Cytomegalovirus pleuropericarditis after orthotopic liver transplantation

J. Meesters[1], L. Beckers[1], S. Francque[1,2], G. Roeyen[3], K. De Greef[3], V. Hartman[3], P. Michielsen[1,2], K. Dams[4], T. Vanwolleghem[1,2]

(1) Antwerp University Hospital, Department of Gastroenterology and Hepatology ; (2) Laboratory of Experimental Medicine and Pediatrics, University of Antwerp ; (3) Antwerp University Hospital, Department of Hepatobiliary Surgery ; (4) Antwerp University Hospital, Department of Intensive Care.

Abstract

Cytomegalovirus (CMV) reactivation is a common complication after liver transplantation. In patients with CMV infection, indicated by a positive CMV DNA titer, the presence of any clinical symptom is termed CMV disease. The most common organ affected in CMV disease is the gastrointestinal tract, causing esophagitis, gastritis, enteritis or colitis. CMV infection of the pleura and pericard has been reported in immunocompromised patients, but is rarely seen following liver transplantation.We report a case of a 59-year-old male who developed CMV pleuropericarditis after liver transplantation. Initial ganciclovir treatment did not improve the patient's symptoms and therapy was switched to Foscarnet which ultimately resulted in resolution of infection. However, a few weeks after Foscarnet cessation, the patient again developed bilateral pleural effusion. Ultimate biochemical and clinical response was achieved with IV ganciclovir treatment. The patient was discharged from the hospital with oral Valganciclovir for 3 weeks and has since remained relapse free for >1 year. (Acta gastroenterol. belg., **2018**, 81, **427-429**).

Introduction

We report a case of a 59-year-old male who developed CMV pleuropericarditis after liver transplantation. CMV infection of the pleura and pericard has been reported in immunocompromised patients, but is uncommon following liver transplantation. The most common organ affected in CMV disease is the gastrointestinal tract.

Case presentation

A 59-year-old man received an orthotopic liver transplantation of a heart-beating donor because of decompensated post-ethylic cirrhosis of the liver (Child-Pugh class C). The CMV seropositive recipient received an allograft from a CMV seropositive donor (double positive donor-recipient combination: CMV D+/R+) for which no standard CMV prophylaxis was given according to the local transplantation protocol based on international guidelines and Belgian drug reimbursement criteria. The immediate post-transplantation period was uneventful and rapid discharge from intensive care followed within 3 days.

Nosocomial bacterial infections predominate immediately post transplantation. Bacterial infections can occur in any body compartment the abdomen, bloodstream, lungs, urine and at the surgical site are the most frequent infection foci (1). In our case the patient had a previous episode of bacterial infection two weeks postoperative, which resolved with adequate antibiotic treatment. One month post-operatively fever relapsed with concomitant rise in inflammatory parameters. A chest CT scan showed bilateral pleural fluid effusions. A moderate pericardial effusion (18 to 22 mm thick) was found on cardiac ultrasound surrounding both atria, ventricles and apex. Diagnostic pleural drainage showed biochemical signs of pleural exudate effusion (LDH ratio 2.29 and albumin ratio 0.69) and yielded a positive PCR for CMV (4.36 log10IU/ml), while other bacterial cultures remained negative. The diagnosis of CMV pleuropericarditis was withheld.

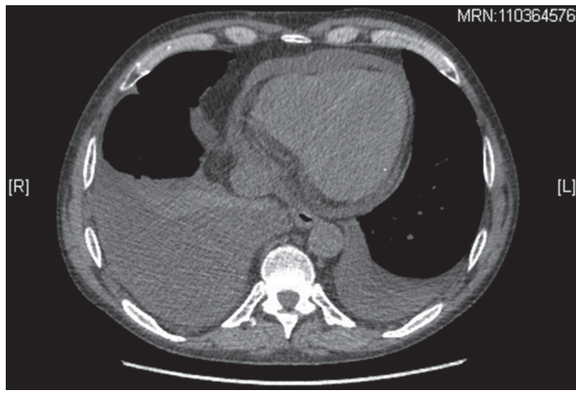

Fig. 1 — CT scan of pleuropericarditis at diagnosis.

Treatment consisted of pericardial and pleural fluid drainage, combined with IV ganciclovir and a reduction of the immunosuppressive regimen. The dose of methylprednisolon and tacrolimus were reduced from 8 mg to 6 mg and 2 mg to 1 mg respectively. However serum CMV titer increased almost 0,5 log IU/ml (from 2.89 log10IU/ml to 3.35 log10IU/ml CMV DNA), fever persisted and the patient developed progressive pancytopenia (Table 1).

Correspondence to : Johanna Meesters, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem.
E-mail : Johanna.meesters@uza.be

Submission date : 01/11/2016
Acceptance date : 21/12/2016

Table 1. — **Evolution of biochemical parameters after diagnosis of CMV disease**

Time after first positive serum titer	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Antiviral treatment	Ganciclovir	Ganciclovir	Ganciclovir	Foscarnet	Foscarnet	Foscarnet	Valganciclovir per os
Hemoglobine (g/dl)	8.3	7.4	7.1	7.8	7.4	7.7	7.4
Leucocytes	6.2	1.5	1.3	4.0	4.6	3.5	5.9
Trombocytes	151	71	70	29	100	91	79
Creatinine (mg/dl)	2.00	1.26	2.08	1.47	2.08	1.30	2.30
Serum CMV titer (log10IU/ml)	4.36	4.21	2.89	3.35	2.77	2.34	< 2.3

As CMV resistance to ganciclovir was suspected and pancytopenia was attributed to ongoing ganciclovir use for over 3 weeks, the treatment was switched to IV foscarnet (2). While pancytopenia stabilized and gradually improved, foscarnet treatment induced kidney function deterioration (Table 1), but eventually led to improvement of the inflammatory parameters and negativation of the CMV DNA titer. Treatment with foscarnet was interrupted after two negative consecutive CMV DNA PCR determinations with 1 week interval. A few weeks after foscarnet cessation, signs of infection combined with bilateral pleural effusion and kidney function deterioration reappeared and serum CMV DNA titer was positive (2.99 log10IU/ml). As by then the results of the initial CMV DNA mutant analysis, taken during the first pleuropericardial effusion episode, resulted as wild type, treatment with IV ganciclovir was restarted. CMV resistance was not present in this case. Within 18 days good virological, biochemical and clinical responses were seen. The patient was discharged from the hospital with oral valganciclovir treatment. At discharge immunosuppression consisted of combination treatment with tacrolimus (5 mg/day) and everolimus (0.75 mg bid) with through levels of 3.2 ng/mL and 1.5 ng/mL respectively.

After discharge from the hospital the CMV titer remained negative and oral valganciclovir treatment was stopped after 21 days. The patient remains well more than 1 year after transplantation, except for a stable chronic kidney disease with an calculated creatinine clearance of 37 mL/min.

Discussion

CMV is one of the most common viral pathogens causing clinical disease in liver transplant recipients (3). CMV infection, as defined by a positive CMV DNA viral load in serum without clinical symptoms, is associated with direct and indirect effects (3).

The direct effects of CMV after liver transplantation can be classified as CMV syndrome or CMV disease (4). The CMV syndrome is characterized by fever, malaise and bone marrow suppression. CMV disease is coined for a patient with CMV infection once organ specific clinical symptoms occur. The most common organ affected in CMV disease is the gastrointestinal tract, causing esophagitis, gastritis, enteritis or colitis (3) (4). We present a case of CMV pleuropericarditis after liver transplantation. CMV infection of the pleura and pericardium has been reported in immunocompromised patients, but is uncommon following liver transplantation. CMV also has a variety of indirect effects including acute and/or chronic graft rejection, allograft failure, opportunistic infections and increased patient mortality. These effects are attributed to the ability of the virus to modulate the immune system (3).

The CMV serostatus of the donor and the recipient is the most important risk factor for the development of CMV disease (4). In solid organ transplantation the risk for CMV disease is the highest among the D+/R- group (CMV seropositive donor and CMV seronegative recipient), in which antiviral prophylaxis is given during the initial 3-6 months after liver transplantation (4). CMV R+ patients have a moderate risk for the development of CMV disease (8-19%) (3,4), which is the case in our patient. Antiviral prophylaxis during 3 months may be sufficient for the CMV seropositive liver recipient (4). The risk of developing CMV disease is reduced when antiviral prophylaxis is given. Valganciclovir is most commonly used for CMV prophylaxis (4). Other risk factors for developing CMV disease in solid organ transplantation include intense immunosuppressive therapy, HLA mismatch and older age of the donor and/or recipient. Patients receiving mTOR inhibitors as immunosuppressive therapy after transplantation have a low incidence of developing CMV disease (5). Since the use of mTOR inhibitors give a lower risk of developing CMV disease it is advised to use these agent with patients at high risk of developing CMV disease (3).

To prevent the progression of asymptomatic CMV infection to CMV disease Singh et al developed an algorithm, so called pre-emptive treatment (6). During the first 12 weeks after transplantation weekly monitoring of CMV viral load is required. When a viral load threshold is reached (locally defined as 3,5 log IU/ml), IV ganciclovir or valganciclovir is started, in order to prevent CMV disease. Antiviral treatment is continued until the virus is no longer detected in the blood in 2 consecutive determinations. In our case, the treatment was started after CMV disease was diagnosed, as at that time pre-emptive treatment in CMV R+ was not reimbursed in Belgium.

The standard of care for the treatment of CMV disease after liver transplantation is IV ganciclovir or

oral valganciclovir (3). In a multi-center non-inferiority trial, where 321 solid organ (including liver) transplant recipients with non-severe CMV disease were included, IV ganciclovir was compared to oral valganciclovir. In this trial patient with severe CMV disease were not included. The overall time to viral eradication in the valganciclovir group was 21 days compared to 19 days in IV ganciclovir. Clinical resolution was not different between the two groups. Treatment success, as assessed by investigators, was 77.4% versus 80.3% at day 21 and 85.4% versus 84.1% at Day 49 (7). IV ganciclovir is preferable to valganciclovir in patients with severe or life-threatening disease or in patients where there is a problem with gastrointestinal absorption of the oral drug. In all other cases, oral valganciclovir is a good alternative and is usually used as a step down treatment after induction treatment with IV ganciclovir (3).

Compartmentalized CMV disease presents a therapeutic challenge as viral load monitoring in blood can often not be used to guide treatment response. It is not uncommon to have a negative serum viral load even when the virus is detected in the affected tissue. As an alternative to repetitive tissue sampling, clinical and biochemical symptoms should resolve before treatment can be interrupted.

Drug resistance should be suspected if there is a more than 1 log rise in viral load during treatment, or if viral load does not decline despite effective antiviral treatment for at least two to three weeks (4). Persisting clinical symptoms even when there is a decline in viral load, should raise the suspicion of compartmentalized disease. CMV mutant analysis can confirm specific drug resistant mutations. CMV ganciclovir resistance occurs when there is a mutation of the UL97 phosphotransferase gene thereby interfering with the transformation of ganciclovir to its active metabolite. A switch of therapy to foscarnet is advised when ganciclovir resistance is identified. Important to note is that cidofovir and foscarnet both act on the UL54 DNA polymerase to terminate viral replication. Mutations in this enzyme may therefore result in cross-resistance to ganciclovir, foscarnet and cidofovir. CMV D+/R- transplant recipients are at the highest risk to develop drug resistance with an incidence of 5-10 % (4). In our case as the analysis of the CMV returned as a wild type and a consecutive treatment with IV ganciclovir argues against resistance. The choice to start foscarnet was based on the lifethereatening nature of the infection.

To conclude, we report a case in which relapsing CMV pleuropericarditis in a CMV seropositive liver transplant recipient, resulted in prolonged hospitalization and the need for long-term and toxic antiviral treatment. Side effects included bone marrow suppression and renal toxicity. Antiviral drug resistance was presumed and managed timely by switching valganciclovir to foscarnet.

References

1. PEDERSEN M, SEETHARAM A. Infections after orthotopic liver transplantation. *Journal of clinical and experimental hepatology*., 2014, **4**(4) : 347-60.
2. KOTTON CN, KUMAR D, CALIENDO AM, ASBERG A, CHOU S, DANZIGER-ISAKOV L, *et al.* Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*, 2013, **96**(4) : 333-60.
3. BRUMINHENT J, RAZONABLE RR. Management of cytomegalovirus infection and disease in liver transplant recipients. *World journal of hepatology*, 2014, **6**(6) : 370-83.
4. MARCELIN JR, BEAM E, RAZONABLE RR. Cytomegalovirus infection in liver transplant recipients: updates on clinical management. *World journal of gastroenterology*, 2014, **20**(31) : 10658-67.
5. AZEVEDO LS, PIERROTTI LC, ABDALA E, COSTA SF, STRABELLI TM, CAMPOS SV, *et al.* Cytomegalovirus infection in transplant recipients. *Clinics*, 2015, **70**(7) : 515-23.
6. SINGH N, GAYOWSKI T, WAGENER MM, MARINO IR. Increased infections in liver transplant recipients with recurrent hepatitis C virus hepatitis. *Transplantation*, 1996, 61(3) : 402-6.
7. ASBERG A, HUMAR A, ROLLAG H, JARDINE AG, MOUAS H, PESCOVITZ MD, *et al.* Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2007, **7**(9) : 2106-13.