Hepatic microabscesses during CMV reactivation in a multiple sclerosis patient after alemtuzumab treatment

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Introduction

- The Cytomegalovirus (CMV) reactivation risk increases in immunocompromised patients and rarely can lead to severe organ complications.
- Much of medical literature implicating CMV as the causative agent for hepatic involvement either immunocompromised hosts or previous orthotopic liver transplant recipients.[1]
- Alemtuzumab is now indicated for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) but previously, it was approved for use in the chronic lymphocytic leukemia (CCL).
- Although the CMV reactivation is an event ranged from 4% to 29% of patients treated with alemtuzumab for CCL, this eventuality is just recently described in MS patients treated with this drug.[2]
- **We describe a case of CMV reactivation with hepatic involvement in a RRMS patient treated with alemtuzumab.**

Case report

A **45-year-old woman** affected by RRMS, with a 10-year history of inefficacy and intolerance to different treatments.
In **September 2016, she began Alemtuzumab** (12 mg/day i.v. for 5 consecutive days).
On the first day of infusion, she started to take **oral prophylaxis for Herpes infection with acyclovir 200 mg/twice a day**.
After three weeks of last alemtuzumab infusion, she was hospitalised for **fever (38°C).**

➢ The laboratory tests showed:
- *a modest increase in transaminases* (ALT 46 UI/l; AST 41 UI/l, GGT 63 UI/l)
- *a considerable increase in inflammation index* (C-reactive Protein 75,5 mg/l).
- White Blood Cells (WBC) were 2,8 x 10^3/uL (microliter) and lymphocytes count was 0,08 x 10^3/uL.
- *The follow infective and autoimmune panel of tests has been performed with negative results:* blood and urine cultures, procalcitonin, acute hepatitis (A/B/C) markers, HIV antibodies, Epstein-Barr virus (EBV) IgM, Varicella Zoster (VZV) IgM, Syphilis tests (rapid plasma reagin – RPR; Treponema Pallidum Hemagglutination Assay – TPHA), QuantiFERON®-TB, Widal-Wright reaction, IgG and IgM antibodies against Bartonella, Brucella, Borrelia, Treponema and Toxoplasma, anti-dsDNA antibodies, antinuclear antibodies (ANA), Waaler-Rose reaction, anti-mitochondrial antibodies (AMA), anti-Liver Kidney Microsomal Antibodies (LKM), anti-smooth muscle antibody (ASMA).

➢ **The CMV viral DNA polymerase chain reaction (PCR) was positive for 17.318 copies/ml**, anti CMV IgG antibodies were positive at 48 U/ml and anti CMV IgM antibodies were negative **indicating a CMV reactivation.**

➢ **The liver ultrasonography,** made because of the transaminase increase, **demonstrated multiple small hypoechoic lesions (maximum sizes 1 cm) diffusely scattered in the hepatic lobes suggesting multiple hepatic microabscesses** [Figure (A-B)], not detected in previous hepatic ultrasonography.

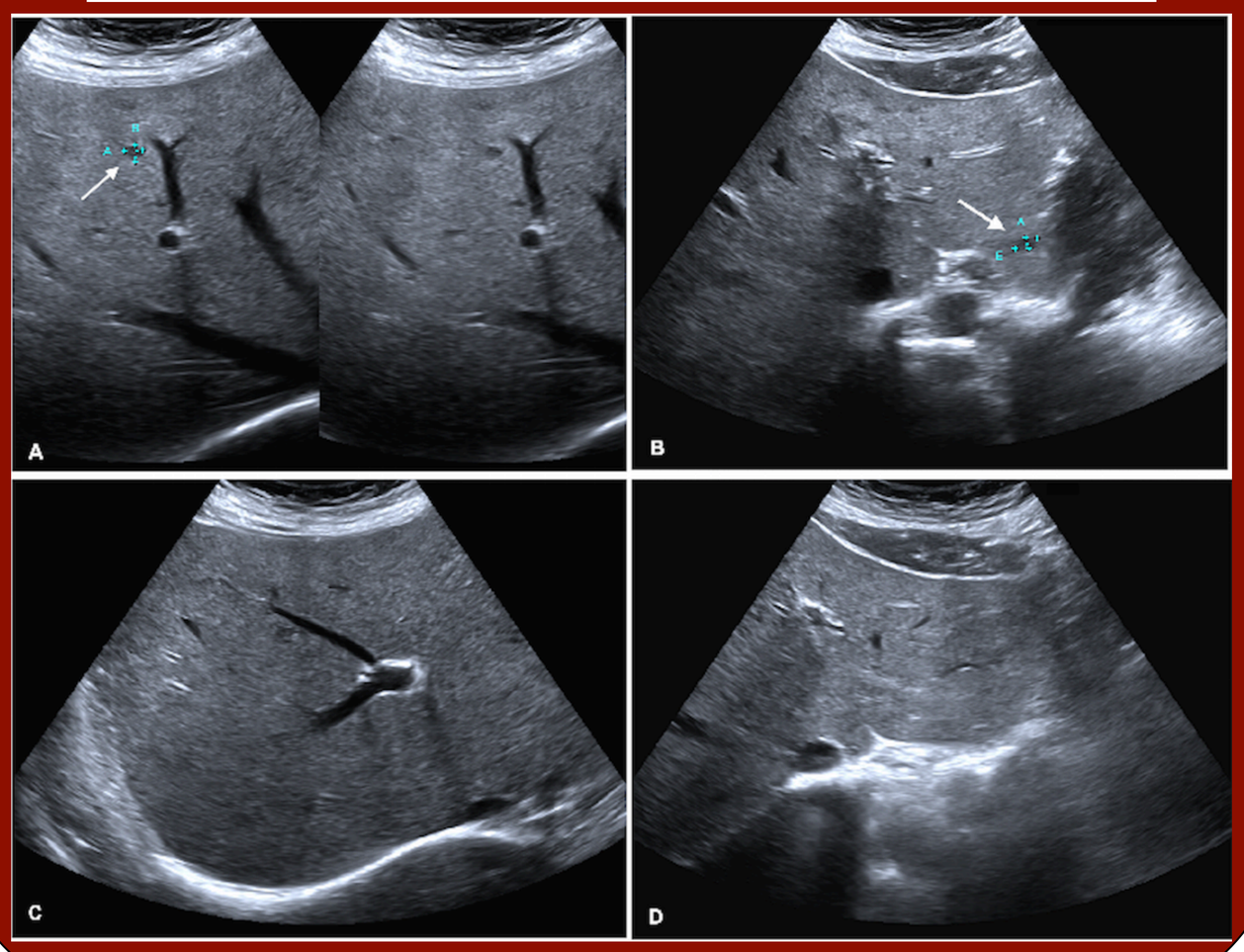
➢ **Oral valganciclovir was administered at dose of 450 mg twice daily for 4 weeks.**

➢ The **CMV viral load became undetectable 13 days after the beginning of antiviral treatment.** Fever, inflammation indexes and hypertransaminasemia resolved in two weeks.

➢ At the **follow-up liver ultrasonography two months later the microabscesses regression was demonstrated** [Figure (C-D)]

Figure

(A, B) small hypoechoic lesions in the liver, suggestive of multiple microabscesses and (C, D) no evidence of residual hypoechoic lesions after treatment with valganciclovir.



Discussion

The data so far available about CMV reactivation in patients treated with alemtuzumab concern his use in lymphoproliferative disorders.
The guidelines on the Management of CMV reactivation in patient with CLL treated with alemtuzumab recommend *performing the CMV DNA essay in all patients that develop fever soon after the treatment and treating all symptomatic patients with positive CMV DNA using valganciclovir or ganciclovir.*[3]
The case here reported has several points of similarity with those recently described[2] :
- the fever as presentation symptom of CMV reactivation
- the onset within one month after Alemtuzumab infusion
- the complete recovery achieved with specific antiviral therapy (valganciclovir)

In addition, **in our case the liver was involved by microabscesses resolved after therapy with valganciclovir.** Hepatic microabscesses during CMV reactivation have been described in immunosuppressed patients, especially in liver transplant recipients, where the hepatic involvement by CMV tends to be focal. [4] Liver microabscesses and parenchymal alteration are also common in CMV hepatitis.[5]
Because of the acyclovir prophylaxis could be ineffective against the CMV reactivations[6] **all patients that develop fever and increase of transaminases after alemtuzumab treatment should undergo CMV PCR essay and, in our opinion, also the liver ultrasonography** to demonstrated hepatic involvement how in this case.
Furthermore, *could be suggested to perform in all MS patients the baseline CMV status before starting the alemtuzumab and implement a weekly monitoring with CMV PCR essay during first month after infusion*, such as indicated in the guidelines for CCL.
This surveillance would allow a **promptly switch from acyclovir to** antiviral specific treatment (**ganciclovir or valganciclovir) in case of CMV reactivation**.

Conclusions

This report highlight further the risk of CMV reactivation in the first month following alemtuzumab infusion and suggest that an appropriate surveillance is needed in this period to manage this potential and treatable opportunistic infection.

References:
1. Kanj SS, Sharara A, Clavien PA, et al., 1996. Cytomegalovirus infection following liver transplantation: review of the literature. Clin Infect Dis. 22(3):537-549.
2. Clerico M, De Mercanti S, Artusi CA, et al. Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab. Mult Scler. 2017 Feb [Epub ahead of print]
3. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma. 2006 Sep;7(2):125-130.
4. MacDonald GA, Greenson JK, DelBuono EA, et al. Mini-microabscess syndrome in liver transplant recipients. Hepatology. 1997 Jul;26(1):192-197.
5. Minemura M, Tajiri K, Shimizu Y., 2014. Liver involvement in systemic infection. World J Hepatol. 6(9):632-642.
6. Hartung HP, Aktas O, Boyko AN. 2015. Alemtuzumab: a new therapy for active relapsing-remitting multiple sclerosis. Mult Scler. 21(1):22-34

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