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CHALLENGES IN PULMONARY TUBERCULOSIS MANAGEMENT IN A LIVER TRANSPLANT RECIPIENT WITH CROHN'S DISEASE: A CASE REPORT

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ABSTRACT

Background: Tuberculosis (TB) poses a substantial risk as an opportunistic infection in individuals who have received solid organ transplants, particularly in those with liver transplants compounded by inflammatory bowel disease. Managing TB in this group is particularly challenging due to possible drug interactions and the heightened risk of liver toxicity. **Case study:** We present a 35-year-old male liver transplant recipient with Crohn's disease, who developed pulmonary TB despite prior prophylaxis and immunosuppression. The first anti-TB treatment was modified and dose-reduced due to the patient's immunocompromised status. This regimen failed, with recurrent positive sputum cultures. Upon retreatment with a full-dose triple regimen excluding pyrazinamide, the patient responded well with full recovery and no adverse hepatic or Crohn's-related events. **Conclusion:** This case illustrates the challenges of treating TB in liver transplant patients with Crohn's disease, emphasizing the delicate balance between achieving therapeutic effectiveness and minimizing hepatotoxicity. In carefully selected patients, administering a complete tuberculosis treatment protocol without pyrazinamide can provide a safe and effective therapeutic outcome.

INTRODUCTION

Liver transplant recipients are especially vulnerable to TB, which carries significant morbidity and mortality[1]. The use of potent immunosuppressive therapies further increases susceptibility to opportunistic infections. Infection with Mycobacterium tuberculosis is among the most serious post-transplant complications[2], with studies indicating that the risk of acquiring active TB is as much as 74 times higher than the general population[2-4].

Globally, TB was one of the main causes of mortality worldwide in 2017, and it is estimated that about 25% of the world's population is estimated to harbor latent TB infection[5]. About 1. 6 million people died and 10 million new cases of TB were reported in that year alone. Despite a 21% reduction in global prevalence between 2000 and 2017, TB continues to represent a major public health problem (WHO). Among transplant patients, reported TB incidence varies widely from 1. 2% to 6. 4% in developing nations, and it can reach 15% in areas where TB is widespread[5].

Significant morbidity and mortality in liver transplant recipients is caused by Mycobacterium tuberculosis (MTB)[6]. According to a study by Holty, 1. 3% of transplant patients had active MTB infections. Nearly half of all recipients with active MTB infection had an identifiable pretransplant MTB risk factor. Among recipients who developed active MTB infection, extrapulmonary involvement was common (67%), including multiorgan disease (27%). The short-term mortality rate was 31%.[6]

Patients with inflammatory bowel disease (IBD) exhibit an increased susceptibility to both new and reactivated opportunistic infections, especially when factors such as hospitalization, malnutrition, or the use of biologic agents and immunosuppressive therapies are present[1].

The prevalence of active MTB infection is 18 times higher in liver transplant patients than in the overall population, and the case fatality rate is four

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times higher. Isoniazid seems to be safe for transplant candidates who are at high risk, and it is likely that it helps lower MTB reactivation[6].

In this report, we describe pulmonary tuberculosis in a liver transplant patient with Crohn's disease, in which standard treatment protocols were unsuccessful.

CASE REPORT

Patient T.A., age 35, liver transplant recipient (LTR) with coexisting Crohn's disease, was hospitalized in the Clinic for Pulmonary Diseases, JZU UKC Tuzla in June 2023 due to BACTEC positive sputum cultures for Mycobacterium tuberculosis. Patient has been previously treated for Crohn's disease for 16 years. The patient had a liver transplant in 2015 because of overlap syndrome (autoimmune hepatitis) and sclerosing cholangitis. In the post-transplantation period, the patient recieves the normal triple-immunosuppression protocol for LTRs consisting of steroids, tacrolimus, and mycophenolate mofetil (MMF). From 2017 until 2023, Vedolizumab was used as a biological therapy for Crohn's disease. Before starting this biologic tratment, a six-month course of isoniazid was given to prevent latent tuberculosis from reactivating.

On admission to the hospital in June 2023, the patient had a positive BACTEC sputum culture for Mycobacterium tuberculosis, despite being asymptomatic for respiratory issues. He did not report coughing, hemoptysis, breathing difficulties, or weight loss. A chest radiograph taken upon hospital admission showed no infiltrative changes.

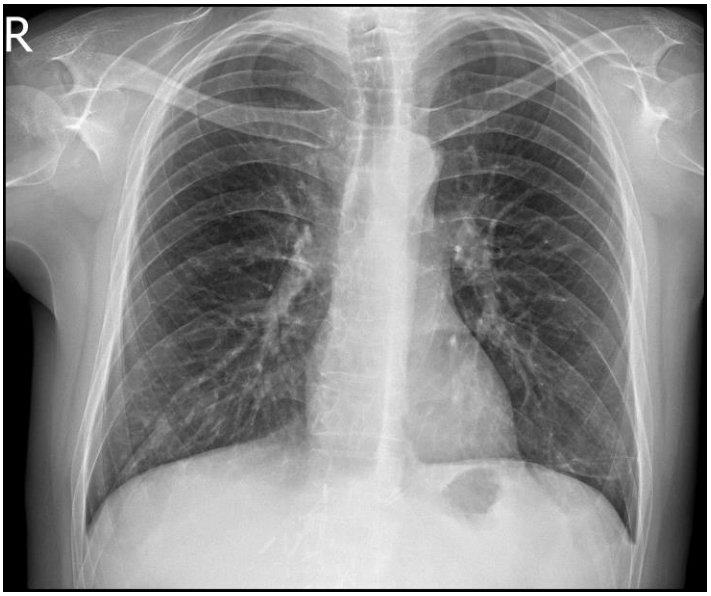

Figure 1. Chest radiograph on admission (June 2023)

The patient was previously hospitalized for pulmonary tuberculosis in 2022, confirmed by a BACTEC positive sputum culture. During the first hospitalization due to the transplanted liver and Crohn's disease, reduced doses of antituberculosis drugs were administered according to a modified protocol. This included initial therapy with isoniazid 200 mg orally, ethambutol 1200 mg orally, and streptomycin 1 g intramuscularly for two months, followed by an extended treatment phase of isoniazid 200 mg and ethambutol 1200 mg orally for another ten months. The first tuberculosis treatment lasted a total of 12 months.

After one year of treatment with reduced doses of antituberculosis medications, positive Bactec sputum cultures for Mycobacterium tuberculosis were confirmed again, indicating failure of the initial tuberculosis treatment. During the second hospitalization, the patient remained asymptomatic and in good clinical condition.

Acid-fast bacillus sputum smear was negative, while BACTEC sputum cultures were positive. Antimicrobial susceptibility testing (AST) revealed

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sensitivity to isoniazid, rifampicin, ethambutol, and pyrazinamide for all sputum samples.

CT CHEST (June 2023): In the anterobasal parts of both lobes of the left lung, less dense consolidation of parenchyma with partially subatelectic parenchyma in terms of sequelae and a smaller residue of pneumonic infiltration. Left hemidiaphragm lying higher with consequent condensation of the parenchyma of the basal parts of the lower lobe of the lung. Bilateral basal pleuropulmonary scar changes. On both sides more to the left initial dilatation of individual bronchial branches. Pleural effusion is not visible. Signs of anterior lower mediastinal lipomatosis. Single mediastinal lymph nodes up to about 11 mm in diameter, hilopulmonary about 10 mm. No pathologically enlarged axillary lymph nodes were visible.

ABDOMINAL AND PELVIC CT (June 2023): Postoperative status: state after liver transplantation (2015) with surgical clips at the level of the surgical intervention. The transplanted liver is of adequate size, in some places it appears initially reduced parenchyma density values, possibly as part of the initial inhomogeneous fatty infiltration. In the parenchyma of the liver, no focal lesions can be observed except a punctiform hypodense area in the right hepatic lobe, similar to a cyst. Dilation of extrahepatic bile ducts is not observed. Initially, the intrahepatic bile ducts of the left lobe were highlighted with signs of pneumobilia. Papilla Vateri prominent. Spleen with a diameter of 145 mm, without focal lesions. Pancreas, kidneys and adrenal glands with normal CT findings. The ceco-ascending colon has a diffusely unevenly thickened wall, up to 15 mm thick, with lower densities with pronounced vascularization in the associated adipose tissue of the mesocolon and smaller locoregional lymph nodes, all possible as part of inflammatory changes - colitis of open etiology. Similar, but less pronounced changes in places and at the level of the transverse and descending column at the level of the transition towards sigma. Transverse diameter prostate 40 mm, differentiated. Urinary bladder inadequately distended, resulting in an accentuated wall without noticeable solid masses.

Laboratory: Leukocytes 6.00 x 10^9/L; Erythrocytes 3.81 x 10^12/L; Platelets 277 x 10^9/L; Urea 4.2 mmol/L; Creatinine 74 µmol/L; Total Bilirubin 4.6 µmol/L; AST 14 U/L; ALT 14 U/L; Total Proteins 58 g/L; Albumin 32 g/L; Globulin 26 g/L; CRP 25.3 mg/L; Tacrolimus 4.20 ng/mL. Laboratory control: Leukocytes 8.90 x 10^9/L; Erythrocytes 4.66 x 10^12/L; Platelets 268 x 10^9/L; Urea 8.1 mmol/L; Creatinine 143 µmol/L; Total Bilirubin 4.0 µmol/L; AST 18 U/L; ALT 8 U/L; Total Proteins 73 g/L; Albumin 46 g/L; Globulin 27 g/L; CRP 18 mg/L. Tacrolimus levels were from 1.10 to 8.10 ng/mL.

During the initial hospitalization (2022), acid-fast bacillus sputum smear was negative, while Bactec and Low were positive for Mycobacterium tuberculosis. No other pathogenic bacteria were isolated in sputum culture. Chest X-ray were normal.

During the repeated hospitalization, after initially unsuccessful treatment, the patient was gradually initiated on triple anti-tuberculosis drug therapy isoniasid 225 mg, rifampin 450 mg and ethambutol 800 mg daily, along with hepatoprotectives and vitamin B6. Neither the first nor the second time was pyrazinamide prescribed to the patient due to hepatotoxicity and a transplanted liver. After the initial treatment (isoniasid, rifampin, ethambutol), lasting for 3 months, an extended treatment phase (isoniasid, rifampin) was continued for the next 9 months at the primary healthcare center. Total treatment duration od anti-tuberculosis drug therapy was 12 months. The entire course of prescribing anti-tuberculosis drug therapy, following the initially unsuccessful treatment, proceeded well, without signs of hepatotoxicity, without worsening of graft function, gastric intolerance, allergies, and without exacerbation of Crohn's disease. The patient’s tacrolimus dose was carefully monitored and adjusted throughout treatment to account for potential interactions with anti-tuberculosis medications. Liver parameters were monitored weekly throughout the treatment course and remained normal. It was recommended not to initiate biological therapy for Crohn's disease until culture negativity is achieved and without the agreement of the pulmonologist.

After a year of repeated anti-tuberculosis drug therapy, the patient's recovery has been achieved. In June 2024 acid-fast bacillus sputum smear was negative x2, cultures (Bactec and Lowenstein-Jensen medium) were negative. In August 2024 acid-fast bacillus sputum smear was negative, cultures (Bactec

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and Lowenstein-Jensen medium) were negative. The patient was asymptomatic with no pathological changes on chest radiography. The function of the liver graft was norm al and Crohn's disease was well controlled.

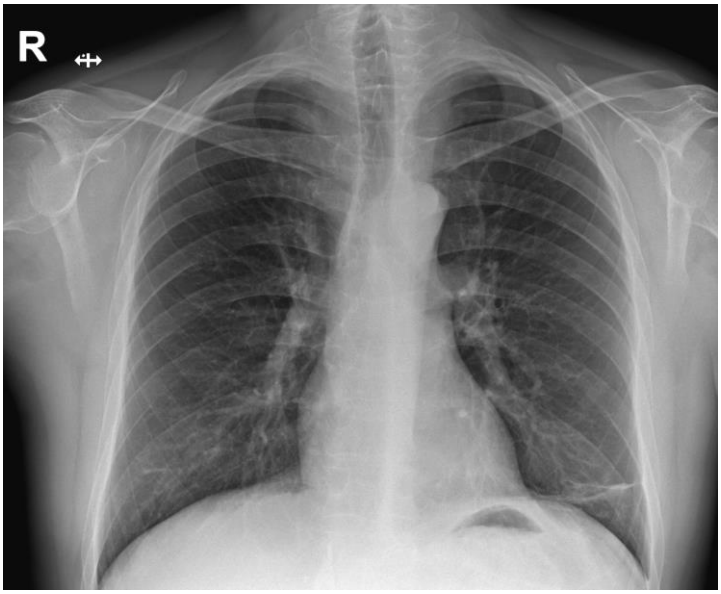

Figure 2. Chest radiograph after re-treatment (June 2024)

DISCUSSION

Risk factors for TB development in SOT recipients have been described in a number of studies[3,4,7]. Transplant recipients are typically 20–74 times more likely than the general population to develop tuberculosis[5]. Numerous factors, including positive HIV status, male sex, ethnicity, low body mass index (BMI), substance abuse, other comorbidities, prior treatment, drug resistance, low level of education, ignorance of treatment duration and the significance of treatment completion, household income, the need for hospitalization during treatment, medication side effects, improved symptoms leading to therapy cessation, lack of family support, and unsupervised treatment administration, have been linked in prior studies to unsuccessful TB treatment outcomes[8–12].

Tuberculosis in transplant recipients primarily arises from reactivation of latent TB, though the risk is also influenced by the type of transplanted organ, the intensity of immunosuppression, and the presence of other opportunistic infections[1].

The eternal dilemma of clinicians is which treatment protocol to apply in liver transplant recipients? Is the fear of hepatotoxicity rational? Should the doses of antituberculosis drugs be reduced? In our case report, the question arises whether reducing the dose of anti-tuberculosis drugs is correct, or whether tuberculosis treatment without rifampicin is acceptable at all in patiens with liver transplant.

Understanding and addressing the determinants that contribute to poor tuberculosis (TB) treatment outcomes is essential for improving TB control strategies and limiting the emergence of drug-resistant strains[14]. Standard therapy for drug-sensitive TB consists of a six-month course that includes four first-line medications; isoniazid, rifampicin, ethambutol, and pyrazinamid This therapy typically achieves treatment success in roughly 85% of patients.[14]

Individuals who have undergone liver transplantation are at heightened risk of developing TB due to several mechanisms: reactivation of latent infection, new exposure within the community, donor-derived transmission, or infection acquired in healthcare settings. However, the specific risk factors for post-transplant TB remain incompletely defined[5]. Liver transplantation influences how TB manifests clinically, affects the interpretation of diagnostic tests, complicates treatment due to drug interactions,

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increases susceptibility to hepatotoxic effects, and impacts overall outcomes[5,13].

More than half of liver transplant recipients diagnosed with active TB present with extrapulmonary forms of the disease. Quantiferon testing is advised for all liver transplant recipients, and isoniazid prophylaxis for latent TB should be administered to patients with a positive Quantiferon result or other pre-transplant risk factors for Mycobacterium tuberculosis, unless contraindicated[6].

In a cohort of 4,818 individuals with inflammatory bowel disease (IBD), 37 cases of active TB were identified. Multivariable analysis highlighted several independent predictors of TB: exposure to anti-TNF agents within the previous year, recent hospitalization (within six months), and decreased serum albumin levels. Among these, prior anti-TNF therapy was the strongest predictor according to CHAID algorithm analysis was anti-TNF treatment within the previous 12 months. This study shows that two main factors put patients with IBD at risk for active TB in our setting: anti-TNF therapy and recent hospitalization[15]. Current corticosteroid use has been associated with higher risk for TB in the general population[16].

Patients treated with anti-TNF medications are particularly susceptible to active TB, predominantly due to reactivation of latent infection[17]. Implementing screening and management of latent TB before starting anti-TNF therapy can reduce the incidence of active disease by around 80%[18]. Nonetheless, active TB continues to appear, driven by factors such as new primary infection, incomplete adherence to screening recommendations, and the limited sensitivity of available diagnostic assays, especially in immunocompromised individuals[20].

Risk patterns in IBD patients who do not receive anti-TNF therapy are less clearly mapped, although smoking and corticosteroid therapy have been associated with increased susceptibility. Some evidence also suggests that IBD itself may predispose patients to TB[21]. Recent studies report that individuals with untreated Crohn's disease show a higher rate of active TB compared with the general population, with additional risk increases among those treated with corticosteroids, anti-TNF monotherapy, or combinations of corticosteroids, immunomodulators and/or anti-TNF agents[22].

This case highlights that active TB can still develop in liver transplant recipients with IBD, underscoring the need to reconsider and potentially revise therapeutic protocols for TB management in this high-risk population.

ETHICS STATEMENT

This case report was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication.

COMPETING INTEREST STATEMENT

The authors declare no competing interests.

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