Clinical Case Report

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# Tubercular hemoptysis in a young liver transplanted patient

## Case report

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**Abstract**

**Rationale:** Liver transplanted patients have excellent survival rates, but infectious complications are a major cause of morbidity and mortality. Diagnosis and treatment of tuberculosis (TB) in liver recipients are very challenging. Specific recommendations for anti-TB treatment in liver transplanted patients are lacking.

**Patient concerns and diagnosis:** A 22-year-old male liver transplanted patient because of biliary atresia showed unexpected acute hemoptysis while he was on immunosuppressive therapy with tacrolimus and mycophenolate mofetil. Computed tomography (CT) identified a pulmonary arteriovenous malformation (PAVM) successfully treated with endovascular embolization. A post-embolization thoracic CT revealed pulmonary cavitation and miliary pattern suggesting pulmonary TB causing PAVM. TB diagnosis was confirmed by microbiological assays and genetic amplification techniques.

**Intervention:** Anti-TB 4-drug regimen was started. Following the beginning of treatment, liver enzymes increased. In order to clarify if liver cytolysis was due to hepatotoxicity or hepatic rejection linked to the reduction of immunosuppression or a worsening of pre-existing graft hepatitis, a liver biopsy was performed. A mild graft rejection was found so that tacrolimus doses were increased despite the risk of tubercular dissemination.

**Outcome:** The patient completed anti-TB therapy in 8 months with resolution of TB disease and stable liver disease.

**Lessons:** TB management in liver transplanted patients is challenging and needs to be individualized especially if chronic graft hepatitis is present.

**Abbreviations:** CT = computed tomography, IGRA = interferon-gamma related assays, OLT = orthotopic liver transplantation, PAVM = pulmonary arteriovenous malformation, SOT = solid-organ transplanted, TB = tuberculosis, TST = tuberculin skin test.

**Keywords:** drug-induced liver toxicity, graft rejection, immunocompromised patient, orthotopic liver transplantation (OLT), pulmonary arteriovenous malformation (PAVM), tuberculosis (TB)

## 1. Introduction

Young adults with liver transplant have excellent survival rates, over 80% of them surviving more than 10 years. Graft loss is most often associated with complications such as chronic rejection, hepatic artery thrombosis, and biliary complications. However, outcomes after transplantation are favorable for the majority of recipients.[1] Infectious complications are a major cause of morbidity and mortality following transplantation.[1] Prevention of infections and an aggressive diagnostic strategy are cornerstones in solid organ transplanted (SOT) patient management. The risk for active tuberculosis (TB) in these patients is estimated to be 20 to 74 times higher than in the general population.[2] Diagnosis of TB in SOT recipients is harder than in general population because of higher frequency of extrapulmonary and disseminated disease, subtle presentation, obscure locations and presence of coinfections. Furthermore, screening test for TB by tuberculin skin test (TST) and interferon-gamma related assays (IGRA) may not be reliable in SOT recipients because test sensitivity is diminished by immunosuppressants use and, in liver transplanted patients by chronic liver disease.[3,4] As a result, TB diagnosis must be considered on the basis of multiple parameters, such as anamnesis, clinical and radiographic features, microbiological assays and molecular amplification techniques from cultures. If the usual techniques cannot confirm the clinical suspicion, invasive diagnostic procedures should be considered.[5] Furthermore, clear indications are not available about management of anti-TB treatment in liver transplanted subjects, especially in those with chronic graft disease.[1,5,6]

Hemoptysis is often a self-limiting event but in fewer than 5% it may be severe or massive, representing a life-threatening condition.[7] The differential diagnosis of hemoptysis is broad

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and the relative frequency of possible etiologies varies significantly. Acute respiratory tract infections, asthma, chronic obstructive pulmonary disease, malignancy, and bronchiectasis are the most common causes of hemoptysis. The likelihood of TB infection associated with hemoptysis varies throughout the world with the lowest incidence in the United States and highest incidence in South Africa. Uncommon but well-known causes of hemoptysis include pulmonary embolism, pulmonary endometriosis, Goodpasture syndrome, foreign body aspiration, and arteriovenous malformations.[8] Pulmonary arteriovenous malformations (PAVMs) were first described in 1897 and consist of abnormal communications between pulmonary veins and arteries.[9] PAVMs of the lung are congenital in the majority of case and hereditary hemorrhagic telangiectasia causes up to 85% of all PAVMs.[10,11] PAVMs have also been described in acquired conditions; association between pulmonary TB and PAVMs has been reported and it was hypothesized that inflammatory processes surrounding a tubercular focus may help recruit local vessels causing a PAVM.[12–14]

In this case report, we describe a liver transplanted immunosuppressed young man who showed hemoptysis because of a PAVM as first sign of TB infection. The difficulties of anti-TB therapy in a SOT patient with an underlying chronic liver disease are addressed.

## 2. Case presentation

We report the case of a 22 year-old male presenting with an unexpected episode of large-volume hemoptysis. He was followed for orthotopic liver transplantation (OLT) received at the age of 1 year because of biliary atresia not resolved by Kasai-intervention. Liver biopsy performed at the age of 17 years showed mild graft hepatitis and fibrosis for which mycophenolate mofetil was added to tacrolimus therapy, as suggested.[1,15–17]

A slight and intermittent increase in liver enzymes was present in the previous 12 months (alanine-aminotransferase [ALT] maximum 2-times normal values with average values of 54 ± 14 U/L, gamma-glutamyltraspeptidase [GGT] maximum 1.8-times normal values with average values of 94 ± 15 U/L), and attributed to the mild graft hepatitis, with levels of immunosuppressive drugs in the reference range for the posttransplant period. During previous 6 months the patient presented 4 episodes of fever without localization, with a short duration and spontaneous defervescence in 2 times and after empiric antibiotic treatment the other times. There was no history of hemoptysis or gastrointestinal bleeding, chest radiography was negative and no portal hypertension neither esophageal varices were present. When hemoptysis occurred, the patient was examined at emergency department: dyspnea, pallor, and tachycardia were observed and blood pressure levels were at lower limits. After initial clinical stabilization, a thoraco-abdominal contrast-enhanced computed tomography (CT) with angiographic-sequences was performed, revealing a complex PAVM in the right lung upper lobe, involving intercostal artery and pulmonary vein, which caused a massive endoalveolar bleeding (Fig. 1). Transcatheter endovascular embolization was successfully performed resulting in resolution of symptoms.

Since multiple malformations may be associated with biliary atresia, a noninvasive malformation screening, including cerebral neuroimaging, was performed but no other anomalies were found. Meanwhile, follow-up CT performed 12 days after embolization revealed an alveolar consolidation with central

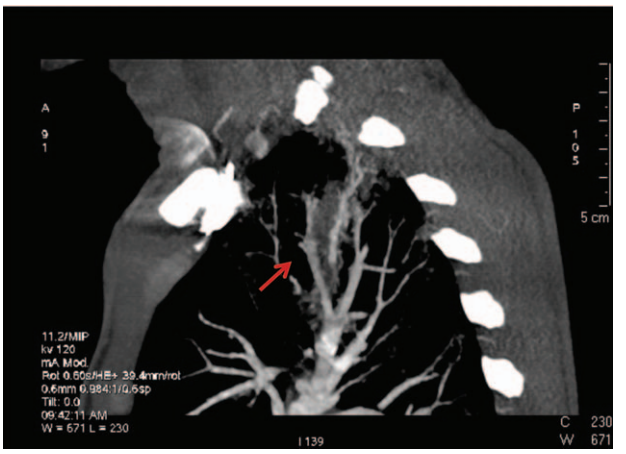


**Figure 1.** Complex pulmonary arteriovenous malformation in the right lung upper lobe, involving intercostal artery and pulmonary vein, surrounded by endoalveolar bleeding; thoracic contrast-enhanced computed tomography with angiographic sequences, sagittal scansion.

cavitation in the area of PAVM and a diffuse miliary pattern, suggesting an infectious-inflammatory process likely caused by pulmonary TB (Fig. 2). TST by Mantoux intradermal reaction and IGRA test (Enzyme-Linked ImmunoSpot assay) were performed under immunosuppressive therapy and gave negative results, but genetic amplification techniques by PCR and cultures of sputum and of bronchoalveolar lavage identified a *Mycobacterium tuberculosis complex* with rifampicin-sensitivity. A revaluation of the first pulmonary CT revealed suggesting features of pulmonary TB that had not been previously identified, probably because the radiological picture was dominated by the massive pulmonary hemorrhage. Diagnosis of pulmonary TB was made and treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol was promptly started.

After the beginning of treatment, a further increase in liver enzymes occurred (ALT maximum 4-times normal values with average values of 106 ± 49 U/L, GGT maximum 6-times normal values with average values of 149 ± 111 U/L) with normality of

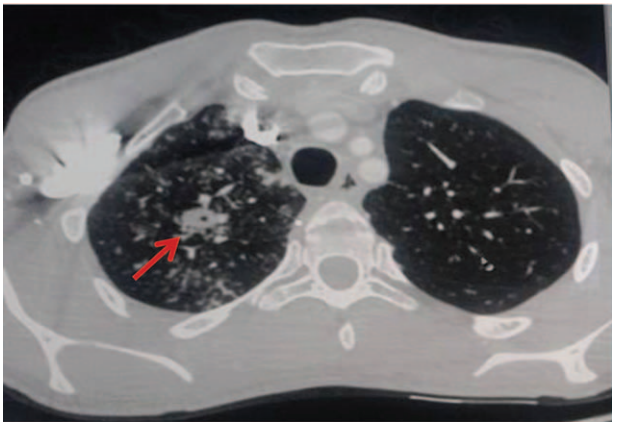

**Figure 2.** Consolidation area in the central upper region of the right lung due to a likely specific tubercular complex, associated with bilateral signs of miliary infection, more extensive to the right lung; thoracic computed tomography, axial scansion.

bilirubin, albumin, cholinesterase, and international normalized ratio (INR). Viral infection serology and assessment for autoimmune hepatitis were negative.

Pyrazinamide and ethambutol were suspended (+2 months of treatment) according to anti-TB treatment standard guidelines.[18] Subsequently, since an improvement in the biochemical trend described above was not observed, a liver biopsy was performed at +3 months of treatment, which found a mild inflammatory infiltrate in the minority of the triads, confined within the portal spaces and associated with slight signs of endothelitis (Banff stage 1), suggesting a late-onset mild acute rejection.[17]

This histopathological picture was attributable to the reduction in blood levels of tacrolimus since the first weeks of treatment, likely due to interaction with antitubercular drugs. We progressively continued to increase tacrolimus dose (until 3 times basal dose) in order to lead it to the upper limit of reference recommended range for the time of transplantation. Careful clinical and laboratory checks were performed, finding substantially stable values of liver enzymes (ALT maximum 4, 7-times normal values with average values of 149 ± 33 U/L, GGT maximum 8-times normal values with average values of 327 ± 74 U/L), normality of albumin and INR, tacrolimus blood levels in the reference range while the patient remained asymptomatic in good clinical conditions without showing threatening evolution of the infectious disease. Liver enzymes and tacrolimus levels' profile is reported in (Fig. 3).

Isoniazid and rifampicin were continued until +8 months; negativity of several sputum smears and cultures for *M. Tuberculosis* were registered since the second month of therapy; pulmonary CT at the end of anti-TB treatment described a substantial regression of the infectious lung involvement with a residual small fibrotic area in the right upper lobe.

Clinical, biochemical, and radiological follow-up of our patient at +36 months from discontinuation of TB treatment reveals an encouraging balance, with persistent remission from tubercular disease and satisfying liver biochemical parameters which were substantially comparable to the baseline.

## 3. Discussion

Our case emphasizes the challenges existing in both diagnostic evaluation and therapeutic management of TB in liver transplanted patients with underlying chronic graft hepatitis pre-existing to TB infection.

TB is considered as a serious complication for organ transplant recipients; prevalence of infection range from 1% to 6% and active TB can be diagnosed in 0.47% to 2.3% of liver transplanted patients, mostly in the first 12 months after OLT.[19,20] Clinical presentation of TB in immunosuppressed patients is insidious and often causing delay in diagnosis and resulting in a poor prognosis.[3,21] In our patient, who was liver transplanted for more than 20 years, before hemoptysis pulmonary TB probably presented as some episodes of fever without localization, which did not lead to a suspect of TB considering the spontaneous resolution and the absence of other peculiar features of the disease included a negative chest X-Ray. As it usually happens in OLT patients, in our case TST and IGRA yield falsely negative results due to anergy secondary to pharmacological immunosuppression and chronic liver disease.[22] In this case, TB infection was suggested only by CT images. Furthermore, diagnosis of TB was made even more difficult because it clinically appeared with an acute hemoptysis associated with a PAVM that could be interpreted as malformation in a patient with biliary atresia. In fact, several congenital malformations have been described in patients with biliary atresia.[23]

As for causal relationship between pulmonary TB and PAVM in our patient, PAVM seemed to be more likely related to the inflammatory tubercular process rather than a congenital PAVM, on which TB process was subsequently implanted.

Pharmacological management of TB in OLT recipients is often challenging for clinicians because of liver toxicity of most first-line anti-TB drugs and their pharmacokinetic interaction with chronic anti-rejection immunosuppressive therapy.[21,24] The present case underlines the main problems that can be observed in the liver transplanted patient suffering from TB: the potential hepatotoxicity of most anti-TB drugs; the lack of definite

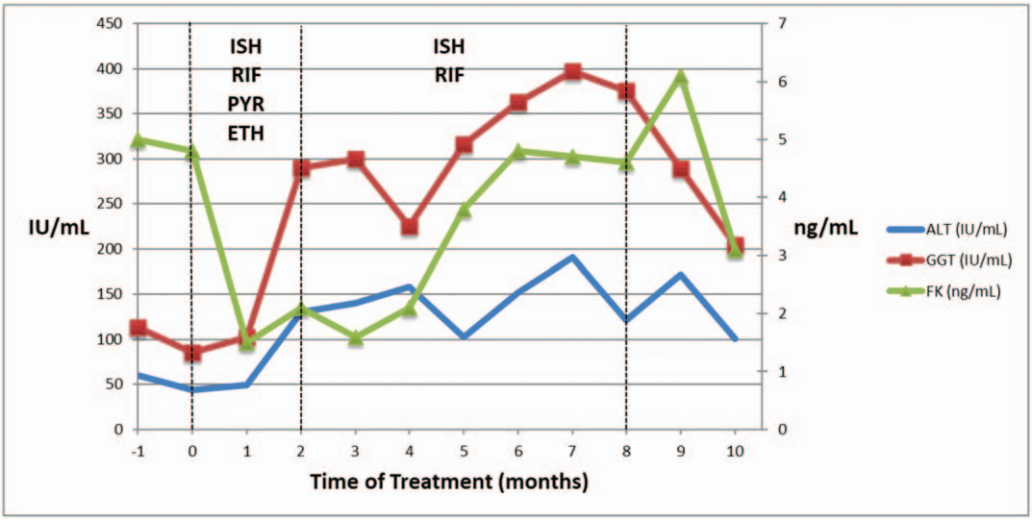


**Figure 3.** Profiles of ALT, GGT, and FK levels during antitubercular treatment. ALT = alanine-aminotransferase, ETH = ethambutole, FK = tacrolimus, GGT = gamma-glutamyltraspeptidase, ISH = isoniazid, PYR = pyrazinamide, RIF = rifampicin.

indications on composition and duration of anti-TB therapy; the need to continually adjust the immunosuppressive levels avoiding the progression of TB infection and at the same time graft rejection; the drugs interactions between antituberculars and immunosuppressants. As for the persistent increase in amino-transferases and gamma-glutamil transpeptidase levels, observed soon after the start of anti-TB treatment and persisting even after pyrazinamide withdrawal, it was difficult to establish if it was due to pre-existing chronic liver disease or to reduction in tacrolimus levels probably due to rifampicin mediated CYP3A4 induction[25,26] or to antitubercular drugs toxicity. Liver biopsy suggested a late-onset mild acute rejection we treated increasing baseline immunosuppression for 2 reasons: it was a histologically mild case of cellular rejection; a short course of increased immunosuppression with steroids could be dangerous for TB progression in our case.[6]

Although guidelines for OLT recipients suggest that, for localized or non-severe forms of TB and no suspicion or evidence of resistance to isoniazid, rifampicin is not recommended,[1,24] our patient received rifampicin for his history of life-threatening hemoptysis and presence of diffuse miliary pattern.

Another critical point was duration of anti-tubercular treatment. Although there are no controlled trials assessing the optimal schedule and duration of therapy in SOT recipients, the Guidelines of the Expert Group in Renal Transplantation[27] suggest a standard 6-month regimen including rifampicin, as suggested in general population. Nevertheless, it is reasonable to use a prolonged course of treatment in the immunosuppressed SOT population.[24] Moreover, several studies have observed a higher risk of death and relapse in patients receiving short duration treatments, in particular lasting less than 9 months.[3,28]

For our patient, considering the good microbiological and radiological response of pulmonary TB and the vulnerability of liver during therapy, we decided to stop anti-tubercular treatment after 8 months. Our patient reached complete remission from pulmonary TB maintaining a good respiratory function and a good liver balance.

Our hypothesis is that liver biochemical and histological picture of the patient was the result of a complex interaction between inadequate immunosuppression (caused by rifampicin's cyto-chrome-induction on tacrolimus metabolism) and a multi-drug induced liver toxicity, inscribed into a pre-existing context of chronic graft hepatitis. Furthermore, we registered a significative reduction in liver cytolysis and cholestasis parameters after suspension of TB therapy; nevertheless, the values did not return to reference range, maybe due to the pre-existing mild chronic graft disease, which is well-described in the literature and is congruous with our patients history of long time from transplant.

In conclusion, our report suggests that the complex setting of the immunocompromised patient usually offers diagnostic and therapeutic questions, whose solutions are not always explicitly coded in the literature and may rather be the result of an individualized physician's weigh up of risks and benefits.

## Author contributions

**Conceptualization:** Fabiola Di Dato, Margherita Rosa, Raffaele Iorio.
**Data curation:** Fabiola Di Dato, Francesco Nunziata.
**Writing – original draft:** Fabiola Di Dato, Margherita Rosa.
**Writing – review and editing:** Raffaele Iorio, Maria Immacolata Spagnuolo.

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