6.0×5.0 cm in diameter with infiltrated walls and with parietal formation inside the cavity up to 2.0 cm in diameter; pericavitary infiltration of lung tissue; from the destruction cavity "path" to the lung root; in the right lung without features; the roots are structural.

According to the obtained data from anamnesis, complaints and changes were found on the X-ray TCO the patient was referred for further examination to CNE "ZRCDPP" ZRC.

The following changes were revealed during the follow-up examination.

Mycobacteria of tuberculosis (MBT) resistant to rifampicin (R) were detected in sputum by molecular genetic method (MG): MG + Rif +.

Fibrobronchoscopy (FBS) revealed infiltrative TB of the upper part of the bronchus on the left with stenosis of the first degree, left-sided disseminated purulent endobronchitis of the second degree. The result of bronchial aspirate: the material is represented by inflammatory cells, alveolar cells, bronchial epithelial cells, there are groups of cells with signs of moderate hyperplasia, erythrocytes 1/3 in the field of view; atypical cells were not found, MBT (1+).

The glycemic profile: 15.9–16.2–18.5 mmol/L.

Endocrinologist's conclusion: Type 1 diabetes mellitus, decompensation stage.

The results of the general blood analysis (GBA): hemoglobin (HGB) – 119 g/l, erythrocytes (RBC) – $3.8 \times 10^{12}/l$, leukocytes (WBC) – $12 \times 10^9/l$, eosinophils (EOS) – 1 %, banded neutrophils (b/n) – 5 %, segmented neutrophils (s/n) – 55 %, lymphocytes (LYM) – 36 %, monocytes (MONO) – 3 %, erythrocyte sedimentation rate (ESR) – 41 mm/hour.

Biochemical analysis of blood: bilirubin total – 9.1 $\mu\text{mol}/l$, thymol test – 1.19 U, ALT – 0.16, AST – 0.48, total protein (TP) – 79.5 g/l, glucose – 5.04 mmol/l.

Blood test for HIV was negative.

Spirography revealed: Respiratory insufficiency (RI) of the I degree.

Based on the obtained data, the diagnosis was established: rifampicin-resistant tuberculosis infiltrative of the left lung Destructive +, MBT +, microscopy (M) –, MG +, Rif +. Extrapulmonary tuberculosis (EPTB) infiltrative TB of the upper part of the bronchus on the left with stenosis of the first degree, left-sided widespread purulent endobronchitis of the second degree. Category 4 (newly detected tuberculosis – NDTB). RI of the I degree. Type 1 diabetes mellitus, moderate, decompensation stage. Aspergilloma of the left lung?

The patient was hospitalized in the pulmonary tuberculosis department No. 2 MNPE «ZRPMDC»

ZRC, where was prescribed a course of AMBT according to the scheme for category 4. Also, taking into account the glycemic profile and the patient's complaints, the endocrinologist corrected of insulin therapy.

After 5 days, liquid culture of the sputum was obtained, which showed resistance to isoniazid (H) and levofloxacin (Lfx). The diagnosis of Rif TB was changed to multidrug-resistant tuberculosis (MDR-TB), culture (K) +, resistance 1 (HRLfx). AMBT was corrected with drug susceptibility test (DST) data.

After 4 days, the result of culture of bronchial aspirate was obtained, where the growth of *Aspergillus* (10^{-5}) was detected, that why the diagnosis of "Aspergillum of the left lung" was confirmed. An antifungal therapy was added to the patient's treatment.

During the week after hospitalization, despite AMBT and corrected insulin therapy, the patient did not stop massive hemoptysis, and symptoms of decompensated type 1 diabetes (hyperglycemia, excessive urination, thirst, fatigue, numbness, numbness, numbness, constipation), and intoxication increased. He received antifungal therapy for only 3 days, during this time. Surgery for aspergilloma of the left lung was postponed, as the type 1 diabetes was decompensation. The patient died, after 1 week of the start of hospitalization. The endocarditis was cause of death.

Discussion

According to the literature, pulmonary aspergillosis is often accompanies of tuberculosis, especially in residual tuberculous cavities [4,9], and type 2 [11] diabetes mellitus [1] is one of the most common premorbid backgrounds for *Aspergillus* invasion into the bronchi. It established, that hyperglycemia in diabetes mellitus contributes to the development of immunodeficiency [11], so the control of blood glucose levels is requirement for success in both the treatment of aspergillosis and its combination with other diseases [4,10,11].

In the presented clinical case, the patient had been suffering from diabetes mellitus for 8 years and had been receiving insulin therapy for all these years. One year before the TB disease, he had contact with an index patient, but he categorically refused a course of preventive chemotherapy. Also, the patient did not make a comparison X-ray TCO after 6 months, as a contact person.

MDR-TB and aspergilloma of the left lung in the patient were diagnosed simultaneously on the background of severe condition with decompensated form of type 1 diabetes mellitus, severe intoxication syndrome and inflammatory process, massive hemoptysis. Aspergilloma of the left lung was diagnosed using X-ray TCO and cultural examination of bronchial aspirate for *Aspergillus*, which was not difficult to diagnose. Diagnosis of MDR-TB was also not difficult, because the patient had MBT, which contributed to the timely and correct appointment of AMBT. Surgery for aspergilloma of the left lung was contraindicated, as the type 1 diabetes was decompensation. And, according to the literature [4,10,11], removal of aspergilloma contributes to a good prognosis for recovery. Persistent hyperglycemia

remained, despite the fact of antifungal therapy and constant correction of insulin therapy prescribed for patient. The endocarditis quickly developed in patient, which was the reason of the patient's death.

Conclusions

The decompensated form of type 1 diabetes mellitus caused of persistent hyperglycemia, which was a reason of immune disorders and this made the patient's body susceptible to bacterial (MDR-TB) and fungal (aspergillosis) infections, which led to the development of a complication of endocarditis and death. A big mistake in his case, was a categorical refusal of the patient to receive a course of preventive chemotherapy, as a contact person with an index patient. In view of this, the presence of type 1 diabetes, the patient should not neglect it. And as a result, the patient had a MDR-TB, after one year. At the same time, the patient did not make a comparison X-ray TCO, after 6 months, as a contact person, which was a possible reason for the missing of early diagnosis of pulmonary aspergilloma. That's why, a correct treatment of type 1 diabetes mellitus and timely preventive radiological examination of the thoracic cavity organs are especially important, as the diabetes mellitus is most common premorbid background for TB and aspergillosis.

Prospects for further research. The next research of features, of the course of tuberculosis in combination with other rare diseases, in order to improve doctors' caution for their timely diagnosis and correct management tactics.

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Information about authors:

Raznatovska O. M., MD, PhD, DSc, Professor, Head of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical University, Ukraine.

ORCID ID: [0000-0003-2252-9063](https://orcid.org/0000-0003-2252-9063)

Myronchuk Yu. V., MD, Assistant of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical University, Ukraine.

ORCID ID: [0000-0002-4608-2991](https://orcid.org/0000-0002-4608-2991)

Shalmin O. S., MD, PhD, DSc, Professor of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical University, Ukraine.

ORCID ID: [0000-0002-1727-0408](https://orcid.org/0000-0002-1727-0408)

Fedorets A. V., MD, Assistant of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical University, Ukraine.

ORCID ID: [0000-0003-0994-5265](https://orcid.org/0000-0003-0994-5265)

Svitlytska O. A., MD, PhD, Assistant of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical University, Ukraine.

ORCID ID: [0000-0003-4987-8458](https://orcid.org/0000-0003-4987-8458)

Відомості про авторів:

Разнатовська О. М., д-р мед. наук, професор, зав. каф. фізіатрії і пульмонології, Запорізький державний медичний університет, Україна.

Мирончук Ю. В., асистент каф. фтизіатрії та пульмонології,
Запорізький державний медичний університет, Україна.
Шальмін О. С., д-р мед. наук, професор каф. фтизіатрії і
пульмонології, Запорізький державний медичний університет,
Україна.
Федорець А. В., асистент каф. фтизіатрії та пульмонології,
Запорізький державний медичний університет,
Україна.
Світлицька О. А., канд. мед. наук, асистент каф. фтизіатрії та
пульмонології, Запорізький державний медичний університет,
Україна.

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