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Difficulties in Diagnosing of Pancreatic Cancer in HIV Infection with Generalised Lymphadenopathy: Tuberculosis, Non-Tuberculosis Mycobacterial Infection or Metastases (Clinical Case)

Our observation of the pancreatic cancer diagnosing difficulties in a patient with HIV infection with generalised lymphadenopathy is presented. The patient's HIV infection was diagnosed 8 months before hospitalisation, he did not receive antiretroviral therapy. He came to the doctor already in a serious condition, when severe intoxication syndrome, weight loss, abdominal pain radiating to the lower back and diarrhea were noted. The patient was hospitalised in a serious condition, where he spent 42 days. The patient had severe immunosuppression since hospitalisation time ($CD4^+$ lymphocyte count was 20 cells, viral load was more than 3,000,000 RNA copies/mL). He did not suffer from tuberculosis before. Considering the severe immunosuppression and doubtful lipoarabinomannan test (LF-LAM), it was impossible to exclude a tuberculous etiology of lymphadenopathy. *Mycobacterium tuberculosis* was not detected either in the sputum or in the pleural fluid. However, non-tuberculosis mycobacteria were found in the sputum. The patient underwent two contrast-enhanced computed tomography scans of the abdominal cavity, which revealed increasing generalised lymphadenopathy and hepatosplenomegaly, with no signs of neoplastic lesions of the pancreas. Therefore, the diagnosis of oncopathology was confirmed only pathohistologically. Despite massive complex therapy during inpatient treatment the general condition progressively worsened, intoxication syndrome, multiple organ failure and polyserositis increased. The cause of death was the progression of multiple organ failure on the background of an HIV-related disease with manifestations of malignant neoplasms (undifferentiated pancreatic cancer with foci of necrosis and destruction of tumor tissue with metastases in the lymph nodes and liver, along with a non-tuberculous mycobacterial infection affecting the intra-thoracic lymphatic nodes. Thus, timely intravital diagnosis of pancreatic cancer in HIV-infected patient with generalised lymphadenopathy and those with severe immunosuppression may cause difficulties, because CT signs and other manifestations of pancreatic lesions may not be detected. Severe immunosuppression and a doubtful LF-LAM test made it impossible to rule out the tubercular etiology of lymphadenopathy. At the same time, generalised lymphadenopathy was a manifestation of metastases and non-tuberculosis mycobacterial infection.

Keywords

Pancreatic cancer, HIV, lymphadenopathy, tuberculosis, nontuberculous mycobacterial infection, metastases.

Cancer remains the leading cause of death among individuals living with HIV [11]. The pancreas ranks among the organs most vulnerable to damage from conditions such as diabetes or pancreatic cancer [8]. Darvishian et al. [2] found that HIV-positive patients face a heightened risk of pancreatic cancer compared to their uninfected counterparts, emphasising the necessity for targeted cancer prevention strategies and meticulous clinical monitoring within this demographic.

S. Oka et al. [9] eestablished, through a prospective analysis, that recently non-AIDS-defining malignant neoplasms, including pancreatic cancer constitute the primary causes of death in AIDS patients receiving antiretroviral therapy (ART). These neoplasms in HIV-infected patients are characterised by earlier manifestation and a more aggressive course [13].

D. Serraino et al. [12] found through their study that patients diagnosed with AIDS face a significantly higher risk of mortality from pancreatic cancer compared to the general population. Additionally, an increase in the incidence of pancreatic cancer has been observed among individuals living with HIV precisely during the era of ART. This rise is attributed to the increased frequency of diabetes associated with ART usage, which is a well-established risk factor for pancreatic cancer in the general population.

Based on the results of their data analysis, D. Plotkin et al. [10] concluded that HIV infection is a factor associated with a two-fold increase in the severity or duration of pancreatitis, irrespective of the presence of immunosuppression. Additionally, they found that the etiological structure of HIV-associated acute pancreatitis is directly influenced by the immune status of the patient.

Lymphadenopathy in HIV infection can stem from various causes, including immune recovery syndrome, tuberculosis and non-tuberculosis mycobacterial infections, neoplasms, Castleman's disease, among others. Identifying the underlying causes of lymphadenopathy requires consideration of multiple factors, such as clinical manifestations, CD4 lymphocyte count, radiological findings, and more [1, 3, 5].

P. Wannakrairot et al. [13] studied the histological spectrum of lymphadenopathy in HIV-infected patients. The researchers established that the majority of histological changes were associated with acid-resistant microorganisms and mostly corresponded to the morphological features of *Mycobacterium avium*. At the same time, histological changes resemble changes in heart attack and infectious lymphadenitis, sarcoidosis, neoplasms, etc.

A. Hadadi et al. [4] in their study established that the most frequent causes of lymphadenopathy in HIV/AIDS (both generalised and limited) were tuberculosis and lymphoma. Additionally, they found that the frequency of lymphadenopathy was slightly higher in patients with a CD4 lymphocyte count < 200 cells/μL.

B. Neves et al. [7] described a case from their own observations involving an HIV-infected patient with a CD4 lymphocyte count < 200 cells/μL who presented with clinical manifestations including fever, weight loss, abdominal discomfort and generalised lymphadenopathy. Despite thorough examination, diagnosis was only achieved through excisional biopsy of the lymph node and histological analysis, revealing Castleman's disease associated with human herpes virus-8 (HHV-8). This case highlights the importance of considering uncommon etiologies in HIV-infected patients presenting with fever and generalised lymphadenopathy, as these manifestations may signify various underlying diseases.

A. Hernández-Solís et al. [5] indicate that despite the low frequency (4.7 %) of non-tuberculosis mycobacteria as a possible cause of lymphadenopathy, timely identification is crucial because it allows for the initiation of specific treatment.

The risk of pancreatic cancer is notably high in HIV-infected patients. Recently, non-AIDS-defining malignant neoplasms, including pancreatic cancer, have emerged as the primary causes of death among patients with HIV/AIDS receiving ART. Lymphadenopathy in HIV infection can have various causes, including tuberculosis and non-tuberculosis mycobacterial infections, as well as neoplasms.

Therefore, the objective of this work was to address the challenges associated with diagnosing pancreatic cancer in HIV-infected patients presenting with generalised lymphadenopathy. Our study focused on a patient receiving treatment at the Zaporizhzhia Regional Phthisiopulmonology Clinical Treatment and Diagnostic Center, based on our own clinical observations.

Clinical case

Patient E is a 48-year-old individual with no previous history of tuberculosis. HIV infection was initially diagnosed in the autumn of 2022, and the patient had not received antiretroviral therapy (ART) at that time. Starting from the beginning of May 2023, he experienced a deterioration in his condition, characterised by general weakness, weight loss, a body temperature rise to 38 °C, abdominal pain radiating to the lower back and diarrhea. Seeking medical attention, he consulted a doctor on May 14, 2023, prompting further examination.

On May 15, 2023, a blood analysis indicated a $CD4^+$ lymphocyte count of 20 cells (1.96 %). The viral load was found to be greater than 3,000,000 RNA copies/ml. Results of a rapid test for viral hepatitis (HV)-C were negative, as were those of the blood test for HBsAg.

On May 15, 2023, computed tomography (CT) of the abdominal organs (AO) with intravenous contrast and excretory urography revealed manifestations indicative of a systemic lymphoproliferative disease. These included lymphadenopathy in the abdominal, retroperitoneal and retrocrural regions,

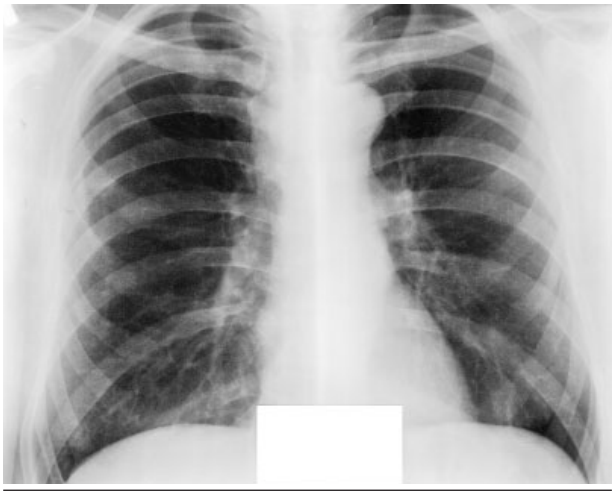

Fig. 1. **X-ray of the chest conducted on May 19, 2023**
The lung fields demonstrate no focal or infiltrative changes. An increase in the size of the inferior tracheolymphatic nodes (ITLN) is observed.

as well as hepatosplenomegaly and signs of portal hypertension. Additionally, findings included a cyst in the right lobe of the liver and nodular hyperplasia of the left adrenal gland. Notably, the pancreas appeared unremarkable, with clear contours, normal structure and absence of focal abnormalities or pathological contrast accumulation within the pancreatic tissue.

Immunochromatographic lipoarabinomannan test (LF-LAM urine analysis) conducted on May 16, 2023, yielded a result categorised as doubtful.

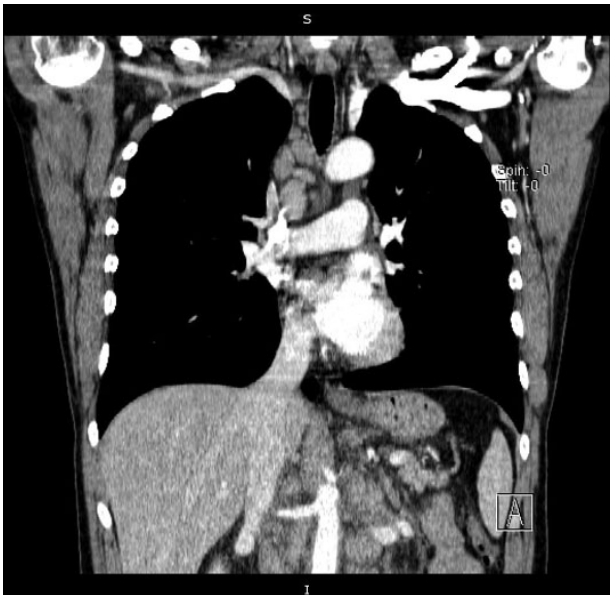

Fig. 2. **CT of the chest cavity (CC) conducted on May 22, 2023**
The scan reveals numerous pre-tracheal and paratracheal lymph nodes measuring 5—20 mm in size. Additionally, bilateral supradiaphragmatic and paravertebral lymph nodes measuring 5—14 mm are observed on the right side. Single axillary lymph nodes measuring 6—10 mm in size are identified bilaterally. Numerous para-aortic lymph nodes measuring 6—24 mm are also detected.

The result of sputum analysis for Mycobacterium tuberculosis (MBT) conducted on May 19, 2023, showed negative results for MBT based on molecular genetic testing (MG) and sputum microscopy (M).

On the X-ray of the chest cavity (CC) organs taken on May 19, 2023 (Fig. 1), only an increase in the size of the intra-thoracic lymph nodes (ITLN) was detected.

On May 22, 2023, MBT was also not detected in the sputum analysis.

The CT scan of the chest cavity (CC) with contrast conducted on May 22, 2023 (Fig. 2), revealed signs of mediastinal, bilateral axillary and retroperitoneal lymphadenopathy, likely indicating a lymphoproliferative process. Following these findings, it was recommended to proceed with a CT scan of the abdominal organs (AO) and pelvis, along with a consultation with an oncologist.

As evident from the X-ray and CT scans of the chest cavity (CC) and CT of the abdominal organs (AO) with contrast, conducted on May 19 and May 22, 2023, respectively, the findings indicate generalised lymphadenopathy in the context of HIV infection, IV clinical stage. This assessment aligns with the consultative opinion provided by the infectious disease specialist on May 24, 2023.

Based on the findings from the additional examination conducted on May 24, 2023, a preliminary diagnosis was established, indicating HIV infection at the IV clinical stage and multiple organ failure. Additionally, a new case of tuberculosis (NTB) was diagnosed, characterised as extrapulmonary tuberculosis (EPTB) affecting the intrathoracic and extraperitoneal lymph nodes. The tuberculosis was identified as being non-destructive, with negative results for Mycobacterium tuberculosis (MBT) based on molecular genetic testing (MG) and sputum microscopy (M). Histological examination yielded a LF-LAM(+) result. In light of these diagnoses, the patient was promptly admitted to the Zaporizhzhia Regional Phthisiopulmonology Clinical Treatment and Diagnostic Center in a serious condition. Treatment was initiated, consisting of antimycobacterial therapy (HREZ regimen), antiretroviral therapy (TDF/3TC/DTG), prophylaxis against opportunistic infections with Biseptol, and symptomatic management.

On May 30, 2023, a culture obtained from sputum analysis conducted on May 19, 2023, revealed the presence of non-tuberculosis mycobacteria (NTM). In light of this new information, the diagnosis was revised to include HIV infection at the IV clinical stage, multiple organ failure and a non-tuberculosis mycobacterial infection affecting the intra-thoracic lymph nodes (ITLN). As a result of this diagnosis, azithromycin was added to the prescribed treatment

regimen to address the NTM infection in addition to the ongoing treatment for HIV/AIDS and tuberculosis.

On June 8, 2023, an ultrasound examination (UE) of the AO was conducted, revealing ultrasound signs of hepatosplenomegaly and diffuse changes in the liver. Additionally, diffuse thickening of the pancreas was observed.

Despite the implementation of a complex treatment regimen, the patient's general condition continued to deteriorate progressively.

On June 23, 2023, UE of the pleural cavities was conducted, revealing a small amount of free fluid in the lateral sinuses: up to 75 mL on the right and up to 60 mL on the left. Following these findings, a right pleural puncture was performed to analyze the pleural fluid. The results of the analysis showed a protein concentration of 33 g/L, a weakly positive Rivalt reaction, leukocytes at a count of 10—20 per visual field (v/f), with lymphocytes accounting for 62 %. Additionally, erythrocytes were observed at a count of 1/2—1/3 per visual field, and only a few mesothelial cells were present, with no atypical cells detected. The analysis also showed negative results for Mycobacterium tuberculosis (MBT), based on sputum microscopy (M) and culture (C).

The X-ray dynamics in the chest cavity remained unchanged, as depicted in Fig. 3.

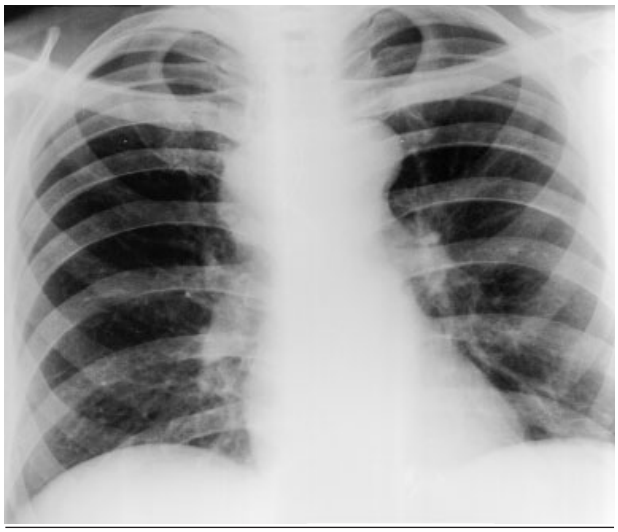

Fig. 3. **X-ray of the chest cavity (CC) conducted on June 26, 2023**

The lung fields demonstrate no focal or infiltrative changes. An increase in the size of paratracheal lymph nodes is observed on the right side.

During the UE of the AO conducted on June 26, 2023, notable findings were observed in the context of significant gas accumulation in the large intestine. These included ultrasound signs of hepatosplenomegaly, marked diffuse changes in the spleen (indicating negative dynamics compared to the UE of the AO performed on June 8, 2023), diffuse induration of the pancreas and lymphadenopathy in the abdominal cavity and retroperitoneal space. Additionally, inguinal lymphadenitis was noted, with characteristics resembling those seen in HIV infection or lymphomas of non-plastic origin.

On June 29, 2023, a CT scan of the AO revealed signs consistent with lymphoproliferative lesions in the abdominal cavity, retroperitoneal space, pelvis and inguinal areas. Additionally, the following changes were diagnosed: bilateral hydrothorax, hepatosplenomegaly, diffuse changes in the liver, cyst in the right lobe of the liver, chronic cholecystitis, hyperplasia of the left adrenal gland, ascites, diffuse changes in the prostate gland. Furthermore, the pancreas appeared normal, with clear contours, unchanged structure and no dilation of the pancreatic duct. The parenchyma was partial and no foci of pathological contrast accumulation were detected, indicating no abnormal features in the pancreatic tissue.

During the fibro-gastro-duodenoscopy conducted on June 29, 2023, endoscopic examination revealed signs of hernia of the esophageal orifice of the diaphragm, along with erythematous gastropathy and duodenopathy.

The patient's general condition continued to deteriorate progressively. During the UE of the AO conducted on July 5, 2023, notable findings were observed in the context of significant gas accumulation in the large intestine. These included ultrasound signs indicative of polyserositis, characterised by small ascites, pleurisy and hydropericarditis. Additionally, hepatosplenomegaly, marked diffuse changes in the spleen (indicating negative dynamics compared to previous ultrasound examinations on June 8, 2023, and June 26, 2023), diffuse pancreatic intensifications and lymphadenopathy in the abdominal cavity and retroperitoneal space were noted. The lymphadenopathy was observed to be increasing, suggestive of a lymphatic neoplastic process.

The dynamics of the indicators of the general blood analysis during the patient's hospitalisation are presented in Fig. 4. According to the results on July 6, 2023, the patient exhibited a decrease in the following levels: hemoglobin – to 57.5 g/L, platelets – to 76 g/L, erythrocytes – to $1{,}9 \cdot 10^{12}$/L, lymphocytes – to 9 %, monocytes – up to 1 %, segmented neutrophils – up to 6 %. In addition, leukocytosis increased (up to $17{,}2 \cdot 10^{9}$/L), the erythrocyte sedimentation rate (ESR) accelerated to 80 mm/h, the number of band neutrophils increased to 18 %. Myelocytes and metamyelocytes appeared, each accounting for 6% respectively on July 6, 2023.

Figure 5 depicts the dynamic changes in biochemical blood analysis indicators, including creatinine (53—115 mmol/L), urea (normal 2.5—8.3 mmol/L) and residual urea nitrogen (normal

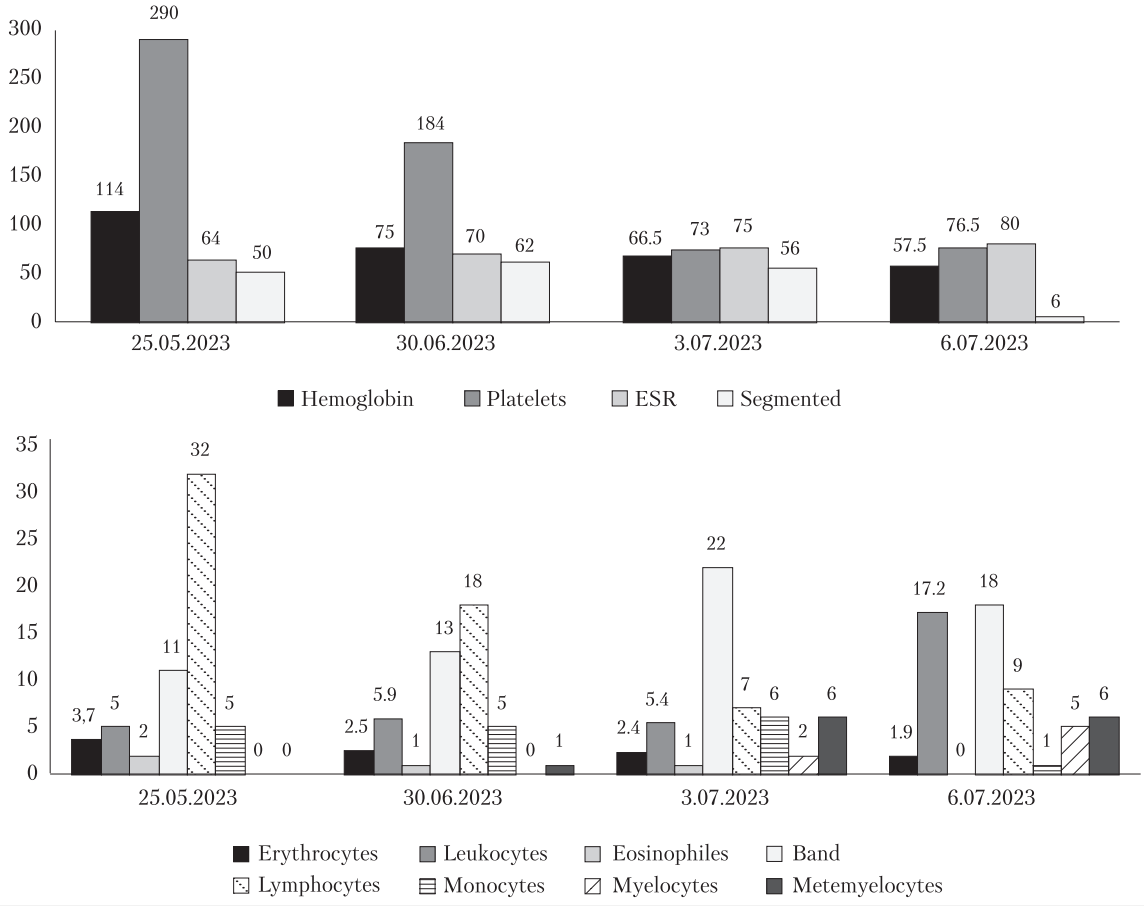

Fig. 4. **Dynamics of general blood analysis indicators**

Hemoglobin (normal 130—160 g/l), erythrocytes (normal 4.4—5.0 · 10^{12}/L), leukocytes (normal 4—9 · 10^{9}/L), platelets (normal 180—320 g/L), ESR (normal 1—10 mm/h), band neutrophils (normal 1—6 %), segmented neutrophils (normal 47—67 %), lymphocytes (normal 18—40 %), monocytes (normal 3—11 %), eosinophils (normal 0—5 %), myelocytes (normal 0 %), metamyelocytes (normal 0 %).

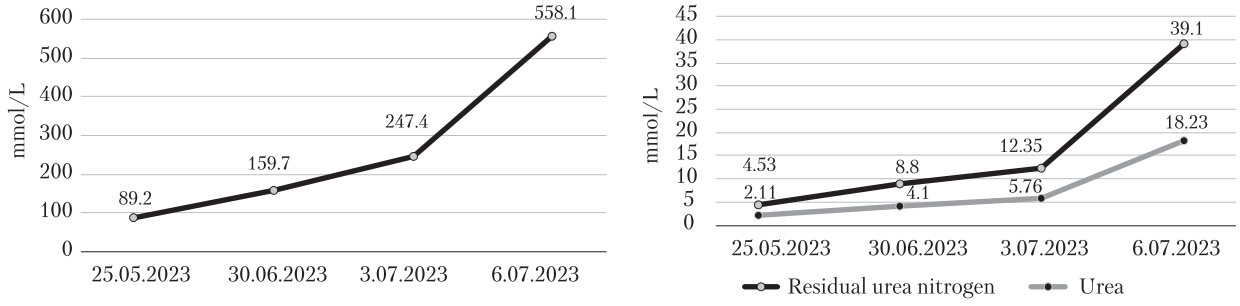

Fig. 5. **Dynamics of indicators of biochemical blood analysis: creatinine, urea and residual urea nitrogen**

14.3—28.6 mmol/L). It is evident from the figure that all these indicators exhibited a progressive increase in the patient over time.

The dynamics of liver function indicators are presented in Fig. 6. According to the results, a progressive increase in the level of bilirubin was determined against the background of increased levels of thymol test (TT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and a reduced level of total protein.

On July 6, 2023, the biological death of the patient was confirmed.

Morphological diagnosis: The disease caused by HIV with manifestations of malignant neoplasms, presents as undifferentiated pancreatic cancer with foci of necrosis and destruction of tumor tissue with metastases in the lymph nodes and liver. Tumor intoxication. There was a non-tuberculosis mycobacterial infection with ITLN lesion. Edema of the brain. Alveolar edema of the lungs. Multiple organ failure.

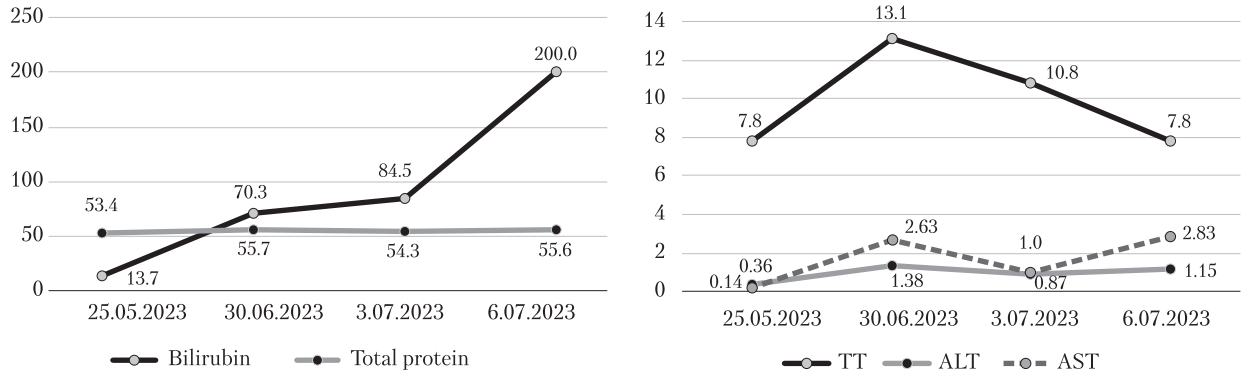

Fig. 6. **Dynamics of liver function indicators (liver tests)**

Total bilirubin (3,1–17 μmol/L), TT (norm 0—5 units), ALT (norm 0.10—0.68 mmol/h/L), AST (norm 0.10—0.45 mmol/h/L), total protein (65–85 g/L).

The primary cause of death was determined to be the progression of multiple organ failure.

Discussion

The first observation drawn from the analysis of the clinical case presented is the patient's neglect of their health, evident in their non-adherence to HIV treatment. Specifically, HIV was diagnosed in the autumn of 2022, yet the patient never initiated ART. Furthermore, the patient sought medical attention already in a severe condition, characterised by symptoms such as severe intoxication syndrome, weight loss, abdominal pain radiating to the lower back and diarrhea. It is worth noting that since the patient did not receive ART, this treatment could not have contributed to the development of pancreatic cancer, as established by D. Serraino et al. [12]. The aggressive course of pancreatic cancer in the patient aligns with the findings of Y. Ji et al. [6].

The patient was admitted to the hospital in a serious condition, where he remained for 42 days. Upon admission, the patient exhibited severe immunosuppression, with a $CD4^+$ lymphocyte count of 20 cells and a viral load exceeding 3,000,000 RNA copies/ml. Prior to hospitalisation, the patient had no history of tuberculosis. Due to the severity of the immunosuppression and doubtful LF-LAM test results, tuberculosis as the etiology of lymphadenopathy could not be ruled out. Despite thorough testing, *Mycobacterium tuberculosis* was not detected in either the sputum or pleural fluid samples. However, non-tuberculosis mycobacteria were identified in the sputum.

The patient underwent two contrast-enhanced computed tomography scans of the abdominal cavity, revealing progressive generalised lymphadenopathy and hepatosplenomegaly. No signs of neoplastic lesions of the pancreas were detected. Therefore, the diagnosis of oncopathology was confirmed solely through pathological examination. Clinical manifestations such as generalised lymphadenopathy, hepatosplenomegaly and fever, observed in the patient, are also characteristic of Castleman's disease associated with human herpes virus-8 [7].

Despite extensive and comprehensive therapy during inpatient treatment, the patient's overall condition continued to deteriorate progressively. Intoxication syndrome, multiple organ failure and polyserositis worsened over time. The primary cause of death was attributed to the progression of multiple organ failure, occurring against the backdrop of an HIV-related disease with manifestations of malignant neoplasms, notably undifferentiated pancreatic cancer with areas of necrosis and destruction of tumor tissue, along with metastases in the lymph nodes and liver. Additionally, there was evidence of a non-tuberculous mycobacterial infection with lesions in the intra-thoracic lymph nodes.

Conclusions

The timely diagnosis of pancreatic cancer in HIV-infected patients with generalised lymphadenopathy and severe immunosuppression can be challenging, as CT signs and other manifestations of pancreatic lesions may not be readily detected. Severe immunosuppression and inconclusive LF-LAM test results posed challenges in ruling out tuberculosis as the etiology of lymphadenopathy. Furthermore, generalised lymphadenopathy served as a manifestation of both metastases and non-tuberculosis mycobacterial infection.

No conflict of interests.
Participation of authors: research concept and design — O.M. Raznatovska, V.I. Petrenko, O.S. Shalmin; collection of material — A.V. Fedorec, A.O. Svitlitsky, O.A. Svitlytska; data analysis — O.M. Raznatovska, V.I. Petrenko, O.S. Shalmin; writing the text and statistical data processing — O.M. Raznatovska, R.M. Yasinskyi; editing of the text — O.M. Raznatovska, V.I. Petrenko.

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Складнощі діагностики раку підшлункової залози при ВІЛ-інфекції з генералізованою лімфаденопатією: туберкульоз, нетуберкульозна мікобактеріальна інфекція чи метастази (клінічний випадок)

Представлено власне спостереження складнощів діагностики в пацієнта із раком підшлункової залози при ВІЛ-інфекції з генералізованою лімфаденопатією. ВІЛ-інфекція у пацієнта діагностована за 8 міс до описаного випадку, антиретровірусну терапію не отримував. До лікаря перед госпіталізацією звернувся вже в тяжкому стані, коли спостерігалися тяжкий інтоксикаційний синдром, втрата маси тіла, біль у животі з іррадіацією в поперек і діарея. Госпіталізований в тяжкому стані до стаціонару, де перебував 42 доби. На момент госпіталізації мала місце тяжка імуносупресія (кількість CD4-лімфоцитів — 20 клітин при вірусному навантаженні понад 3 тис. РНК-копій/мл). Раніше на туберкульоз не хворів. З урахуванням тяжкої імуносупресії та сумнівного результату тесту LF-LAM неможливо було заперечити туберкульозну етіологію лімфаденопатії. Мікобактерії туберкульозу ні в мокротинні, ні в плевральній рідині не виявлено, але виявлено нетуберкульозну мікобактерію в мокротинні. Хворому двічі проводили комп'ютерну томографію органів черевної порожнини з контрастуванням. Діагностовано генералізовану лімфаденопатію, яка наростала, та гепатоспленомегалію, ознак неопластичного ураження підшлункової залози не виявлено. Тому діагноз онкопатології підтверджено лише патогістологічно. Під час стаціонарного лікування, незважаючи на масивну комплексну терапію, загальний стан прогресивно погіршувався, наростали інтоксикаційний синдром, поліорганна недостатність і полісерозит. Причиною смерті стало прогресування поліорганної недостатності на тлі хвороби, зумовленої ВІЛ, з виявами злоякісних новоутворень (недиференційований рак підшлункової залози з вогнищами некрозу та розпаду пухлинної тканини, метастазами в лімфовузли та печінку). Мала місце нетуберкульозна мікобактеріальна інфекція з ураженням внутрішньогрудних лімфатичних вузлів. Таким чином, у ВІЛ-інфікованого пацієнта з генералізованою лімфаденопатією на тлі тяжкої імуносупресії прижиттєва вчасна діагностика раку підшлункової залози може спричинити складнощі через

відсутність комп'ютерно-томографічних ознак та інших виявів раку. Тяжка імуносупресія та сумнівний результат тесту LF-LAM не дали змоги заперечити туберкульозну етіологію лімфаденопатії. При цьому генералізована лімфаденопатія була виявом метастазів і нетуберкульозної мікобактеріальної інфекції.

Ключові слова: рак підшлункової залози, ВІЛ-інфекція, лімфаденопатія, туберкульоз, нетуберкульозна мікобактеріальна інфекція, метастази.

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