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SHORT COMMUNICATION

Fatal acute respiratory distress by Toxoplasma gondii in a toxoplasma seronegative liver transplant recipient

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SUMMARY

The risk of *Toxoplasma gondii* infection in solid organ transplant recipients is well known but mainly after heart transplantation. We discuss a case of acute respiratory distress caused by *Toxoplasma gondii* on Day 32 after liver transplantation. The reported case, which is extremely rare, emphasizes how direct examination and Quantitative Polymerase Chain Reaction (QPCR) in broncholaveolar lavage help to diagnose the infection. Given Trimethoprim/Sulfamethoxazole toxicity, systematic prescription of *Toxoplasma gondii* chemoprophylaxis is not commonly approved in liver transplantation.

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The incidence of toxoplasmosis in immunocompromised patients is closely related to the prevalence of the disease in the general population, which is high in Western Europe (Tenter *et al.*, 2000). The risk of *Toxoplasma gondii* infection in solid organ transplant (SOT) recipients is well known but involves mainly heart transplantation since the cysts are located in the myocardium. Only a dozen cases of pulmonary or disseminated toxoplasmosis following liver transplantation have been registered over the past 40 years (Campbell *et al.*, 2006; Bellali *et al.*, 2013). A case of acute respiratory distress caused by *Toxoplasma gondii* after liver transplantation is discussed here. Toxoplasmosis was considered to be a primary infection as the host patient's preoperative serological tests were all negative while the donor's toxoplasmosis test was positive.

CASE REPORT

A 62 year-old woman underwent liver transplantation due to alcoholic cirrhosis revealed by corticoresistant acute alcoholic hepatitis (AAH) within the framework of the national Quick Trans protocol for AAH. The liver donor was a 69-year-old woman with the same blood type. Immediate postoperative surveillance showed good recovery of the graft. Prednisone, Tacrolimus and Mycophenolate mofetil were used as immunosuppressive therapy. The patient left the surgical intensive care unit (ICU) on Day (D) 8. The first signs of orthopnea with crepitant rales were observed during chest auscultation on D19. The echocardiography confirmed high left-sided ventricular filling pressure. Symptomatology was improved by Furosemid but kidney function gradually declined (Creatinine 174 µmol/L). Cardiorenal syndrome was considered, as well as iatrogenic hypovolemia associated with diuretic treatment. Renal vascular etiology was ruled out. On D29, new signs of orthopnea were registered; anuria led to respiratory distress on D30. Blood gases revealed respiratory acidosis with hypercapnia and hypoxia. A Furosemid infusion was prescribed as creatinine and hyperkalemia increased (220 µmol/L and 5.8 mmol/L respectively). The patient was transferred to the ICU with multiple organ failure. The different tests revealed preload low cardiac output caused by severe systemic inflammatory response syndrome associated with predominant pulmonary edema. Extra-renal purification was performed before acute kidney injury with metabolic complications.

Anti-infective treatments were expanded with Caspofungin and Colimycin. Rapid decline with metabolic, hemodynamic, respiratory, renal and multiple organ failure and coagulopathy followed. The patient died on D32, 11 hours after being transferred to the ICU.

The overall pre-transplant microbiological tests were negative except for cytomegalovirus (CMV) reactivation (3000 copies/mL) treated with Ganciclovir. After the treatment, CMV PCR testing remained negative until the patient died. During transplantation, every bacteriological analysis was negative except for the *Staphylococcus warneri*-seropositive transplant conservation liquid, which was considered to be contaminated. Prophylactic antibacterial chemotherapy included Piperacillin/Tazobactam for 48 hours. The donor presented a positive Toxoplasma IgG result (negative IgM result). The recipient's Toxoplasma serological tests were all negative, including on the day

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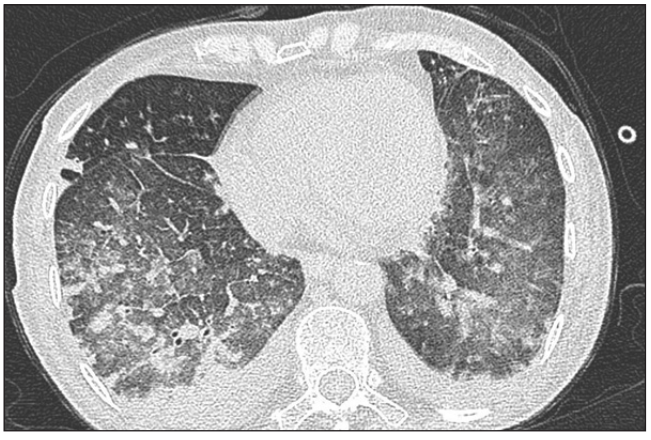

Figure 1 - *Bilateral pneumopathy developing predominantly in the lower lobes associated with bilateral pleural effusion.*

she died, based on enzyme-linked immunosorbent assay (Platelia Toxo IgG and IgM, Bio-Rad kit) and Toxo-Spot IF (bioMérieux kit).

Throughout the declining phase which caused her second transfer to the ICU, the patient showed a biological inflammatory syndrome associated with fever. On D31, C-Reactive Protein (CRP) level increased to 205 mg/L with no leukocytosis but high levels of procalcitonin (PCT) (2.21 ng/ml) and lactate dehydrogenase (LDH) (1,270 IU/L). Computed tomodensitometry (TDM) revealed bilateral pneumopathy developing predominantly in the lower lobes (*Figure 1*).

Numerous *Toxoplasma gondii* tachyzoites were observed by direct examination in bronchoalveolar lavage (BAL) sampled on D31 (*Figures 2a* and *2b*). This finding was confirmed by *Toxoplasmosis* quantitative polymerase chain reaction (QPCR) (Ct=16.5) in BAL (Robert-Gangneux *et al.,* 2015). BAL testing for *Pneumocystis jirovecii* was negative but BAL culture was positive for *Aspergillus fumigatus* and *A. nidulans*. Further analysis in the blood sample (or in blood samples) showed positive galactomannan *Aspergillus* antigen (>4.31, Platelia) and positive *Aspergillus* QPCR (mean Ct=30) (Millon *et al*., 2011).

Toxoplasmosis is generally asymptomatic in immunocompetent individuals. In France, its prevalence in the general population varies from 40 to 60% (Bellali *et al.,* 2013). In immunocompromised individuals, toxoplasmosis is severe with encephalitis, hypoxemic pneumopathy or disseminated forms that often lead to death in the absence of early diagnosis (Patel, 1999; Barcan *et al.,* 2002; Wendum *et al.,* 2002; Brumpt-Lahumiere *et al*., 2006;). AIDS patients, subjects receiving immunosuppressive treatments for hematological malignancy, solid organ transplant (SOT) or hematopoietic stem cell transplantation (HSCT) are at risk, due to bradyzoites located in the cysts reconverted back to tachyzoites when cell-mediated immunity is low. Patients can be contaminated through endogenous transmission resulting from the reactivation of tissue cysts remaining in their body, or exogenous transmission through their donor's blood or organ in case of transplant.

Transmission via noncardiac SOT is extremely rare (Assi *et al*., 2007).

Most of the time, this occurs when transplantation is performed between a *Toxoplasma*-seronegative recipient and a seropositive donor, but cases of reactivation have also been reported. The present case has been the only one so far in the Gastroenterology-Hepatology Department of the University Hospital of Besançon (France), out of 605 liver transplantation procedures since 1986. Liver is not a common site for *Toxoplasma* cysts to develop and post-transplant immunodeficiency is less pronounced. Given Trimethoprim/Sulfamethoxazole toxicity, the systematic prescription of *Toxoplasma gondii* chemoprophylaxis is not commonly approved (Mayes *et al*., 1995; Gourishankar *et al*., 2008; Paya *et al.*, 2012). The reported case emphasizes the difficulty in establishing an early diagnosis of toxoplasmosis infection in immunocompromised patients.

Most clinical signs were nonspecific (fever, hypoxemic pneumopathy complicated by serious sepsis). In the particular case of treatment-resistant acute alcoholic hepatitis (AAH), early liver transplantation could be recommended but the patient's increased vulnerability towards opportunistic infections had to be taken into account (Mathurin *et al*., 2011; Mathurin *et al*., 2012). Chest imaging and standard biological analyses showed abnormalities but did not provide any further contributions (Brumpt-Lahumiere *et al.,* 2006). Parasitological testing and especially direct ex-

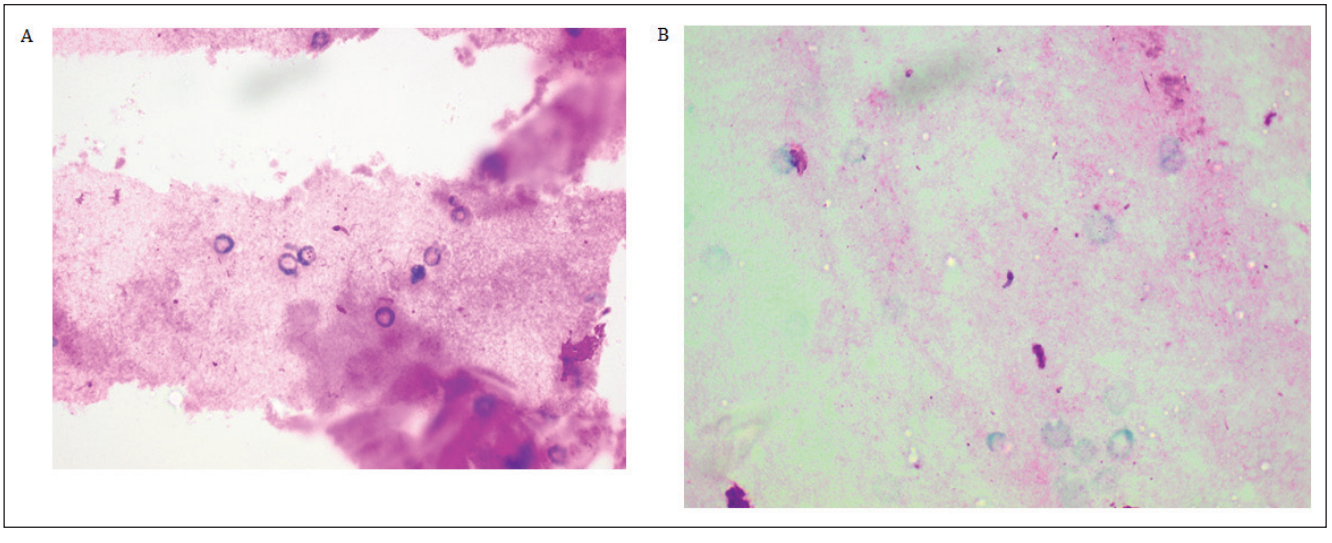

Figure 2 A,B - *Toxoplasma gondii (tachyzoites) in BAL fluid. Magnification x100. RAL staining.*

amination in biological fluids proved to be crucial. Direct examination offers rapid results but requires particular attention as samples might feature very small quantities of parasites. Toxoplasma serology can be contributive but its sensitivity is rather low due to the delay in seroconversion and the transplant recipient's immunodeficiency. Searching for *Toxoplasma gondii* by QPCR in both blood and biological fluids is the most sensitive and specific technique and should be done systematically for transplant recipients by screening in blood throughout the immunosuppression period, especially when the donor is seropositive (Bellali *et al*., 2013).

As in the present case, increased LDH is often found in these severe infections (Brumpt-Lahumiere *et al.,* 2006). Only one patient had survived out of 12 cases reported in addition to the present case, meaning that most diagnoses were actually autopsies. In the present case, the high quantity of parasites found in the BAL, preoperative Toxoplasma seronegative results, and the patient's uninterrupted post-transplant hospitalization led us to the conclusion that *Toxoplasma gondii* transmission had been induced by the infected transplant rather than by exogenous contamination. However, it is worth noting that the presence of *Aspergillus fumigatus* in BAL could have played a co-pathogenic role in the overall clinical severity.

Severe pneumopathy induced by *Toxoplasma gondii* has to be urgently treated at both diagnostic and therapeutic levels. Although they remain exceptional in liver transplant recipients, they have to be considered in case of unexplained fever with unsatisfactory outcome with broad-spectrum anti-infective treatment, especially when multiple organ failure occurs. Given the few cases of toxoplasmosis infections following liver transplantation and the potential toxicity of Trimethoprim/Sulfamethoxazole, systematic preventive measures for this disease have not been recommended thus far.

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